Mechanism of Enamine Reactions. II.[1] The Hydrolysis of Tertiary Enamines

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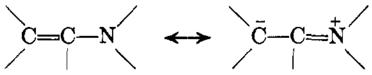
The rates of hydrolysis of 1-N-morpholino-1-isobutene (I), 1-N-piperidino-1-isobutene (II), and 1-N-pyrrolidino-1-isobutene (III) have been investigated in aqueous buffer solutions at different temperatures. In the solutions an equilibrium is established between the enamine and its N-protonated conjugate acid. The reaction is general acid catalyzed. The solvent isotope effect $k_{H_3O^+}/k_{D_3O^+}$ is 2.5 and k_{HOAc}/k_{DOAc} has a value of 9. On account of these results a mechanism is proposed, in which the rate-determining step is a proton transfer to the β carbon atom of the free base. The dissociation constants of the conjugate acids of I, II, and III have been calculated from the kinetic data. The order in reactivity is III > II >> I.

In 1954 Stork and co-workers[2] introduced a new synthetic method for the arylation and alkylation of aldehydes and ketones *via* enamines. Since that time a large number of papers has appeared,[3] which show the usefulness of enamines as important intermediates and blocking groups in organic syntheses.

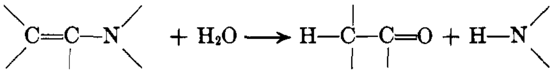
Up till now the mechanism of the Stork reaction, which involves an attack of an electrophilic reagent upon the enamine, is not known in detail.[4]

Moreover, the enamine structure, shown below,



is very interesting, because the electrophilic attack can occur on the β carbon as well as on the nitrogen atom.

However, little quantitative information is available concerning the reactivity of the enamine system. Therefore, the mechanism of the frequently applied hydrolysis of tertiary enamines has been investigated.



Methods and Results

From preliminary rate determinations it appeared that the hydrolysis of 1-N-morpholino-1-isobutene (I) proceeds with a measurable rate at 25° in aqueous solutions in the pH range of 5.80 to 7.30, using a KH_2PO_4–Na_2HPO_4 buffer. The ionic strength was always adjusted to 0.100 mole/l. by the addition of sodium chloride. The reaction rates were determined by measuring the rate of disappearance of I spectrophotometrically at 2170 Å. The reactions are first order, which appeared from the excellent straight lines in plots of log $(E_t - E_\infty)$ *vs.* time.

The first-order rate constant, k, follows from the equation

$$\log (E_t - E_\infty) = -0.434kt + \text{constant}$$

where E_t is absorbance at time t, E_∞ is absorbance after 10 half-life times, and t is time in seconds.

Values of k were determined from least-squares calculations in which the points up to 90% conversion were used.

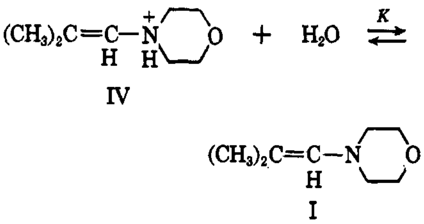
Figure 1 shows the first-order rate constants as a function of the concentration of $H_2PO_4^-$ ions at four different pH values. This plot clearly shows that at a fixed pH value a linear relation exists between the concentration of the $H_2PO_4^-$ ions and the first-order rate constant, k. At the lower pH values of the buffer Figure 1 shows a small but real contribution to the rate not ascribable to $H_2PO_4^-$ ions. Because the rate of hydrolysis of I in 0.1 N sodium hydroxide solution is negligible ($k < 10^{-5}$ sec.$^{-1}$), contributions of water or OH^- ions can be excluded.

On the other hand the hydrolysis of I proceeds rapidly in more acidic solutions at approximately pH 2. Therefore, besides $H_2PO_4^-$ ions, hydronium ions also act as proton donors in the hydrolysis reaction. Using a dilute acetate buffer, the contribution of hydronium ions to the rate was much larger and the second-order rate constant for the hydronium ions, $k_{H_3O^+}$, was calculated from a series of measurements in this buffer. Because not only the hydronium ions, but also $H_2PO_4^-$ ions and acetic acid, contribute to the rate, it follows that the hydrolysis is general acid catalyzed and for each straight line of Figure 1 (pH constant) the first-order rate constant, k, may be represented by the expression[5]

$$k = k'_{H_3O^+} \cdot a_{H_3O^+} + k'_{H_2PO_4^-} \cdot c_{H_2PO_4^-} \qquad (1)$$

where $a_{H_3O^+}$ is the activity of the hydronium ions as measured with a pH meter and $c_{H_2PO_4^-}$ is the concentration of the $H_2PO_4^-$ ions, both in mole/l.

The straight lines in Figure 1 have different slopes, however. Thus, $k'_{H_3O^+}$ and $k'_{H_2PO_4^-}$ are apparent catalytic coefficients. This phenomenon can be explained by the observation that I acts as a base, which is in equilibrium with its conjugate acid in aqueous solutions.


(2)

In a few experiments the rate was not only determined from the decrease in the absorbance at 2170 Å. (λ_{max} of I), but also from the decrease in the absorbance

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[1] Part I: E. J. Stamhuis and W. Maas, *Rec. trav. chim.*, **82**, 1155 (1963).

[2] G. Stork, R. Terrell, and J. Szmuszkovicz, *J. Am. Chem. Soc.*, **76**, 2029 (1954).

[3] J. Szmuszkovicz, *Advan. Org. Chem.*, **4**, 1 (1963).

[4] G. Stork, A. Brizzolara, H. Landesman, J. Szmuszkovicz, and R. Terrell, *J. Am. Chem. Soc.*, **85**, 207 (1963).

[5] R. P. Bell, "The Proton in Chemistry," Methuen and Co., Ltd., London, 1959, p. 130.

TABLE I

SECOND-ORDER RATE CONSTANTS AND DISSOCIATION CONSTANTS OF THE CONJUGATE ACID OF I IN WATER

Temp., °C.	$k_{H_3O^+}$, l. mole^{-1} sec.$^{-1}$	$k_{H_2PO_4^-}$, l. mole^{-1} sec.$^{-1}$	k_{HOAc}, l. mole^{-1} sec.$^{-1}$	K, mole l.$^{-1}$	pK
25.00	3.1×10^2	0.76	1.8	3.4×10^{-6}	5.47 ± 0.04
39.60	9.5×10^2		5.4	5.8×10^{-6}	5.24 ± 0.05
50.65	19.3×10^2		11.6	8.1×10^{-6}	5.09 ± 0.04

TABLE II

SECOND-ORDER RATE CONSTANTS AND DISSOCIATION CONSTANTS OF THE CONJUGATE ACID OF II IN WATER

Temp., °C.	$k_{H_3O^+}$, l. mole^{-1} sec.$^{-1}$	k_{H_2O}, l. mole^{-1} sec.$^{-1}$	$k_{H_3BO_3}$, l. mole^{-1} sec.$^{-1}$	K, mole l.$^{-1}$	pK
25.00	0.14×10^6	0.97×10^{-5}	1.1×10^{-2}	4.4×10^{-9}	8.35 ± 0.1
39.60	0.63×10^6	4.4×10^{-5}	4.0×10^{-2}	4.3×10^{-9}	8.35 ± 0.1
50.24	1.8×10^6	11.3×10^{-5}	6.0×10^{-2}	3.3×10^{-9}	8.5 ± 0.1

at 1960 Å. (λ_{max} of IV). The agreement in these first-order rate constants was excellent. This indicates that the equilibrium of eq. 2 is built up very rapidly. The fast protonation of the nitrogen atom in enamines has also been demonstrated by Opitz and Griesinger.[6]

The reaction is acid catalyzed and therefore involves a proton transfer. Because IV has already a positive charge, it is obvious that the free base I and not the conjugate acid IV is the reactive species.[7] The concentration of I is only a fraction of the total concentration, $c_t = c_I + c_{IV}$, and is pH dependent

$$c_I = \frac{K}{K + a_{H_3O^+}} \cdot c_t$$

where K is the dissociation constant of IV. The apparent coefficients from eq. 1 may now be formulated as

$$k'_{H_3O^+} = k_{H_3O^+} \cdot \frac{K}{K + a_{H_3O^+}} \text{ and } k'_{H_2PO_4^-} = k_{H_2PO_4^-} \cdot \frac{K}{K + a_{H_3O^+}}$$

where $k_{H_3O^+}$ and $k_{H_2PO_4^-}$ are the true catalytic coefficients.

The general expression for the first-order rate constant, k, is

$$k = \frac{K}{K + a_{H_3O^+}} \cdot k_{H_3O^+} \cdot a_{H_3O^+} + \frac{K}{K + a_{H_3O^+}} \cdot k_{AH} \cdot c_{HA} \quad (3)$$

k_{HA} is the true catalytic coefficient for the acid HA and c_{HA} is the concentration of HA in mole/l.

From a series of measurements, carried out in aqueous phosphate buffers at 25° and in aqueous acetate buffers at different temperatures, the constants of eq. 3 were determined by least-squares calculations. These values are given in Table I.

The validity of eq. 3 was demonstrated in the following way. (i) Inspection of eq. 3 shows that at one concentration of the acid HA, namely $c_{HA} = Kk_{H_3O^+}/k_{HA}$, the rate is independent of the pH and has the value $k = Kk_{H_3O^+}$. Figure 1 shows indeed this concentration at the intersection of the straight lines ($c_{H_2PO_4^-} = 0.0014$ mole/l.). The rate at this concentration is pH independent ($k = 1.05 \times 10^{-3}$ sec.$^{-1}$). (ii) When a buffer is not used and $a_{H_3O^+} >> K$, eq. 3 reduces also to $k = Kk_{H_3O^+}$. From rate determinations of I in 0.01 N hydrochloric acid at 1960 Å. at 25° the following values of k were obtained: 1.01×10^{-3}, 1.07×10^{-3}, and 1.05×10^{-3} sec.$^{-1}$. This is in good agreement with the value of 1.05×10^{-3} sec.$^{-1}$, calculated from the constants of Table I.

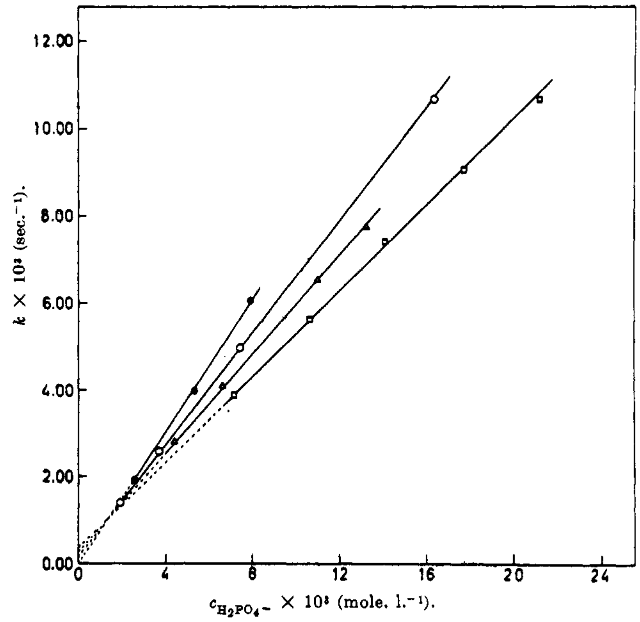

Figure 1.—First-order rate constants for the hydrolysis of 1-N-morpholino-1-isobutene in aqueous phosphate buffers at 25° as a function of the concentration of $H_2PO_4^-$ ions. pH values: ●, 7.30; ○, 6.30; △, 6.00; □, 5.79.

The enamines 1-N-piperidino-1-isobutene (II) and 1-N-pyrrolidino-1-isobutene (III) are much more reactive and, as appeared afterwards, the dissociation constants of their conjugate acids are much smaller. Therefore, hydrolysis runs were performed in borax buffers in the pH range of 8 to 9.5. Also in these buffer solutions the ionic strength was kept constant at 0.100 mole/l. by the addition of sodium chloride. In aqueous solutions of 0.010 to 0.100 N sodium hydroxide II and III hydrolyze with a constant rate. This indicates that now water contributes also to the total rate. Hence eq. 3 must undergo an extension (eq. 4).

$$k = \frac{K}{K + a_{H_3O^+}} \cdot a_{H_3O^+} \cdot k_{H_3O^+} + \frac{K}{K + a_{H_3O^+}} \cdot k_{HA} \cdot c_{HA} + \frac{K}{K + a_{H_3O^+}} \cdot k_{H_2O} \cdot c_{H_2O} \quad (4)$$

In dilute solutions of sodium hydroxide (pH 12 to 13) eq. 4 reduces to $k = k_{H_2O} \cdot c_{H_2O}$, for $K >> a_{H_3O^+}$. Determination of the rate of hydrolysis of II and III in 0.01 N hydrochloric acid at 1960 Å. appeared to be practically impossible in consequence of the rather high absorbances of the piperidinium and pyrrolidinium ions, respectively, which are formed at the same rate.

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(6) G. Opitz and A. Griesinger, *Ann.*, **665**, 101 (1963).

(7) See Discussion.

TABLE III

SECOND-ORDER RATE CONSTANTS AND DISSOCIATION CONSTANTS OF THE CONJUGATE ACID OF III IN WATER

Temp., °C.	$k_{H_3O^+}$, l. mole^{-1} sec.$^{-1}$	k_{H_2O}, l. mole^{-1} sec.$^{-1}$	$k_{H_3BO_3}$, l. mole^{-1} sec.$^{-1}$	K, mole l.$^{-1}$	pK
0.00	0.69×10^6	1.2×10^{-5}	2.6×10^{-2}	1.7×10^{-9}	8.77 ± 0.05
15.00	3.1×10^6	6.6×10^{-5}	12×10^{-2}	1.4×10^{-9}	8.84 ± 0.07
25.00	8.4×10^6	17×10^{-5}	20×10^{-2}	1.4×10^{-9}	8.84 ± 0.09

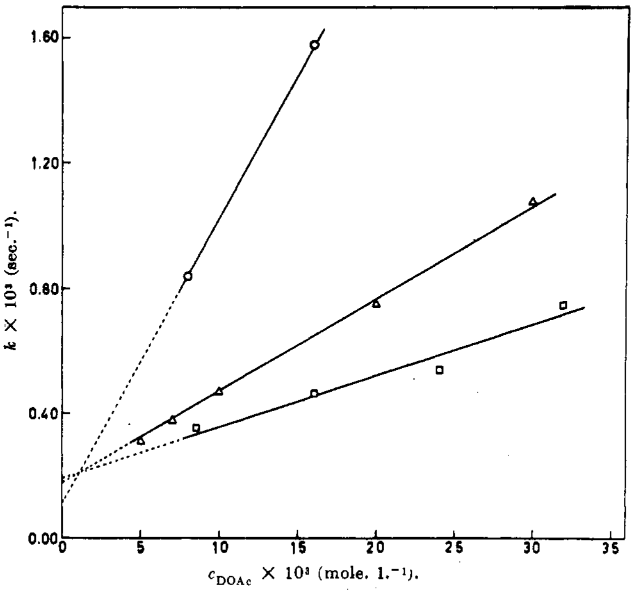


Figure 2.—First-order rate constants for the hydrolysis of 1-N-morpholino-1-isobutene in D_2O, buffered with DOAc–NaOAc, at 25° as a function of the concentration of DOAc. pD values (cor.): ○, 5.70; △, 5.03; □, 4.72.

The values of the second-order rate constants for the hydrolysis of the enamines II and III and the dissociation constants of their conjugate acids at different temperatures are given in the Tables II and III, respectively.

In order to determine the solvent deuterium isotope effect, a well-known and frequently used criterion in the elucidation of mechanisms of this type of reactions, a number of experiments was carried out with 1-N-morpholino-1-isobutene in heavy water, buffered with DOAc–NaOAc (ionic strength, 0.100 mole/l. by adding sodium chloride). The results are shown in Figure 2. The catalytic constants (eq. 3) and the dissociation constant of the conjugate acid in this solvent were calculated from the experimental first-order rate constants by least-squares calculations (Table IV).

From the data in the Tables I and IV the deuterium isotope effect $k_{H_3O^+}/k_{D_3O^+}$ amounts to 2.5 ± 0.7, while k_{HOAc}/k_{DOAc} has a value of 9 ± 1.

Enthalpies of activation and entropies of activation were derived from the second-order rate constants of the Tables I, II, and III. The values are collected together in the Tables V and VI. The deviations in these values are chiefly a consequence of the error in the pH determinations of the buffer solutions (±0.01 pH unit).

Discussion

TABLE IV

SECOND-ORDER RATE CONSTANTS AND DISSOCIATION CONSTANT OF THE CONJUGATE ACID OF I IN DEUTERIUM OXIDE AT 25°

$k_{D_3O^+}$, l. mole^{-1} sec.$^{-1}$	k_{DOAc}, l. mole^{-1} sec.$^{-1}$	K, mole l.$^{-1}$	pK
1.3×10^{-2}	0.20	1.60×10^{-6}	5.79 ± 0.05

TABLE V

ENTHALPIES OF ACTIVATION

(kcal. mole^{-1})

Enamine	ΔH^* (H_3O^+)	ΔH^* (H_2O)	ΔH^* (HOAc)	ΔH^* (H_3BO_3)
I	13 ± 2.6		14 ± 1.2	
II	19 ± 3	18 ± 0.5		12 ± 2.5
III	16 ± 3	17 ± 0.5		12 ± 2.5

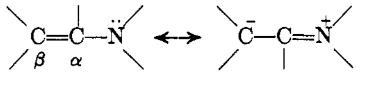
TABLE VI

ENTROPIES OF ACTIVATION

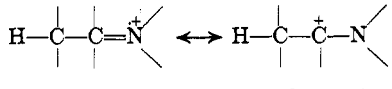
(cal. mole^{-1} deg.$^{-1}$)

Enamine	ΔS^*(H_3O^+)	ΔS^* (H_2O)	ΔS^* (HOAc)	ΔS^* (H_3BO_3)
I	-4 ± 5		-11 ± 2	
II	29 ± 7	-21 ± 1		-28 ± 4
III	26 ± 6	-20 ± 1		-21 ± 4

In the hydrolysis of the enamines I, II, and III the experimental results clearly show not only catalysis by hydronium ions, but also catalysis of other Brønsted acids. Thus, the observed kinetics satisfy the conditions for general acid catalysis. This indicates that a rate-determining proton transfer to the enamine molecule is involved in the reaction sequence.[8] An enamine molecule possesses two basic centers, *viz.*, the nitrogen atom and the β carbon atom, and hence a proton transfer can occur to both centers. However, a proton transfer in the slow step to the basic nitrogen



atom seems very unlikely[9] and can be rejected, because on this basis no explanation can be given for the immediately formed absorption band at 1960 Å. in more acidic solutions, which has to be ascribed to the conjugate acid IV.[10] Therefore, a slow proton transfer to the β carbon atom is proposed, resulting in a very reactive intermediate, which reacts rapidly with



solvated water molecules to the products, isobutyraldehyde and the corresponding secondary amine.

An accumulation of this primary formed carbonium ion would result in the appearance of an absorption band in the range of 2200 to 2300 Å.[11] ($>C=\overset{+}{N}<$).

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(8) A. A. Frost and R. G. Pearson, "Kinetics and Mechanism," John Wiley and Sons, Inc., New York, N. Y., 1959, p. 204.

(9) R. H. DeWolfe, *J. Am. Chem. Soc.*, **82**, 1585 (1960).

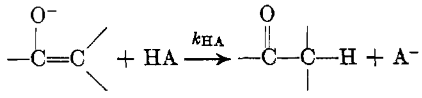
(10) (a) H. E. Ungnade, "Organic Electronic Spectral Data, "Vol. II, Interscience Publishers, Inc., New York, N. Y., 1960; (b) G. Opitz, H. Hellmann, and H. W. Schubert, *Ann.*, **623**, 117 (1959).

(11) Reference 10b.

An increase in the absorbance at this wave length has not been observed, however.

The proposed mechanism is supported by the value of the solvent deuterium isotope effect, calculated from the hydrolysis rates of 1-N-morpholino-1-isobutene in light and heavy water at 25°. The obtained normal isotope effect ($k_{H_3O^+}/k_{D_3O^+} = 2.5 \pm 0.7$) indicates a rate-determining proton transfer.[12,13] For general acid catalyzed reactions with initial slow proton transfer Long and Bigeleisen[14] expect a k_{HOAc}/k_{DOAc} ratio, which is two to four times greater than that observed for $k_{H_3O^+}/k_{D_3O^+}$. The value of k_{HOAc}/k_{DOAc} of 9 ± 1 is in agreement with this statement.

Enamines, like enolate anions, have two reactive centers and they have many important synthetic reactions that are closely related to those of enolate ions.[15] Therefore, it is of particular interest to note the solvent isotope effects for the slow general acid catalyzed reaction of enolate ions to the corresponding ketones as investigated recently by Riley and Long.[16]



These workers obtained $k_{H_3O^+}/k_{D_3O^+}$ values of 1.7 and 1.35 for the conversion of the enolate ions of 2-acetylcyclohexanone and methylacetylacetone to these ketones, respectively, whereas with acetic acid as reactant values for k_{HOAc}/k_{DOAc} of 5.9 and 6.9, respectively, could be calculated. Although these values are somewhat smaller than those obtained in the hydrolysis of I, there is a striking agreement in the ($k_{HOAc}/k_{DOAc}/k_{H_3O^+}/k_{D_3O^+}$) ratios which may be considered a further support on the proposed mechanism.

From the Tables I and IV it can be seen that $\Delta pK_I = pK_I^D - pK_I^H$ has a value of approximately 0.3, which is a little smaller than those obtained in most cases.[17]

Table V shows that the spreading in the values of the enthalpies of activation is not extensive for the different catalytic species. The values of the entropies of activation (Table VI), as far as the catalytic species H_2O, AcOH, and H_3BO_3 are concerned, are all negative as is to be expected.[18] On the other hand the origin of the large difference between the entropy of activation for the hydronium ion catalyzed reaction of I and those of II and III is not clear.

The reactivity of the three enamines, III > II >> I, is in agreement with the qualitative results obtained in the case of formation of enamines with respect to the secondary amines, pyrrolidine, piperidine, and morpholine, respectively.[4]

An alternative interpretation of the observed kinetic behavior is a mechanism in which a nucleophilic attack on the α carbon atom of the N-protonated conjugate acid of the enamine is involved in the slow step. Besides contributions of H_2O, OH^- ions, and the conjugate bases of the buffer acids used, a real contribution of Cl^- ions may then be expected. However, no relation exists between the amount of sodium chloride, added to the buffer solutions to obtain an ionic strength of 0.100 mole/l., and the first-order rate constants. The replacement of chloride ions by perchlorate ions, of which the nucleophilicity is much smaller,[19] has no influence on the rate. Hydrolysis of I in aqueous acetate buffer at 39.60° (c_{HOAc} 0.0100, c_{NaOAc} 0.0025, and c_{NaCl} 0.0900 mole/l.) gave a rate constant of 9.98×10^{-3} sec.$^{-1}$ and after replacement of sodium chloride by sodium perchlorate 9.97×10^{-3} and 9.85×10^{-3} sec.$^{-1}$, respectively.

The large value of the isotope effect, k_{HOAc}/k_{DOAc}, of 9 is hard to understand on the basis of this mechanism, because in both solvents, H_2O and D_2O, the acetate ion is the catalytic species.

Also the formation of $(CH_3)_2C{=}CH{-}OCOCH_3$, which may be expected during hydrolysis of I in acetate buffers, did not occur, as could be demonstrated by infrared analysis of the hydrolytic products.

These facts all contradict a nucleophilic attack on the conjugate acid of the enamine in the slow step as an important contribution to the over-all rate of hydrolysis.

Experimental

Materials.—1-N-Morpholino-1-isobutene was synthesized from isobutyraldehyde and morpholine as described by Benzing,[20] b.p. 59–60° (17 mm.), n^{20}_D 1.4668 [lit.[20] b.p. 56–57° (11 mm.), n^{20}_D 1.4670].

1-N-Piperidino-1-isobutene was prepared from isobutyraldehyde and piperidine according to the procedure of Heyl and Herr,[21] b.p. 65° (18 mm.), n^{20}_D 1.4676 [lit.[20] b.p. 52° (14 mm.), n^{20}_D 1.4679].

1-N-Pyrrolidino-1-isobutene was synthesized in the same way from isobutyraldehyde and pyrrolidine, b.p. 56° (18 mm.), n^{20}_D 1.4739 [lit.[20] b.p. 70–71° (38 mm.), n^{20}_D 1.4740].

The enamines were distilled twice before they were used in the kinetic experiments.

The solvent water was purified by demineralization and afterwards distilled in an all-silica distillation unit.

Pro analyse grade chemicals were used in preparing the buffer solutions.

Methods.—The preparation of the buffer solutions was performed in the usual way. The measurements of pH were made on a Radiometer pH meter, type TTT1a, provided with a glass and a calomel electrode, and were reproducible to 0.01 unit. The instrument was calibrated as described earlier.[22]

The pD values of the buffers in D_2O (purity 97%) were obtained as follows. The constant C, in the equation[23]

$$pH = pK_a + \log\,[salt]/[acid] - 0.505\, z_i^2\, \mu^{0.5} + C\mu$$

was calculated from the pH measurements of a series of acetate buffers in H_2O ($\mu = 0.100$) and has a value of 0.3. Assuming that this constant is equal in D_2O and H_2O, the following values of ΔpD = pD (calcd.) −pD (exptl.) were obtained at 25.0°: 0.41, 0.39, and 0.40. For the calculation of the constant C the thermodynamic dissociation constant of acetic acid in H_2O at 25° was used. The dissociation constant of acetic acid in D_2O (97%) at 25° is 0.57×10^{-5} mole/l.[24] Although this value in D_2O has been obtained at an ionic strength of 0.01 mole/l., La Mer and Chittum[24] state that no correction is needed for an extrapolation

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[12] A. V. Willi, *Z. Naturforsch.*, **16a**, 162 (1961).

[13] C. A. Bunton and V. J. Shiner, Jr., *J. Am. Chem. Soc.*, **83**, 42, 3207, 3214 (1961).

[14] F. A. Long and J. Bigeleisen, *Trans. Faraday Soc.*, **55**, 2077 (1959).

[15] J. D. Roberts and M. C. Caserio, "Basic Principles of Organic Chemistry," W. A. Benjamin, Inc., New York, N. Y., 1964, pp. 486, 487.

[16] T. Riley and F. A. Long, *J. Am. Chem. Soc.*, **84**, 522 (1962).

[17] A. O. McDougall and F. A. Long, *J. Phys. Chem.*, **66**, 429 (1962).

[18] K. J. Laidler, "Reaction Kinetics," Vol. II, Pergamon Press Ltd., Oxford, 1963, p. 24.

[19] J. Hine, "Physical Organic Chemistry," McGraw-Hill Book Co., Inc., 1956, p. 140.

[20] E. Benzing, *Angew. Chem.* **71**, 521 (1959).

[21] F. E. Heyl and M. E. Herr, *J. Am. Chem. Soc.*, **75**, 1918 (1953).

[22] E. J. Stamhuis and W. Drenth, *Rec. trav. chim.*, **80**, 797 (1961).

[23] A. I. Vogel, "A Textbook of Quantitative Inorganic Analysis," Longmans, Green and Co., London, 1951, p. 33.

[24] V. K. la Mer and J. P. Chittum, *J. Am. Chem. Soc.*, **58**, 1642 (1936).

to $\mu = 0$. The ΔpD value of 0.40 is in good agreement with data in the literature.[25,26]

The pD values, used for the calculation of the second-order rate constants of eq. 3, were actually obtained by using the correction $\Delta pD = 0.40$ with the pH meter readings of the D_2O solutions, the meter having been standardized with a standard buffer in H_2O.

The rate measurements of the hydrolysis of I were carried out at 2170 Å. by means of a cell with a path length of 3 cm. through which the solution from a reactor of approximately 200 ml. circulated.[27] The enamines II and III are only sparingly soluble in water. The reactor could not be used for the hydrolysis measurements of II and III because too much time was needed to dissolve them. Therefore, silica cells were used with path lengths of 1 cm. and the enamines were dissolved by vigorous shaking of the buffer with 1 drop of a dilute solution of I or II in absolute ethanol during a few seconds. A constant temperature of the solutions during the experiments was obtained by storing the silica cells in small iron vessels containing mercury, which were placed in a constant-temperature bath. The heat transfer is rapid and the silica cells remain clean.

The hydrolysis experiments of III at 0.03° were carried out in a room with a constant temperature of approximately 3°, in order to avoid condensation of water vapor on the cooled silica cells. The absorbances were measured with a Zeiss spectrophotometer, type PMQ II.

Analysis of the Products.—To an aqueous phosphate buffer solution of pH 6.30 (0.320 g. of $Na_2HPO_4 \cdot 12H_2O$, 0.380 g. of KH_2PO_4, and 0.600 g. of NaCl) 500 mg. of I was added. After 2, 8, and 120 min., 100 ml. of this solution was extracted with 2 ml. of carbon tetrachloride. These carbon tetrachloride solutions were dried with magnesium sulfate and their infrared spectra were recorded in 1-mm. cells. The spectra demonstrate the disappearance of the $>C{=}C<$ absorption peak of I at 1665 cm.$^{-1}$, whereas a strong band at 1730 cm.$^{-1}$, which has to be ascribed to the carbonyl absorption of isobutyraldehyde, appeared already in the first infrared spectrum.

Gas chromatographic analysis of the solution of carbon tetrachloride, obtained after 120 min., showed the presence of isobutyraldehyde (checked with pure isobutyraldehyde).

In a few rate experiments the increase in absorbance at 2800 Å. (λ_{max} of isobutyraldehyde) was measured as a function of the time. Although these rates could not be determined in an accurate manner (log ϵ 1.19),[28] they show that the rate of increase in absorbance at 2800 Å. equals the rate of decrease in absorbance at 2170 (I) and 1960 Å. (IV) within the experimental error.

The formation of the secondary amines could be checked by means of their pK values, which were obtained from potentiometric titration curves of aqueous solutions of I, II, and III, after complete hydrolysis had occurred.[29]

Calculations.—All first-order rate constants were obtained by least-squares calculations. The standard deviation in k is approximately 0.2%. The second-order rate constants were calculated by an iterative procedure from the first-order rate constants (eq. 3 and 4). The standard deviation in the values of $k_{H_3O^+}$ and K is 10 to 15%, whereas that in k_{HA} is 5%.

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[25] K. Mikkelsen and S. O. Nielsen, *J. Phys. Chem.*, **64**, 632 (1960).

[26] P. Salomaa, L. L. Schaleger, and F. A. Long, *J. Am. Chem. Soc.* **86**, 1 (1964).

[27] H. Arnoldy, Thesis, Amsterdam, 1961.

[28] Reference 10a, Vol. II, p. 21.

[29] These experiments will be published in a subsequent paper.

Mechanism of Enamine Reactions. III.[1] The Basicity of Tertiary Enamines

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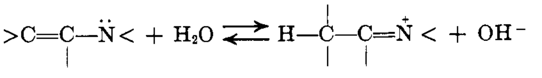
The base strengths of 1-N-morpholino-1-isobutene, 1-N-piperidino-1-isobutene, and 1-N-pyrrolidino-1-isobutene have been determined in aqueous solution by kinetic, potentiometric, and spectroscopic methods at 25°. In addition the basicity of the corresponding saturated amines has been determined by potentiometric titration. The results clearly show that in contrast with current opinion tertiary enamines are much weaker bases than the corresponding saturated compounds. The difference, approximately 2 pK units, can be equally attributed to an inductive and a resonance effect. The basicity of these compounds in order of decreasing base strength is secondary amine > saturated tertiary amine > tertiary enamine.

During the last 10 years tertiary enamines have become an extremely important group of intermediates in numerous organic syntheses.[2] As is well known, simple enamines are very unstable in water and hydrolysis, resulting in the formation of a carbonyl compound and an amine, occurs rapidly.[3] Direct measurement of the basicity of enamines in aqueous solution is therefore a difficult problem. In spite of the high reactivity toward water some papers deal with the base strength of α,β-unsaturated tertiary amines, especially those of cyclic enamines, in pure or partly aqueous solution.[4-7] The results of these measurements have led these authors[4-7] to conclude that tertiary enamines are stronger bases than the corresponding saturated amines. The explanation for this unexpected increase in basicity is sought in the existence of an equilibrium between the enamine and the quaternary hydroxide in aqueous solutions.[4]



$$>C{=}\underset{|}{C}{-}\ddot{N}< + H_2O \rightleftharpoons H{-}\underset{|}{\overset{|}{C}}{-}\underset{|}{C}{=}\overset{+}{N}< + OH^-$$

During our investigations on the mechanism of the hydrolysis of enamines we succeeded in measuring the basicity of 1-N-morpholino-1-isobutene (I), 1-N-piperidino-1-isobutene (II), and 1-N-pyrrolidino-1-isobutene (III) from the kinetics of this reaction.[1] It was also explained that, in contrast with the equilibrium mentioned above, the protonation of these enamines in aqueous solutions occurs at the nitrogen atom.

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[1] Part II: E. J. Stamhuis and W. Maas, *J. Org. Chem.*, **30**, 2156 (1965).

[2] J. Szmuszkovicz, *Advan. Org. Chem.*, **4**, 1 (1963).

[3] G. Stork, A. Brizzolara, H. Landesman, J. Szmuszkovicz, and R. Terrell, *J. Am. Chem. Soc.*, **85**, 207 (1963).

[4] R. Adams and J. E. Mahan, *ibid.*, **64**, 2588 (1942).

[5] N. J. Leonard, A. S. Hay, R. W. Fulmer, and V. W. Gash, *ibid.*, **77**, 439 (1955).

[6] N. J. Leonard, P. D. Thomas, and V. W. Gash, *ibid.*, **77**, 1552 (1955).

[7] N. J. Leonard and A. G. Cook, *ibid.*, **81**, 5627 (1959).