ENAMINES. 7.* KINETICS OF THE HYDROLYSIS OF 1-METHYL-2-BENZOYLMETHYLENEHEXAHYDROAZEPINE IN ACIDIC MEDIA

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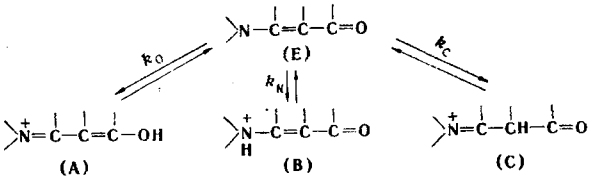
The dependence of the hydrolysis of 1-methyl-2-benzoylmethylenehexahydroazepine on the pH of the solution was studied. It is shown that the dependence of the observed rate constant (k_{obs}) on the pH is represented by a bell-shaped curve. At pH 3-6, k_{obs} depends on the acetic acid concentration in an acetate buffer with the same pH value. The addition of potassium acetate to a 0.1 N HCl solution gives rise to a statistically reliable increase in k_{obs}. It was shown by means of a model compound that the O-protonated form of the enamino ketones is resistant to hydrolysis. A mechanism for the hydrolysis of 1-methyl-2-benzoylmethylenehexahydroazepine in which the rate-determining step at pH 0-6 is C protonation is proposed.

The hydrolysis of enamines is one of the most important reactions of this class of compounds, since, first, this process is usually the last step in the chain of conversions of enamines to various substituted ketones, and, second, it is a convenient model for the study of the reactions of enamines (or immonium cations if one is dealing with acidic media) with nucleophilic reagents. The hydrolysis of enamines has been studied rather thoroughly. It has been shown that the C-protonated form rather than the N-protonated form undergoes hydrolysis in acidic solutions and that the rate-determining step in the process is a function of the pH of the medium and is determined by the structures of the enamines [2-4]. The situation is considerably more complicated in the case of enamino ketones (E) [5]. In fact, the protonation of these compounds may take place at three reaction centers, viz., the oxygen atom (A), the nitrogen atom (B), and the carbon atom (C). According to [6], the rate constants for protonation at these reaction centers are arranged in the order $k_O \gg k_N \gg k_C$.



An examination of the structures presented above shows that the ammonium cation (B) is to a certain extent similar to the N-protonated form of enamines and that hydrolysis through cation (B) is unlikely. In addition, cations (A) and (C) contain a charged imine fragment and should be hydrolyzed to the corresponding diketones and amines.

It is usually assumed that the formation of O-protonated form (A) is most favorable [5, 7, 8], from which it follows that precisely this form should undergo hydrolysis, whereas it is known that only the C-protonated form can be observed in the PMR spectra of some enamine ketones in CF_3COOH [9].

In conformity with this, the aim of the present research was to study the kinetics of hydrolysis of enamino ketones, primarily in the case of 1-methyl-2-benzoylmethylenehexahydroazepine (I), to determine the factors that affect the observed rate constant (k_{obs}) of this process, to clear up the problem of the steps that determine the rate of hydrolysis in various media, and to compare the data on the hydrolysis of enamino ketones with the results of similar studies of the hydrolysis of enamines.

*See [1] for communication 6.

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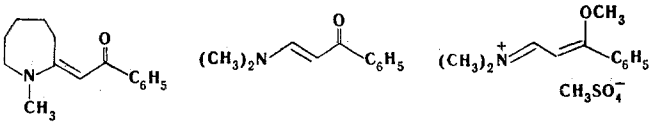
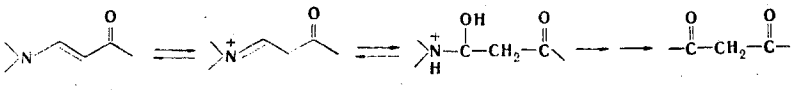
Preliminary data on the hydrolysis of enamino ketone I were previously obtained [1]. In the present research we used polarography to make a more detailed study of the dependence of the hydrolysis of I in buffer solutions with a constant ionic strength of 0.10 mole/liter on the pH (Fig. 1).

It is apparent from Fig. 1 that the dependence of k_{obs} on the pH is represented by a "bell-shaped" curve similar to the curve that was obtained for enamines [3]. To interpret the data on the hydrolysis of the enamino ketones it was necessary to ascertain the intermediate cation (A or C) through which the hydrolysis occurs. For this, we studied the hydrolysis of 1-(N,N-dimethylamino)-2-benzoylethylene (II) and model compound IIa, which was synthesized by the method in [10]. It is apparent that the methyl group in model compound IIa, which



I II IIa

is remote from the reaction center, cannot have a strong effect on the decrease in the hydrolysis rate. In this connection, one could have assumed that if the hydrolysis of enamino ketone II (like that of I and other analogs) proceeds through the O-protonated form (A), the rates of hydrolysis of II and IIa should not differ appreciably. However, this is contradicted by the experimental data. In addition to a decrease in the reduction waves of II, a wave involving the reduction of benzoylacetaldehyde (III) with $E_{1/2}$ = 1.18 V (relative to a saturated calomel electrode), which increases with time (Fig. 2), appears during the hydrolysis of enamino ketone II in a buffer solution with pH 3. A similar pattern is observed in the hydrolysis of IIa. However, whereas the hydrolysis of enamino ketone II proceeds quite rapidly (half-conversion period $\tau_{1/2}$ = 10.8 ± 0.1 min at 25°C and pH 3), the hydrolysis of IIa takes place considerably more slowly (after 17 h at room temperature, the height of the IIa wave undergoes only a 5% decrease). Two conclusions follow from this. First, the hydrolysis reactions of enamino ketone II and model compound IIa proceed via different pathways: in the first case (II) the intermediate cation is the C-protonated form rather than the O-protonated form, since the rate of hydrolysis of II is substantially higher than the rate of hydrolysis of model IIa. Second, as expected, the O-protonated form (A) is capable of undergoing hydrolysis but considerably more slowly than the C-protonated form (C). Thus, proceeding from a scheme in which the hydrolysis of the enamino ketones in moderately acidic media proceeds primarily through the C-protonated form with the subsequent formation of a geminal hydroxy amine (see [5]), one may attempt to discuss the data obtained.



(E) (C)

It is logical to assume that at pH 3-6 (the right-hand branch of the curve in Fig. 1; see also Fig. 3) precisely C protonation determines that rate of the overall process. In fact, if the step involving the formation of the geminal hydroxy amine (attack by water) did determine the rate of the process, one should, in conformity with [4], have expected that the rate constant would be independent of the concentration of the acidic component of the buffer. The distinct dependence of k_{obs} on [AcOH] (Fig. 4) shows that slow proton transfer should occur in the rate-determining step and that the step associated with attack by the (C) cation consequently cannot be regarded as the rate-determining step. Thus at pH 3-6 precisely the formation of C-protonated form (C) determines the rate of hydrolysis.*

The rate of hydrolysis decreases sharply when the pH of the solution is increased further (the left-hand branch of the curve in Fig. 1). The interpretation of these data is in good agreement with the concepts that we developed during a study of the hydrolysis of enamines [11]. In fact, an increase in the acidity of the medium leads to a shift in the

*If it is assumed (there is no basis other than the analogy with enamines for this) that a zwitterion is formed in the next step (after the formation of the geminal hydroxy amine) due to splitting out of a proton from the OH grup, this step cannot be the rate-determining step in this case, since it should not be accelerated but rather slowed down as the pH decreases.

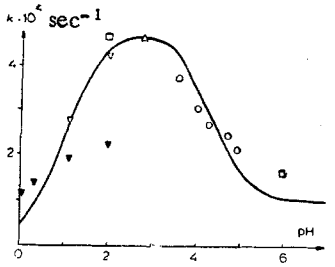


Fig. 1

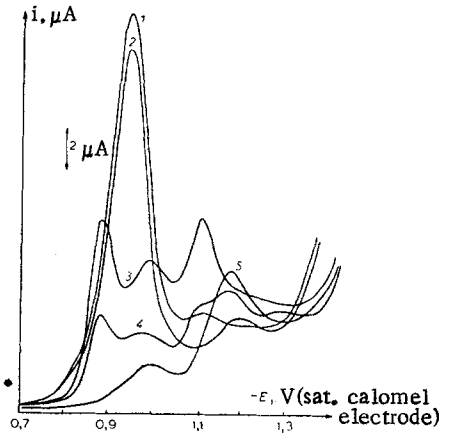


Fig. 2

Fig. 1. Dependence of the hydrolysis of enamino ketone I at 50°C on the pH of the solution: ▼) 1 (the numbers of the points correspond to the numbers of the buffers in Table 1); ▽) 2; Δ) 3, extrapolated to a buffer concentration of zero (c_b = 0); ○) 4, extrapolated to a buffer concentration of zero (c_b = 0); □) 5.

Fig. 2. Differential pulse polarograms of model compound IIa (1, 2), enamino ketone II (3, 4), and hydrolysis product III (5) in a citrate–phosphate buffer with pH 3: 2) recorded 17 h after 1; 4) recorded 5 min after 3 (for starting concentrations c_{IIa} = 0.98, c_{II} = 0.51, and c_{III} = 0.87 mmole/liter).

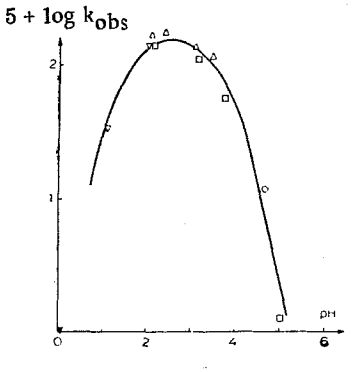


Fig. 3

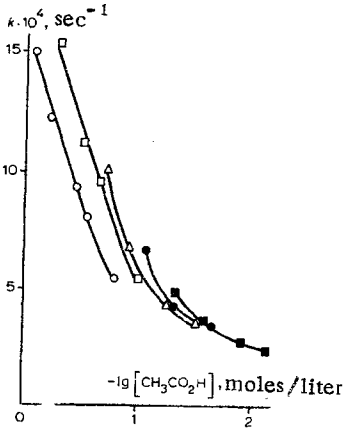


Fig. 4

Fig. 3. Dependence of the hydrolysis of enamino ketone II at 25°C on the pH of the solution: ▼) 1 (the numbers of the curves correspond to the numbers of the buffers in Table 1); ▽) 2; Δ) 3; ○) 4; □) 5.

Fig. 4. Dependence of the constant of hydrolysis (k_{obs}) of enamino ketone I on the acetic acid concentration in the acetate buffer at 50°C and a constant ionic strength of 0.10 mole/liter: ○) pH 3.57; □) pH 4.05; Δ) pH 4.30; ●) pH 4.72; □) pH 4.95.

TABLE 1. Compositions of the Buffer Solutions Used for the Study of the Hydrolysis of Enamino Ketones

No*	pH	Buffer	Ionic strength, mole/liter
1	0—2	HCl+KCl	1,0
2	1—2	The same	0,1
3	2—4	$ClCH_2COONa+HCl+KCl$	0,1
4	3—6	$CH_3COOK+HCl+KCl$	0,1
		$CH_3COOK+CH_3COOH+KCl$	0,1
5	2—7	Citric acid + Na_2HPO_4 + NaCl	0,1

*The numbers of the buffers correspond to the numbers of the points in Figs. 1 and 3.

equilibrium to favor the O-protonated form (the kinetically fast process), just as in the case of enamines it led to a shift in the equilibrium to favor the N-protonated form. This shift is so substantial that "transprotonation" [i.e., the formation of C-protonated form (C), which proceeds through the unprotonated form] is slowed down markedly, and this gives rise to a drop in the left-hand portion of the curve (Fig. 1). The fact that the hydrolysis rate constant increases by (40 ± 3%) (see the similar data on the hydrolysis of enamines [12]) when potassium acetate (5 mmole/liter) is added to a solution of enamino ketone I (0.5 mmole/liter) in 0.1 N HCl also constitutes evidence in favor of the assumptions expressed above.

One should also point out one essential fact: an endocyclic double bond rather than an exocyclic double bond is formed in the case of C protonation of cyclic enamino ketones. It is known [13] that the formation of an endocyclic $\overset{+}{N}=C$ bond is energetically most unfavorable for five-membered rings, followed by seven- and six-membered rings. Consequently, if the C-protonation step is the rate-determining step, one should observe a distinct dependence of k_{obs} on the ring size.* The data that we obtained in [1] provide evidence that 1-methyl-2-benzoylmethylenepiperidine is hydrolyzed more rapidly than enamino ketone I in 0.1 N HCl, whereas their five-membered analog 1-methyl-2-benzoylmethylenepyrrolidine is not hydrolyzed at all during the time of observation. Hence it is logical to conclude that precisely C protonation is the slowest step in the hydrolysis of enamino ketone I at pH 0-3.

Thus the mechanism of the hydrolysis evidently does not change for the enamino ketones at pH 0-6, and the rate-determining step is C protonation.

The data obtained in this study may serve as a basis for finding the optimum conditions for the synthesis of β-diketones from enamino ketones, since the maximum rate of the process can be achieved only over a narrow pH range; one should take into account the fact that an increase in the acidity, i.e., carrying out the process in strong mineral acids, markedly decreases the rate of hydrolysis and makes it a nonpreparative method in a number of cases [14]

EXPERIMENTAL

The kinetic measurements and polarography were carried out in a thermostated (with an accuracy of ±0.1°C) cell [15]; the volume of the reaction mixture was 5 ml. Ultrapure nitrogen was bubbled through the solution to free it of oxygen. The differential pulse polarograms (DPP) and classical polarograms (CP) were recorded by means of a PAR-170 "electrochemical system" with respect to a three-electrode scheme. The reference electrode was a saturated calomel electrode or, at 50°C, an electrode in the form of a silver spiral in the investigated solution. The auxiliary electrode was a platinum electrode. At concentrations ranging form 0.1 to 1 mmole/liter the height of the CP wave measured by the Hohn method and the height of the DPP wave measured by the asymptote method or the arithmetic-mean-height method [16] are directly proportional to the concentration of the substance. The rate constant was calculated by the method of least squares from a first-order equation: the time was reckoned from the instant the substance was added to the solution: $\ln H = a - kt$, where H is the height of the wave or peak. In each case the experiment was carried out at least twice, and the relative error in an individual determination was 3-10%. The rate constants

*It should be noted that these data also repudiate the possibility of the formation of a zwitterion (if its formation is assumed) in the rate-determining step — k_{obs} should not depend on the ring size here.

in the same buffer solution calculated from the change in the height of the CP wave with time and the height of the DPP peak coincided. The buffer solutions used in this research contained 10% by volume alcohol (Table 1). The pH of the solutions was monitored by means of a glass electrode at ∿ 25°C.

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