KINETICS OF THE ACIDIC HYDROLYSIS OF VINYL DERIVATIVES OF BENZIMIDAZOLE-2-THIONE AND BENZOXAZOL-2-ONE AND -2-THIONE

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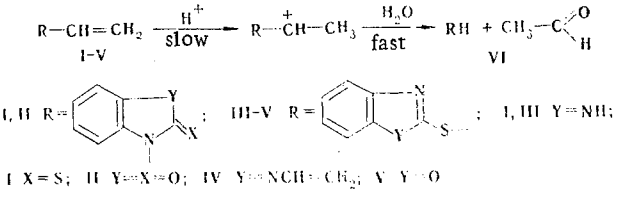
The kinetics of the acidic hydrolysis of seven vinyl derivatives of benzimidazole-2-thione and benzoxazol-2-one and -2-thione were studied by means of polarography. The rate constants and energies of activation of the reaction were determined. The hydrolytic stabilities of the compounds depend on the nature of the heteroring and the site to which the vinyl group is attached.

The ability to undergo cleavage in the presence of water is characteristic for aliphatic and aromatic compounds that contain a vinyl group attached to the heteroatom. A quantitative study of the hydrolytic stabilities of vinyl derivatives of the heterocyclic series reveals the effect of the nature of the heteroring and the site to which the vinyl group is attached on the rate of the process and the mechanism of the medical-biological action of these compounds. It has been previously shown [1, 2] that vinyl derivatives of azolethiones display radiation-protective properties and narcotic activity. The indicated compounds have increased π-electron density on the β-carbon atom of the vinyl group and tend to undergo electrophilic addition.

In the present research we studied the hydrolytic stabilities of 1-vinylbenzimidazole-2-thione (I), 3-vinylbenzoxazol-2-one (II), 2-vinylthiobenzimidazole (III), 1-vinyl-2-vinylthiobenzimidazole (IV), and 2-vinylthiobenzoxazole (V) in an aqueous ethanol medium in the case of catalysis by hydrochloric acid. The hydrolysis of the investigated compounds evidently proceeds, as in the case of vinyl ethers, via the scheme [3]



The kinetics of the hydrolysis were studied from the accumulation in the reaction mixture of acetaldehyde (VI), the concentration of which was determined by polarography. The polarographic wave of the reduction of aldehyde VI ($E_{1/2}$ = 1.67 V) has diffusion character, and its height is directly proportional to its concentration (correlation coefficient r = 0.99). The starting I-V do not give any waves whatsoever in this region.

A linear relationship between the logarithm of the height of the wave (the concentration) and the reaction time at steady-sate values of the temperature (60°C) and the HCl concentration was observed for all of the investigated vinyl derivatives in the initial stage (Fig. 1). On the basis of this fact, we calculated the rate constants using a first-order equation. The reaction was studied over the temperature range 40 to 80°C; the logarithms of the rate constants depend linearly on 1/T (Fig. 2). On the basis of the Arrhenius temperature relationship we calculated the energies of activation. The kinetic and activation parameters are presented in Table 1.

It is apparent from Fig. 3 that an appreciable inductive period is observed in the hydrolysis of thione I. It is possible that the addition of alcohol to the double bond of the vinyl group to give 1-[α-(ethoxy)ethyl]benzimidazole-2-thione (VII) proceeds the hydrolysis reaction carried out in the presence of ethanol. To confirm this assumption we synthesized VII

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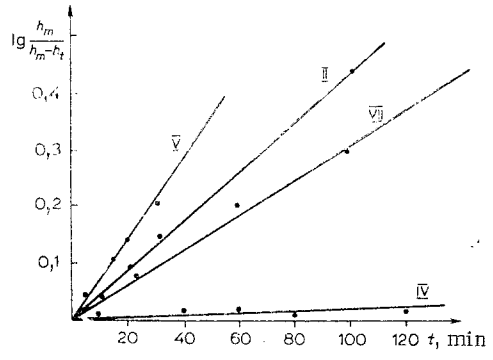


Fig. 1

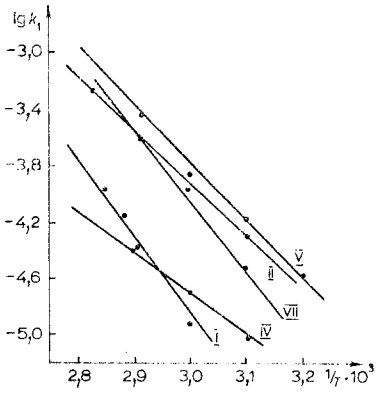
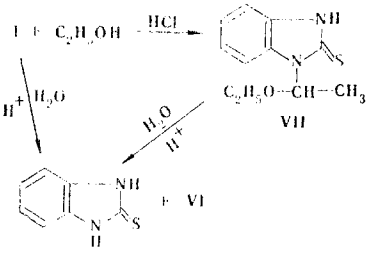


Fig. 2

Fig. 1. Dependence of log $h_m/(h_m - h_t)$ on the reaction time for acidic hydrolysis.

Fig. 2. Dependence of the hydrolysis rate constant on the temperature.

by the reaction of thione I with ethanol:



A study of the kinetics of the hydrolysis of thione VII showed that it is readily hydrolyzed in the presence of mineral acids and that the rate constants and energies of activation of this reaction are close to the corresponding constants for thione I (Table 1). The high energies of activation of I and VII constitute evidence for the high strength of N–C bond.

It is apparent from Table 1 that the introduction of an oxygen atom in place of a nitrogen atom in the ring and replacement of the exocyclic sulfur atom by an oxygen atom do not have an appreciable effect on the rate of hydrolytic cleavage. The dependence of the rate constants on the acid concentration for the N-vinyl derivatives of benzimidazolethione I and benzoxazolone II displays a tendency toward curvature (Fig. 4); this is probably associated with the formation of hemiacetals of the VII type.

The k = f[HCl] dependence for imidazole IV and benzoxazole has rectilinear character (r = 0.99; the calculated orders of the reaction with respect to HCl are equal to unity) and

TABLE 1. Kinetic and Activation Parameters of the Acidic Hydrolysis

Compound	$k_2 \cdot 10^5$, liters/mole-sec (T = 333°C)	E_a, kJ/mole	n*
I	4,8±0,1	103,3±2,1	2 (r=0,98)
II	5,5±0,2	74,9±2,1	1,5 (r=0,98)
III	$(8,0\pm0,1)\cdot10^{-3}$ (T=353 K)	—	—
IV	1,96±0,08	69,0±2,1	1
V	33,4±0,8	79,1±2,5	1
VII	4,5±0,06	102,1±2,1	2 (r=0,99)
VIII	0,1±0,01	—	—

*This is the reaction order in the acid.

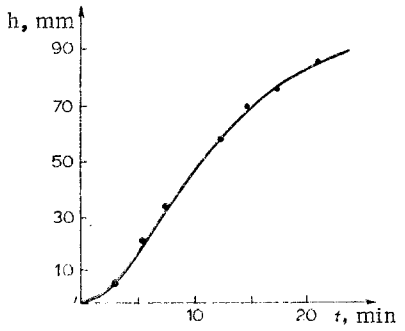


Fig. 3

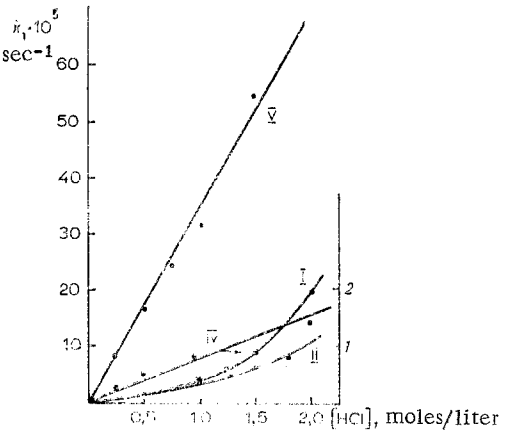


Fig. 4

Fig. 3. Kinetic curve of the hydrolysis of thione I.

Fig. 4. Dependence of the rate constant for hydrolysis on the HCl concentration at 333°K.

passes through the origin. This constitutes evidence for the absence of a noncatalytic reaction.

However, in the case of high degrees of conversion the acidic hydrolysis of divinyl derivatives IV is not subject to a first-order equation. Under these conditions one observes the formation also of the hydrochloride of the starting imidazole with a proton attached to the nitrogen atom in the 3 position of the heteroring. The double bond attached to the exocyclic sulfur atom is deactivated as a result of salt formation, and this hinders hydrolysis. The reaction of IV with hydrogen chloride gave 1-vinyl-2-vinylthiobenzimidazole hydrochloride (VIII), the kinetic study of the hydrolytic cleavage of which actually confirmed the high stability as compared with all of the other investigated vinyl compounds I-V (Table 1).

We found that the hydrolysis of imidazole IV initially proceeds at the vinyl group attached to the nitrogen atom. This reaction pathway is proved by the isolation from the reaction mixture of vinyl sulfide III, which is hydrolyzed very slowly and under more severe conditions. It is likely that this is also due to the decrease in the nucleophilicity of the double bond of the vinyl group due to salt formation. Our studies showthat thehydrolysis reaction cannot be used for the quantitative determination of vinyl derivatives III and VI of benzimidazole-2-thione.

Benzoxazole V is the most active of the investigated vinyl derivatives in the electrophilic addition of water. A large surplus of electron density is localized on the vinyl group in its molecule as a result of disruption of the aromatic character of the heteroring when the nitrogen atom is replaced (III) by an oxygen atom. The hydrolytic stability increases as compared with the stability of vinyl sulfide V in the case of benzoxazolone II with a vinyl group attached to the nitrogen atom.

Thus the reactivity of the vinyl group in the investigated compounds depends on the nature of the heteroring and the heteroatom bonded to it.

EXPERIMENTAL

Starting vinyl derivatives I-V were obtained by the reaction of benzimidazole-2-thione and benzoxazole-2-one and -2-thione with acetylene under pressure [4-7]. The hydrochloride was synthesized by the method in [1].

The kinetics of hydrolysis were investigated with an LP-7 apparatus in a thermostatted cell (25 ± 0.1°C) relative to a saturated calomel electrode. We used a 0.5 N solution of LiOH (chemically pure grade) as the polarigraphic inert electrolyte and a 0.5 N solution of LiCl (chemically pure grade) as the inert electrolyte for the unstable (in an alkaline medium) benzoxazolone II. The acid was neutralized with ammonium hydroxide. The reaction was carried out in ampuls at 40-80°C; the initial concentrations of the substrate were 0.0145 mole/liter, and the acid concentration was 0.25 to 2 moles/liter.

The k_1 and k_2 rate constants were calculated from the equations

$$k_1=[\ln h_m/(h_m-h_t)]\cdot 1/t;\ k_2=k_1/[HCl]^n,$$

where k_1 is the first-order rate constant (in reciprocal seconds), h_m is the height of the wave of the reduction of the aldehyde (in millimeters) corresponding to the total hydrolysis, h_t is the height of the reduction wave at time t (in millimeters), and k_2 is the second-order rate constant (in liters/mole-sec). The error in the determination by the polarographic method was 2-8%.

1-[α-(Ethoxy)ethyl]benzimidazole-2-thione (VII). A solution of 1.76 g (0.01 mole) of thione I in 10 ml of ethanol was added dropwise to 10 ml of absolute ethanol saturated with dry HCl, and the mixture was refluxed for 2 h. It was then cooled and worked up to give 1.42 g (64%) of VII with mp 92-93°C. Found: C 59.4; H 6.4; S 14.5%. $C_{11}H_{14}N_2OS$. Calculated: C 59.4; H 6.3; S 14.4%.

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STRUCTURE OF 3-CHLORO-6-HYDRAZINOPYRIDAZINE IN SOLUTIONS

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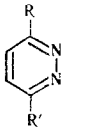
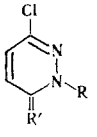
It is shown by means of the fixed-structure method, UV spectroscopy and dipole-moment method that the product of the reaction of 3,6-dichloropyridazine with hydrazine in solution in methanol and acetonitrile has the 3-chloro-6-hydrazinopyridazine structure.

The 3-chloro-6-pyridazinone hydrazone structure (XI, R = H, and R' = NNH_2) was assigned to the product of the reaction of 3,6-dichloropyridazine (II) with hydrazine (compound A), since the UV spectrum of a solution of CH_3OH, like the spectrum of 3-hydroxy-6-pyridazinone, contains an absorption band at 324 nm (ε 1270) [1].



I-X



XI-XVI

A more detailed analysis of the UV spectra recorded in hexane, methanol, dioxane, and acetonitrile of pyridazine I and its derivatives II-VII, which are incapable of tautomeric transformations showed that an absorption band with $\lambda_{max} \geqslant 310$ nm appears in the spectra of most of them, often in the form of a shoulder (Table 1). The spectra of I-VII in hexane,

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