

ON MECHANISM OF BASE-CATALYSED HYDROLYSIS OF THIOAMIDES

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Dissociation constants, in 50 wt.% ethanol, of thioamides of some benzene- and pyridinecarboxylic acids were determined and kinetics of their hydrolysis was studied polarographically. Mechanism of the reaction is proposed which is based on observed rate constants vs pH dependences, activation entropies and dissociation constants.

Thioamides undergo acid-base catalysed hydrolysis to form amides under release of hydrogen sulphide^{1,2}. This reaction has become of synthetic value as a part of the Willgerodt reaction and its Kindler modification. In the present work we report on the study of alkaline hydrolysis of thioamides. Until now, mechanism of this reaction has not been elucidated.

EXPERIMENTAL

Chemicals. Thiobenzamide³ (*I*), N,N-diphenylthiobenzamide⁴ (*II*), thioamides of nicotinic⁵ (*III*) and isonicotinic⁶ acids (*IV*) were prepared by reported procedures as indicated. Thioamide of 2-ethylisonicotinic acid (*V*) was commercial sample (Léčiva, Prague). Nicotinamide (*VI*) was commercial preparation (Loba), isonicotinamide (*VII*) was obtained by ammonolysis of ethyl isonicotinate⁷. The purity of the substances was verified by melting point determination and by elemental analysis (nitrogen content).

Kinetic measurements. The measurements were made with $5 \cdot 10^{-4}$ M solutions of the compounds in 50 wt.% ethanol, except for compound *I* which was used in $3 \cdot 10^{-4}$ M concentration. p*K* measurements were performed with $1 \cdot 2 \cdot 10^{-4}$ M solutions of the compounds in buffered 50 wt.% ethanol. For pH 10 to 12.5 mixtures of $5 \cdot 10^{-3}$ M borax (*p.a.*, Lachema) and $1 \cdot 10^{-2}$ M-NaOH (*p.a.*, Lachema) containing these substances in varying amounts were used as buffers, for the higher pH the buffers consisted of NaOH solutions in 50 wt.% ethanol. pH values were measured with Radelkis OP-205 pH meter using hydrogen and silver chloride electrode, the latter being filled with 0.1 M-NaCl (*p.a.*, Lachema) in 50 wt.% ethanol. The potential of the silver chloride electrode was taken from the literature⁸ and function of the electrode system was checked by a set of buffers⁹. Dissociation constants of unsubstituted thioamides were determined photometrically at an analytical wavelength on a Spectromom 202 instrument (MON, Budapest), using 1 cm quartz cells and the above buffers. p*K* values were calculated according to the literature¹⁰.

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Kinetic measurements were carried out in ampoules. The ampoules were charged with an appropriate solution, sealed, warmed to a given temperature in a thermostat and the temperature was maintained with an accuracy of ± 0.1 K. At fixed time intervals, the ampoules were withdrawn and cooled with water. Changes in concentrations of the starting compounds were followed polarographically. All the compounds studied gave diffusion waves in the solvent chosen, in accordance with the literature¹¹⁻¹³. Rate constants were calculated from the decrease in diffusion waves of thioamides by the method of least squares of errors. The errors were less than 8% of the measured values. In addition to the decrease in the wave of thioamides of pyridinecarboxylic acids, a new wave appeared in the region of more negative potentials which was identical in its shape and half-wave potential with that of VI and VII, respectively. The sum of currents of both waves does not practically changed with time. This shows that the amides are hydrolysed at a given pH at much slower rate than are the corresponding thioamides. This assumption was verified by separate experiments with VI and VII which confirmed the validity of the earlier description^{1,2} of the overall reaction.

In order to determine activation parameters, the measurements were also made at 333.1 K, 343.1 K, 353.1 K, and 363.1 K. Dependence of experimental rate constant on ionic strength of medium was determined with the use of a borax buffer and the appropriate ionic strength was adjusted by sodium perchlorate (*p.a.*, Lachema).

RESULTS AND DISCUSSION

Of the series of the thioamides under study, only substance II does not exhibit acid-base properties and was therefore chosen as a model compound for the study of mechanism of hydrolysis reaction. Kinetics of hydrolysis of this substance was investigated at 362.6 K in NaOH solutions for which conditions reaction rate could be expressed in terms of isolated first-order reaction. At $\text{pH} < 13$, the reaction did not follow this assumption. Experimental rate constants k_{exp} and corresponding pH values are given in Table I and $\log k_{\text{exp}}$ vs pH dependence is represented graphically in Fig. 1. From these data it follows that the reaction is higher than first-order in the activity of OH^- ions.

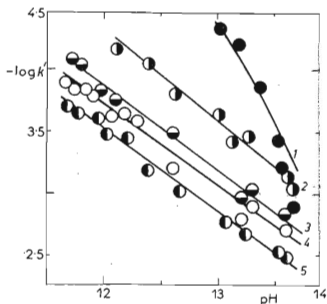


FIG. 1

Dependence of $\log k'$ of Base-Catalysed Hydrolysis of Thioamides upon pH of the Medium

1 N,N-Diphenylthiobenzamide, 2 thio-benzamide 3 thionicotinamide, 4 thio-amide of 2-ethylisonicotinic acid, 5 thio-amide of isonicotinic acid.

The activation entropy of the reaction (Table II) indicates a bimolecular mechanism in the rate determining step of the reaction. In agreement with the dependence of the rate constant on the activity of OH^- ions, this shows that the first reaction step is a slow nucleophilic addition of OH^- ion to the carbon of thiocarbonyl group.

The other thioamides studied in this work exhibited as a rule acid-base properties in alkaline region. The pK values determined photometrically are summarized in Table II. Due to the solvent effect, these are somewhat greater than those determined in water¹⁰. In sufficiently alkaline region, kinetics of hydrolysis of thioamides could be described in terms of isolated first-order reactions. Experimental

TABLE I
Rate Constants of Hydrolysis of Thioamides in 50 wt.% Ethanol

pH	$k_{\text{exp}} \cdot 10^4, \text{s}^{-1}$	pH	$k_{\text{exp}} \cdot 10^4, \text{s}^{-1}$
<i>I</i>	334.6 K	<i>IV</i>	333.5 K
12.13	0.602	11.69	1.10
12.38	0.744	11.76	1.07
12.63	1.21	11.96	1.12
13.02	1.34	12.02	1.34
13.12	1.94	12.21	1.33
13.28	1.40	12.38	1.46
13.64	1.80	12.66	1.42
13.66	2.38	13.09	0.857
		13.27	0.799
<i>II</i>	362.6 K	13.56	0.561
13.02	0.426	13.61	0.555
13.20	0.638	<i>V</i>	334.7 K
13.36	1.46	11.66	0.910
13.52	4.04	11.72	1.02
13.55	6.22	11.82	0.985
13.66	12.56	11.90	1.01
<i>III</i>	333.6 K	12.06	1.15
11.72	0.637	12.17	1.12
11.79	0.699	12.29	1.28
11.97	0.968	12.60	1.53
12.09	0.959	13.20	1.17
12.62	1.13	13.29	0.718
13.20	0.975	13.59	0.619
13.29	0.696		
13.59	0.589		

rate constants are presented in Table I, along with the corresponding pH values. From comparison of pH's (Table I) with pK's (Table II) it follows that hydrolysis of these substances proceeds in the medium in which both undissociated thioamide and its anion may take part in the reaction. If the species hydrolysed is undissociated thioamide (HTA) then the reaction rate ω in the medium of a given OH^- activity can be expressed by Eq. (1) where k' is a function of the activity of OH^- ions ($k' = k^0 a_{\text{OH}^-}$). The activity of undissociated thioamide at a given pH can be expressed by means of dissociation constant. By the earlier reported modifications¹⁴ we obtain Eq. (2) for the experimental rate constant k_{exp} .

$$\omega = k' \text{HTA}, \quad (1)$$

$$k_{\text{exp}} = k' a_{\text{H}^+} / (K + a_{\text{H}^+}). \quad (2)$$

The constants k' calculated from Eq. (2) are a linear function of the activity of OH^- ions for all the thioamides unsubstituted on functional group, as it is obvious from Fig. 1. The rate constant k_{exp} is essentially independent of the ionic strength of the solution. This is demonstrated for substance IV by the following data ($5 \cdot 10^{-4}\text{M}$ solution, pH 12.39, 334.7 K):

μ	1	2	3	4
$k \cdot 10^4, \text{s}^{-1}$	2.52	2.53	2.57	2.79

The activation entropies presented in Table II confirm bimolecular mechanism of the reaction in the rate determining step also for these compounds. In the studied region the neutral molecule of thioamide is hence hydrolysed, and the rate determining step involves nucleophilic addition of OH^- ion to the undissociated molecule.

TABLE II

Activation Parameters for Alkaline Hydrolysis of Thioamides in 50 wt.% Ethanol at a Given pH and pK Values at Room Temperature Determined Photometrically at Wavelength λ

Compound	pH	ΔS^\ddagger $\text{J mol}^{-1} \text{K}^{-1}$	ΔH^\ddagger kJ mol^{-1}	λ, nm	pK
I	12.81	-187	45.6	294	13.16 ± 0.13
II	13.55	-110	72.7	—	—
III	12.20	-153	56.3	296	12.20 ± 0.05
IV	12.38	-137	60.9	296	11.88 ± 0.07
V	12.60	-101	73.1	296	12.11 ± 0.07

The reaction order in the activity of OH^- ions is less clear. Hydrolytic reaction of compound *II* is approximately second-order, that of the other thioamides is first-order in the activity of OH^- ions. This experimental fact can be reasonably interpreted in terms of acid-base properties of the transition state, similarly to the base-catalysed hydrolysis of amides^{15,16}. The addition of OH^- ion to the thiocarbonyl carbon (Scheme 1) yields anion *A* ($k_1 \ll k_2$). This anion may form dianion *B* via acid-base equilibrium. In proton donor solvents such equilibria are usually attained in "immeasurably" fast rate. One can assume that also the equilibrium between anion *A* and dianion *B* is established much faster compared to nucleophilic addition of OH^- ion to the thiocarbonyl carbon. The acid-base equilibrium can be affected by pH of the medium, and at a given pH by substitution. The inductive effect of two phenyls on nitrogen of *II* is greater than the effect of two hydrogens of *I*. One can thus expect $\text{p}K$ of the transition state of substance *II* to be lower than that for substance *I*. Anions *A* and *B* are able to release hydrosulphide or sulphide anion to form the amide, as shown in Scheme 1.

For a given solvent one can write¹⁴ Eq. (3) which has the same meaning for acid-base equilibria in a given solvent as the ionic product has for the pure water. On assuming quasistationary concentrations of intermediate products, and on the basis of Eq. (3) and Scheme 1 one obtains Eq. (4) for the dependence of the experimental rate constant on the activity of hydrogen ions:

$$K_{\text{solv.}} = a_{\text{H}^+} \cdot a_{\text{OH}^-} \quad (3)$$

$$k_{\text{exp}} = (1/a_{\text{H}^+})(\alpha_1 + \alpha_2 a_{\text{H}^+})/\alpha_3 + \alpha_4 a_{\text{H}^+}, \quad (4)$$

where

$$\alpha_1 = k_1 k_6 K_{\text{solv.}} (k_3 + k_5),$$

$$\alpha_2 = k_1 k_4 k_5 K_{\text{solv.}}, \quad \alpha_3 = k_6 (k_2 + k_3 + k_5), \quad \text{and} \quad \alpha_4 = k_4 (k_2 + k_5).$$

The ratios of the constants of Eq. (4) calculated for *II* and a temperature of 363.6 K by the method of the least squares of errors have the following values:

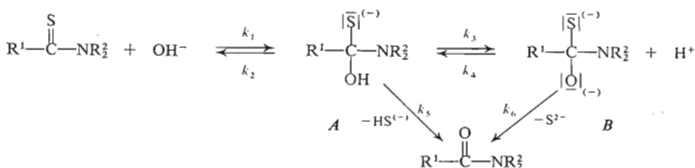
Ratio	α_2/α_1	α_3/α_1	α_4/α_1
Value	$2.43 \cdot 10^{12}$	$2.69 \cdot 10^{16}$	$2.94 \cdot 10^{30}$

With the use of these values and Eq. (4) we calculated theoretical constants k_{theor} whose logarithms, in dependence upon pH, are graphically represented in Fig. 1 (curve 1). Comparison of $\log k_{\text{exp}}$ with $\log k_{\text{theor}}$ shows that the reaction mechanism depicted in Scheme 1 agrees with experimental data for thioamide *II*.

The rate constants of hydrolytic reaction of the other amides were first order in the activity of OH^- ions. This leads us to assume that $\text{p}K$ of the transition state of these compounds is greater than the pH at which the reaction was studied and that the dianion B is not practically present in the reacting system. From this it follows that the release of S^{2-} from the dianion B is kinetically unimportant. Hence, Eq. (4) can be rewritten to Eq. (5) which agrees with the observed linear dependence of $\log k'$ upon pH (Fig. 1).

$$k' = k_1 k_5 a_{\text{OH}^-} / (k_2 + k_5) \quad (5)$$

The angle formed by the straight lines and pH axis is close to theoretical value. According to Eq. (5) experimental rate constants k' are the function of constant k_1 and this function depends on electron density on the thiocarbonyl carbon. However, electron density on this carbon affects also $\text{p}K$ values. This indicates the close relationship between $\text{p}K$ and $\log k'$ at a given pH for the series of studied compounds. This becomes evident on comparing data presented in Table II with Fig. 1. It can be concluded that hydrolysis of thioamides unsubstituted on the functional group proceeds *via* mechanism which is similar to that for base-catalysed hydrolysis of esters.



SCHEME 1

The reaction mechanism depicted in Scheme 1 agrees with experimental data and for *N,N*-diphenylthiobenzamide it is analogous to the reaction mechanism proposed for alkaline hydrolysis of amides^{15,16}. The conclusions of this study extends therefore the validity of Taft's concept also on the group of the compounds studied in the present work.

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