MECHANISM OF ACID-CATALYZED HYROLYSIS OF HYDROXAMIC ACIDS

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The dependence of the hydrolysis rate constant of hydroxamic acids on the proton activity and dielectric constant of medium has been studied. From the dependences found and from the activation entropy values, conclusions have been drawn concerning the mechanism of the reaction investigated, which were in accord with the mechanism of the acid-catalyzed hydrolysis of amides.

Rate constant of the acid-catalyzed hydrolysis of hydroxamic acids in slightly acidic region increases linearly with the proton activity[1], whereas in media of mineral acids it increases with increasing concentration of the acid[2,3]. In the case of aliphatic hydroxamic acids the rate constants correlate according to the Taft equation[4], whereas in the case of the aromatic *ortho*-substituted derivatives they correlate with the Pavelich–Taft equation[5]. The polar effects of the substituted aromatic acids do not practically affect the reaction rate[6]. The above experimental findings suggest the mechanism of the acid-catalyzed ester hydrolysis for the acid-catalyzed hydrolysis of hydroxamic acids. However, the mechanism of the acid-catalyzed ester hydrolysis is more complex. If the ester basicity is lowered by substituents, the dependence of the rate constant on the acid concentration is non-linear. This experimental fact is explained by the protonation of the transition state[7-9], which was also observed with the acid-catalyzed hydrolysis of amides[10]. The present communication deals with the dependence of the rate constant of the reaction studied on the pH of medium for those hydroxamic acids which have slightly basic functional group due to substituent effects. The transition state polarity was studied by following the dependence of the rate constant on the dielectric constant of the solvent.

EXPERIMENTAL

Benzohydroxamic acid[11] (*I*), chloroacetohydroxamic acid[12] (*II*), picolinohydroxamic acid (*III*), nicotinohydroxamic acid (*IV*) and isonicotinohydroxamic acid[13] (*V*) were prepared from the corresponding esters. N-Phenylbenzohydroxamic acid[14] (*VI*) was prepared by benzoylation of N-phenylhydroxylamine. The melting points of the compounds prepared and their nitrogen content (elemental analysis) agreed with the above references.

The pK_a values of the substances *III* to *V* were determined spectrophotometrically by the method described in our previous report[10]. Absorbance of the solutions was measured with a Spectromom 202 spectrophotometer (MOM, Budapest) at the analytical wavelength. The following results were obtained: *III* pK_a 1·41 ± 0·02 (λ 285 nm); *IV* pK_a 2·00 ± 0·04 (λ 268 nm); *V* pK_a 1·97 ± 0·07 (λ 265 nm).

The reaction kinetics were followed by measuring the actual concentration of the hydroxamic acids by the colour reaction with Fe^{3+} ions. With the use of the Job method of continuous variations it was found that the 1 : 1 complex is formed in equimolecular solutions (concentrations of the both components being $3 \cdot 10^{-3}$M) in 1M-$HClO_4$, which stands in accord with the literature data for the other ferric hydroxamates[15]. With a great excess of ferric ions ($c_{Fe^{3+}} = 2 \cdot 10^{-2}$M) the Lambert–Beer law is fulfilled within $2 \cdot 10^{-5}$M to $2 \cdot 10^{-3}$M hydroxamic acids concentrations.

Solutions of *I* ($1 \cdot 10^{-3}$M) were prepared in perchloric acid (analar grade, Jenapharm) in water and 10, 30 and 50% (by weight) ethanol (Lachema). Ionic strength of the solutions was adjusted at 2·5 by addition of sodium perchlorate (analar grade, Lachema). Solutions of *II* ($5 \cdot 10^{-3}$M), *III* ($2 \cdot 10^{-3}$M), *IV* ($1 \cdot 10^{-3}$M), *V* ($8 \cdot 10^{-4}$M), and *VI* ($8 \cdot 10^{-4}$M) were prepared in perchloric acid (0·25 to 2·5M) in 50% (by weight) ethanol. Solutions were prepared of *VI* ($8 \cdot 10^{-4}$M) in 50% (by weight) ethanol in perchloric acid solutions having the ionic strength 2·5 adjusted by addition of sodium perchlorate. Thus the concentration of the hydroxamic acids was adapted to a suitable absorbance value of the ferric hydroxamate. Solutions of *VI* ($8 \cdot 10^{-4}$M) in 0·125 to 0·01M-$HClO_4$ in 50% (by weight) ethanol and in mixtures of 0·01M-$HClO_4$ and 0·01M-$NaH_2PO_4.H_2O$ (analar grade, Lachema) were prepared, too. For investigation of the dependence of the rate constant on ionic strength the solutions of *VI* ($8 \cdot 10^{-4}$M) were prepared in 1M-HCl_4 in 50% (by weight) ethanol, sodium perchlorate being added to make the overall ionic strength 1 to 3. The p_{aH^+} values of the solutions were determined by the method described previously[10].

The prepared solutions of hydroxamic acids were placed in sealed glass ampoules and put in a Hoeppler ultrathermostat (Prüfgeräte, Medingen). After a certain time the ampoules were taken out, cooled, and 5 ml of the solution was mixed with 1 ml 0·03M-$Fe(NH_4)(SO_4)_2.12\,H_2O$ aqueous solution acidified with sulphuric acid. Absorbance of the final solution was measured at the wavelength corresponding to the maximum in the spectrum of the complex formed; the reference cell contained a mixture of 5 ml perchloric acid of the corresponding concentration and 0·03M-$Fe(NH_4)(SO_4)_2$. Dependence of the rate constant of the hydrolytic reaction on the proton activity was followed at 363·1 K. Temperatures 333·1, 343·1, 353·1 and 363·1 K were used for determination of the activation parameters. The dependence of the rate constant on the ionic strength was followed at 368·1 K. The temperatures were maintained within ±0·1 K. Error in the rate constant determination was less than 5% in all the cases.

RESULTS AND DISCUSSION

Dependence of the hydrolysis rate constant on the dielectric constant of medium was studied with the compound *I*. The rate constant was calculated from Eq. (*1*) by the least squares method. In Eq. (*1*) A_0, A, and A_∞ stand for the absorbances at the time 0, t and ∞, respectively.

$$\ln (A_0 - A_\infty)/(A - A_\infty) = k_{\text{exp}} t \,. \qquad (1)$$

For *I* it was found[2] that the rate constant depends on the proton activity. Therefore, the proton activity must strictly be maintained when changing the solvent; it is, however, practically impossible to prepare buffers with a certain pH in various solvents. For the sake of comparison of the rate constants in various solvents at a given proton activity, the dependence of the rate constant in various solvents was followed within the range of about one pH unit. The values found are summarized in Table I. The found linear dependences of the rate constants *vs* the proton activity were used for interpolation of the rate constants at the proton activity 0·3 denoted as k'. The k' values (at the given proton activity) depend on the water activity, water being the nucleophilic agent, and on the rate constant k'_D which depends on the experimental conditions *i.e.* on the dielectric constant of the medium, too ($k' = k'_D a_{H_2O}$). If the difference between water activity and concentration is neglected, then at a constant proton activity it holds $k'/c_{H_2O} = k'_D$. The values of $\log k'_D$ given

TABLE I

Hydrolysis Rate Constants of Benzohydroxamic Acid at the Given Proton Activity, Temperature 363·2 K, Ionic Strength 2·5 in Water and 10, 30 and 50% (by weight) Aqueous Ethanol

a_{H^+}	$k_{exp} \cdot 10^4$, s^{-1}	a_{H^+}	$k_{exp} \cdot 10^4$, s^{-1}
water		30% ethanol	
0·0324	0·351	0·219	2·44
0·0650	0·488	0·268	3·38
0·0853	0·781	0·273	3·61
0·0955	1·050	0·279	4·76
0·155	1·24	0·361	5·82
0·204	1·46	0·431	7·81
0·289	1·72	0·526	8·46
0·358	2·76	0·535	8·54
0·456	3·41	0·813	11·19
0·642	4·65	0·897	11·38
1.081	7·73	0·953	12·22
10% ethanol		50% ethanol	
0·0961	0·939	0·139	2·20
0·119	1·236	0·156	3·23
0·146	1·59	0·197	3·97
0·155	1·63	0·229	4·35
0·168	2·01	0·309	5·59
0·182	2·33	0·324	6·33
0·240	2·36	0·339	6·57
0·371	4·41	0·465	10·09
0·597	6·87		

in Table II are inversely proportional to the dielectric constant of the solvent (calculated from the literature data[16]). The found linear dependence confirms the conclusions[2] according to which the rate-determining step consists in a reaction of dipole with ion. At a given proton activity the rate constant k'_D is the lower, the greater is the dielectric constant of the solvent. Therefrom it follows that the transition state is still less polar than the starting compounds. Values of the activation entropies and enthalpies in various solvents are summarized in Table II. The entropy values found are somewhat higher than those given in ref.[2].

TABLE II

Activation Parameters $\Delta H^{\neq}$ and $\Delta S^{\neq}$ of Hydrolysis of Benzohydroxamic Acid in 1M-$HClO_4$ at 300 K at I 2·5, Values of $\log k'_D$ of the same Compound at 363·2 K, $a_{H^+} = 0·3$, I 2·5 in Water and 10%, 30%, 50% (by wt.) Ethanol, and Reciprocal Values of the Dielectric Constants of the Solvents at 363·2 K

Solvent composition (by wt.% ethanol)	$-\Delta S^{\neq}$ J . deg^{-1} mol^{-1}	$\Delta H^{\neq}$ kJ . mol^{-1}	$-\log k'_D$ s^{-1} mol^{-1} dm^3	$1/D . 10^2$
0	95·8	166·5	5·37	1·73
10	80·4	182·0	5·17	1·88
30	83·7	166·0	4·95	2·30
50	76·6	178·5	4·64	2·89

TABLE III

Hydrolysis Rate Constants of *VI* 8 . 10^{-4}M in 50% (by wt.) Ethanol in the Given Medium at 363·1 K

The constants were computed from the initial velocity.

$HClO_4$ mol dm^{-3}	0·01M-$HClO_4$: : 0·01M-NaH_2PO_4	a_{H^+}	$k_{exp} . 10^5$ s^{-1}	$(k_{exp}/a_{H^+}) . 10^3$ dm^3 s^{-1} mol^{-1}
0·5	—	0·1205	13·12	1·09
0·25	—	0·0631	7·62	1·21
0·125	—	0·044	4·17	0·95
0·05	—	0·0208	3·03	1·45
0·03	—	0·014	1·71	1·22
0·01	—	0·0056	1·10	1·96
—	9 : 1	0·0035	0·609	1·74
—	6 : 4	0·0019	0·331	1·74

TABLE IV

Measured and Calculated Rate Constant Values of Hydrolysis of Hydroxamic Acids in 50% (by wt.) Ethanol at 363·1 K in $HClO_4$ Solutions of the Given Proton Activity

a_{H^+}	$k_{exp} . 10^4$ s^{-1}	$k_0 . 10^4$ $dm^3\ mol^{-1}\ s^{-1}$	$k_{theor} . 10^4$ s^{-1}
		II	
0·0634	4·50	71·0	4·56
0·0962	9·00	93·5	8·66
0·1141	12·40	108·5	10·95
0·1295	13·56	105·0	13·03
0·1436	15·90	111·0	15·0
0·1549	16·7	108·0	16·6
0·1690	18·7	110·4	18·6
0·1984	22·0	111·0	21·8
0·2083	23·1	111·2	24·4
0·2400	28·0	116·5	29·0
0·2994	37·2	124·1	38·0
0·4528	64·0	141·5	61·9
		III	
0·1430	1·23	10·5	1·12
0·1563	1·43	10·9	1·27
0·1905	1·60	9·8	1·69
0·2320	1·79	8·75	2·21
0·2730	2·03	8·42	2·74
0·3243	2·82	10·62	3·40
0·4083	4·14	10·90	4·52
0·5500	6·93	13·31	6·42
0·6325	10·37	17·2	7·53
		IV	
0·1173	1·74	16·17	1·49
0·1295	1·33	11·09	1·75
0·1322	1·58	12·86	1·79
0·1549	1·92	13·12	2·36
0·1617	2·04	13·37	2·55
0·1984	5·11	27·30	3·70
0·2083	5·80	29·15	4·05
0·2538	6·50	26·58	5·69
0·2868	8·23	29·70	6·96
0·4128	12·50	32·00	13·05

TABLE IV

(*Continued*)

a_{H^+}	$k_{exp} \cdot 10^4$ s^{-1}	$k_0 \cdot 10^4$ $dm^3\ mol^{-1}\ s^{-1}$	$k_{theor} \cdot 10^4$ s^{-1}
		V	
0·1430	2·07	15·56	2·14
0·1563	2·85	19·41	2·43
0·1905	3·41	18·88	3·07
0·2495	4·25	17·77	4·63
0·2730	5·30	20·17	5·13
0·3343	6·60	20·37	6·65
0·4083	8·50	21·36	8·49
0·5995	13·90	23·58	13·57
		VI	
0·1429	1·42	9·96	1·66
0·1750	2·90	16·56	2·76
0·1972	3·01	15·26	2·90
0·2292	3·62	15·81	3·73
0·2711	4·62	17·06	4·92
0·3244	6·95	21·42	6·55
0·3388	7·04	20·77	7·02
0·4648	11·05	23·77	11·38

Investigation of the acid-catalyzed hydrolysis of *VI* in solutions of pH about 1 to 3 suggested that the hydrolysis in this medium did not follow the scheme of isolated reactions. Therefore, log $[(A_0 - A_\infty)/(A - A_\infty)]$ was plotted against time, and the tangent of the curve at $t = 0$ was used for calculation of the rate constant at the beginning of the reaction. Composition of the buffers used, measured proton activity, and values of the rate constants are given in Table III. In spite of the known inaccuracy of the abovementioned method, linear dependence of the rate constants on the proton activity was found (see the ratio k_{exp}/a_{H^+} in the last column of Table III, which changes only slightly with the proton activity). A similar dependence was found also for the hydrolytic constants of acetohydroxamic acid[1], which allows to conclude that the hydrolysis reaction is, in its first step, of the first order in the proton.

At the pH values within 1 to 0 the reaction follows the equation of the isolated reactions of 1. order. The measured a_{H^+} values and the k_{exp} constants calculated from Eq. (*1*) at constant ionic strength (I 2·5) are given in Table IV. The lowest values of the proton activities given in the Table are those for which the reaction could be considered to be isolated according to ref.[17], whereas the highest values are those values at which the given reaction could be followed by the chosen experimental method. The further column of Table IV gives the values $k_{exp}/a_{H^+} = k_0$ which depend on the proton activity much more than the corresponding analogous values in Table III. If the ionic strength was not kept constant, the experimental results differed only little from those given in Table IV. This fact agrees with the slight dependence of the rate constant on the ionic strength of the solution as it is given in Table V. A similar dependence of k_0 *vs* the proton activity was found also for hydrolysis of *II* (Table IV).

Hydroxamic acids derived from pyridine are protonated at the ring nitrogen atom in acidic medium. This protonation can be supposed to influence (I effect) the reactivity of the carbonyl carbon atom and facilitate the addition of water. The protonated compound was considered to be the reactive species, and, therefore, the experimental rate constants obtained from Eq. (*1*) were corrected according to Eq. (*2*) to give the values corresponding to concentration of the protonated form (in Eq. (*2*) K_a means the dissociation constant).

$$k_{exp}(K_a + a_{H^+})/a_{H^+} = k_{corr} \, . \qquad (2)$$

The values $k_{corr}/a_{H^+} = k_0$ given in Table IV depend on the proton activity.

The found dependence of k_0 on the proton activity does not confirm the idea of one acid-catalyzed reaction step as it is given in literature[1-5]. The found dependence agrees better with the mechanism of the acid-catalyzed hydrolysis of amides[10]. On the basis of the found pK values it can be stated that in acidic medium pyridinecarbohydroxamic acids are protonated at the ring nitrogen atom according to Eq. (*A*). The subsequent reactions take place at the functional group and are common for all the substances investigated.

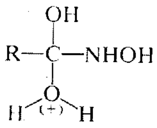
$$\text{HO—NH—CO—C}_5\text{H}_4\text{N} + \text{H}^+ \underset{k_2}{\overset{k_1}{\rightleftharpoons}} \text{HO—NH—CO—C}_5\text{H}_4\overset{(+)}{\text{N}}\text{H} \, . \qquad (A)$$

TABLE V

Dependence of Hydrolysis Rate Constant of *VI* 8 . 10^{-4}M in 1M-HClO$_4$ in 50% (by wt.) Ethanol at 368·1 K on Ionic Strength

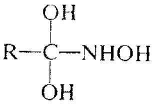
Ionic strength	1·0	1·5	2·0	2·5	3·0
$k_{exp} \cdot 10^4$, s^{-1}	5·26	5·42	5·57	6·04	6·14

In accord with current conception the first reaction step of the mechanism of hydroxamic acids hydrolysis consists in addition of water to the carbonyl carbon atom. In neutral region this reaction is slower than in acid medium by several orders of magnitude[1,6], hence the non-catalyzed addition of water is kinetically insignificant in the medium studied and was not involved in further considerations. The acid-catalyzed addition of water results in formation of the cation C_1. The found activation entropy values (Tables II and VI) prefer the idea of bimolecular character of the rate-limiting step. Therefore, it can be supposed that the addition of water is slow ($k_3 \ll k_4$). (Numbering of the rate constants in this and the following cases is the same as in the previous paper[10]).



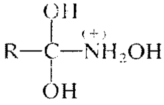
$$\mathrm{R{-}\underset{H\overset{(+)}{O}H}{\overset{OH}{C}}{-}NHOH}$$

C_1



$$\mathrm{R{-}\underset{OH}{\overset{OH}{C}}{-}NHOH}$$

C_2



$$\mathrm{R{-}\underset{OH}{\overset{OH}{C}}{-}\overset{(+)}{N}H_2OH}$$

C_3

The formed cation C_1 is not stable and splits off the proton to give the free base of the tetrahedral intermediate C_2 ($k_5 \gg k_6$). Suppose this intermediate to be unstable, too, being able to split off water not only by acid catalysis but also through hydrogen bonds. Finally, with respect to the acid medium in which the reaction takes place, the tetrahedral intermediate C_2 can be protonated, and the cation C_3 thus formed can (through reshuffling of bonds) split into hydroxylamine, proton and carboxylic acid. Using the method of quasi-stationary concentrations it is possible

TABLE VI

Activation Parameters $\Delta H^{\ddagger}$ and $\Delta S^{\ddagger}$ of Hydrolysis of Hydroxamic Acid in 50% (by wt.) Ethanol in 1M-HClO$_4$ at 300 K and Values of Ratios $\varkappa_3/\varkappa_1$, $\varkappa_2/\varkappa_1$ and $\varkappa_2/\varkappa_3$ at 363·1 K

Compound	$\Delta S^{\ddagger}$ J . mol^{-1} deg^{-1}	$\Delta H^{\ddagger}$ kJ . mol^{-1}	$\frac{\varkappa_3}{\varkappa_1}$	$\frac{\varkappa_2}{\varkappa_1}$	$\frac{\varkappa_2}{\varkappa_3}$
II	−109·6	67·9	62·6	4·78	0·0764
III	−103·6	77·0	727·0	46·0	0·0633
IV	−100·8	77·4	154·0	70·0	0·4545
V	− 85·2	83·3	374·7	35·5	0·0947
VI	−124·0	69·9	207·5	93·3	0·4496

to write Eq. (*3*) for the reacting system,

$$k_{\mathrm{exp}} = \varkappa_1(a_{\mathrm{H}^+})^2/(\varkappa_2 + \varkappa_3 a_{\mathrm{H}^+})\,, \tag{3}$$

where $\varkappa_1 = k_3 a_{\mathrm{H_2O}} k_5 k_8 k_{10}$, $\varkappa_2 = (k_4 + k_5)(k_9 + k_{10})\,k_7$, and $\varkappa_3 = ((k_4 + k_5)\,.\,k_8 k_{10} + (k_9 + k_{10})\,k_4 k_6)$. (The expressions given for $\varkappa_2$ and $\varkappa_3$ in the previous paper[10] were incorrect). Eq. (*3*) can be transformed into an equation of straight line. in which $\varkappa_3/\varkappa_1$ is the slope, and $\varkappa_2/\varkappa_1$ is the intercept at the axis $(a_{\mathrm{H}^+})^2/k_{\mathrm{exp}}$. The values of the ratios $\varkappa_3/\varkappa_1$ and $\varkappa_2/\varkappa_1$ were obtained by the least squares method and are listed in Table VI. From these values and from the measured proton activities the theoretical values k_0 were computed, and from k_0 and the found proton activities the rate constants k_{theor} were obtained which are also given in Table IV.

Comparison of k_{exp} and k_{theor} values suggests that the reaction mechanism of hydrolysis of amides[10] fits also the hydrolysis of hydroxamic acids in the pH region about 1 to 0. At higher pH values the studied reaction is complex. If the rate constant is computed from the initial concentration decrease, as it was the case in Table III and in literature, then the observed decrease of hydroxamic acid corresponds only to the acid-catalyzed addition of water to carbonyl carbon atom, and the respective rate constant is linearly proportional to the proton activity even according to the suggested mechanism. Addition of water results in formation of the intermediates C_1 to C_3. It can be presumed that the cation C_1 is unstable thermodynamically as compared with the cation C_3. In protic solvents acid–base equilibria are established very quickly. Hence the reaction course is better reflected by the formulae C_2 and C_3 which are in acid–base equilibrium. Suitable substitution can bring about a change in the concentration ratio of the two forms under given pH. Therefore, with benzohydroxamic acid greater proportion of the cation C_3 can be expected than with all other compounds studied in this work. If the concentration of C_3 is small as compared to that of the conjugated base C_2, then the splitting off of a water molecule from the transition state by means of hydrogen bonds is kinetically significant ($\varkappa_2$ is smaller than $\varkappa_3 a_{\mathrm{H}^+}$ by less than two orders of magnitude), and the dependence k_{exp} *vs* the proton activity is given by Eq. (*3*). If the concentration of the cation C_3 is of comparable order of magnitude as that of the conjugated base C_2 ($\varkappa_2$ is smaller than $\varkappa_3 a_{\mathrm{H}^+}$ by more than two orders of magnitude), then the rate of splitting off of hydroxylamine from the cation C_3 predominates over the rate of splitting off of water from C_2, and the reaction step characterized by the rate constant k_7 cannot be detected by the method used. In this case $\varkappa_2$ can be neglected (as compared to $\varkappa_3 a_{\mathrm{H}^+}$) in Eq. (*3*), and the rate constant depends linearly on the proton activity, as it was found in literature[2] as well as in the present study with benzohydroxamic acid. The dependence of the hydrolysis rate constant of this compound on the dielectric constant of medium supports the view that the intermediate has lower polarity than the starting substance. The presumed forms C_1 to C_3 fit this view.

It can be concluded that the suggested mechanism of the acid-catalyzed hydrolysis of amides fits also the acid-catalyzed hydrolysis of hydroxamic acids. This mechanism explains the polarity decrease during formation of the transition state from the starting substances (which follows from experiments), and it can also simply explain the changes of the logarithm of rate constant with pH.

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