

HYDROLYSIS OF O-ACETYL BENZOHYDROXAMIC ACID DERIVATIVES

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Received October 27th, 1975

O-Acetylbenzohydroxamate is hydrolyzed in both aqueous acids and strong bases to give acetic and benzohydroxamic acids. In neutral medium the hydrolysis is accompanied by the Lossen rearrangement; the maximum yield of the rearrangement product has been found at pH 8 to 9. The reactions have been followed in media of various pH, and from the analyses of the reaction mixtures the mechanisms of the reactions taking place have been suggested.

Hydrolysis of benzohydroxamic acids was found¹ to proceed practically without side reactions which would give amines (the Lossen rearrangement). However, acyl derivatives of benzohydroxamic acids undergo the rearrangement in alkaline medium, the reaction being also of preparative importance^{2,3}. In connection with the research of acyl derivatives of benzohydroxamic acids as biologically active compounds^{4,5} it would be of use to determine their hydrolytical stability and conditions of the maximum occurrence of the rearrangement. We have chosen O-acetylbenzohydroxamate (*I*) and its 3-nitro derivative as the model substances and studied their behaviour in aqueous media of various pH. The reactions taking place are represented in Scheme 1. The formed benzohydroxamic acid (*II*) is stable under the reaction conditions, the primary rearrangement product – phenyl isocyanate (*III*) – cannot be trapped in water, being rapidly hydrolyzed to aniline.

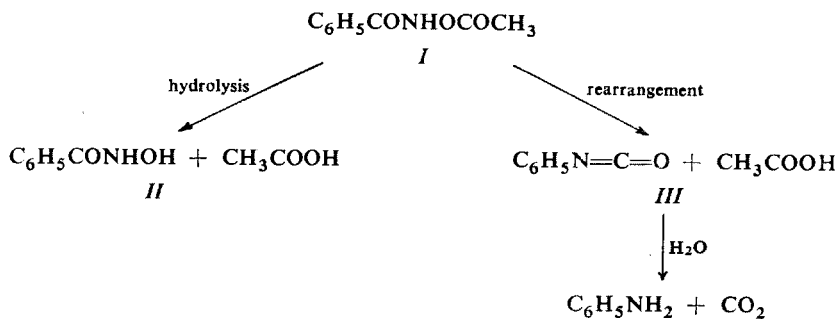
EXPERIMENTAL

O-Acetylbenzohydroxamate (*I*) was prepared by reaction of benzohydroxamic acid with acetic anhydride. Crystallization from benzene gave the product melting at 128°C in accord with ref.⁶. The 3-nitro derivative was prepared analogously, m.p. 135°C.

Kinetic measurements. The hydrolysis of the model substances was carried out in buffers⁷ covering the pH range 0 to 14 and having constant ionic strength 2 under the conditions of pseudo-monomolecular reaction course. Both the hydrolysis and the rearrangement products were determined spectrophotometrically: the formed benzohydroxamic acid by reaction with ferric chloride, and the rearrangement product (aniline) by reaction with N,N-dimethylaminobenzaldehyde. The proper measurement was carried out at $50 \pm 0.1^\circ\text{C}$ by the methods described

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in ref.¹. The found rate constants (experimental error was less than $\pm 5\%$) are given in Table I along with the aniline content (%) in the final reaction mixture.



SCHEME I

TABLE I

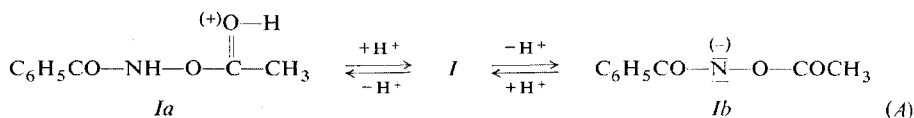
Hydrolysis Rate Constants of O-Acetylbenzohydroxamate (*I*) and 3-Nitrobenzohydroxamate (*IV*) (in s^{-1}) and Per Cent Amount of the Formed Anilines at Various pH Values at 50°C at Constant Ionic Strength I 2.0

pH	$k_{\text{obs}} \cdot 10^4$	% Aniline	pH	$k_{\text{obs}} \cdot 10^4$	% Aniline
Compound <i>I</i>			Compound <i>I</i>		
0.00	2.51	0	9.50	1.10	88
1.09	0.39	0	10.50	2.23	60
1.50	0.15	0	12.10	25.60	0
2.20	0.12	0	13.00	2.22 ^b	0
3.36	0.14 ^a	0	13.00	10.04 ^c	0
3.36	0.04	0	13.00	199.00 ^d	0
3.80	0.14	0	14.00	55.00 ^b	0
4.60	0.15	15	14.00	187.00 ^c	0
5.00	0.14	30	14.00	1 980.00 ^d	0
5.60	0.14	35	Compound <i>IV</i>		
6.01	0.32	55	0.00	2.31	0 ^f
6.53	0.89	75	4.90	0.11	5 ^f
7.50	0.89	85	7.20	0.14	60 ^f
8.00	0.84	92	9.00	0.14	30 ^f
8.50	0.85	92	13.00	23.10 ^e	0 ^f

^a In D_2O ; ^b at 15°C; ^c at 40°C; ^d extrapolated to 50°C from the preceding two measurements; ^e at 25°C; ^f % of 3-nitroaniline.

RESULTS AND DISCUSSION

The pH dependence (pH 0 to 14) of the logarithm of the rate constants (k_{obs}) of O-acetylbenzohydroxamate (*I*) hydrolysis (Table I) is represented in Fig. 1 along with the final aniline content (%). In the pH regions of simultaneous hydrolysis and rearrangement the ratio of aniline to benzohydroxamic acid is constant throughout the kinetic run. It can be anticipated that the both reaction product are formed from a common intermediate. The course of the hydrolysis reactions is affected by the protonation and deprotonation pre-equilibria given in Eq. (A).



In the pH region below 1 the K_{obs} is directly proportional to the hydroxonium ion concentration, and benzohydroxamic acid (*II*) is the reaction product, being not further hydrolyzed under the reaction conditions. Hence, the protonation takes place preferently at the carbonyl oxygen atom of the acetyl group. After the attack by a water molecule (which is most probably the rate-limiting step) the tetrahedral intermediate formed decomposes into products (Eq. (B)).

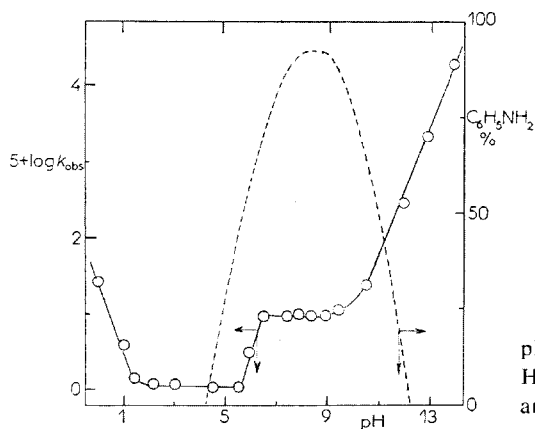
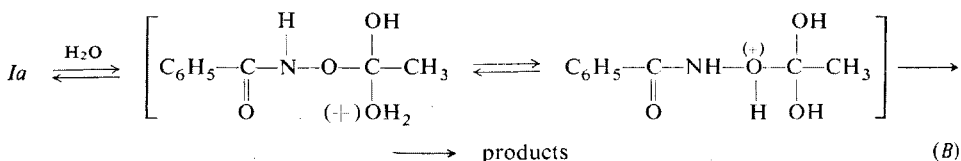
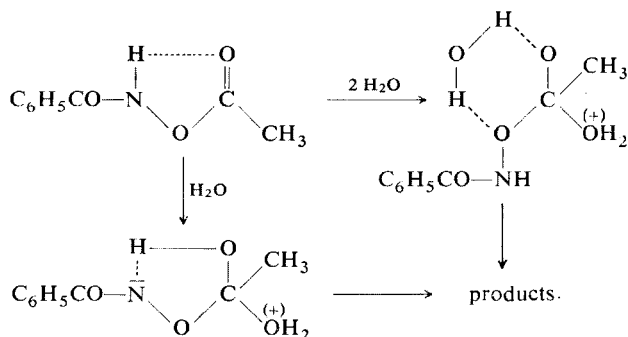


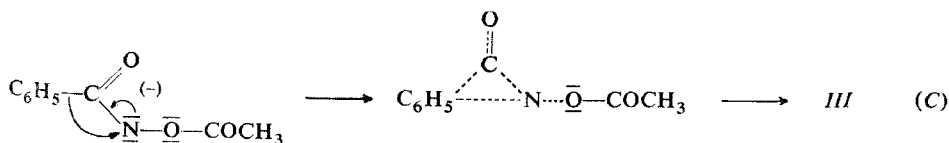
FIG. 1
pH Dependence of Logarithm of k_{obs} for Hydrolysis of O-Acetylbenzohydroxamate and Aniline Content in the Reaction Mixture

In the pH region 1 to 4, where the rearrangement does not occur, the non-protonated form (*I*) is hydrolyzed, and the reaction rate is independent of pH of the medium. The ratio of the reaction rates in water and in deuterium oxide is $k_{\text{obs}}(\text{H}_2\text{O})/k_{\text{obs}}(\text{D}_2\text{O}) = 4$ at pH 3.36. The high value of the kinetic isotopic effect⁸ indicates that O—H resp. O—D bond is being split in the activated complex of the rate-limiting step. With respect to possible intramolecular hydrogen bond it is probable that both the attack of the substrate by water molecule and the decomposition of the tetrahedral intermediate into the products are intramolecularly catalyzed (Scheme 2).

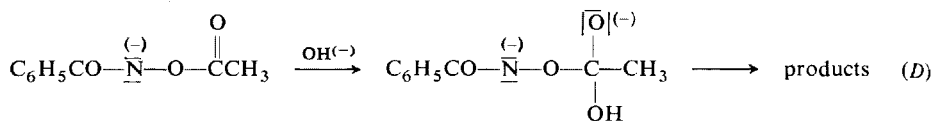


SCHEME 2

In the pH region 4 to 12 rearrangement occurs simultaneously. The maximum aniline content in the final reaction mixture is observed at pH 8 to 9 (Table I). In the pH range 5.6 to 6.6 the overall decomposition rate abruptly changes (it is increased by a factor of 5). The change of the reaction rate corresponds to dissociation of the proton to give the ion *Ib* (pK 6.24, see ref.^{6,9}). The ionized form *Ib* undergoes the rearrangement to phenyl isocyanate more easily. From the molecular diagram of the anion *Ib* (Fig. 2), which was calculated by the Hückel method (average value of the conjugation and the inductive models), it follows that the bond between nitrogen and oxygen of the leaving acetate group is considerably weakened and, therefore, its splitting can occur easily. With respect to the primary isotopic effects found¹⁰ in the Lossen rearrangement of potassium O-benzoylbenzohydroxamate (C^{14} at 1-position of the aromatic nucleus) indicating the C—C bond splitting in the rate-limiting step, the rearrangement mechanism of the anion *Ib* can be formulated as a synchronic reaction (Eq. (C)). Further increase in basicity of medium ($\text{pH} > 10$)



results in the substrate being present as the anion only, and the hydrolysis reaction consists in the attack of hydroxyl ion on carbonyl of the acetyl group (Eq. (D)),



which is more reactive to a nucleophilic attack (see Fig. 2 for the superdelocalizability values for nucleophilic attack). The reaction rate is proportional to hydroxyl ion concentration, the slope being unity (Fig. 1). The hydrolysis mechanism involving the reaction of two negatively charged particles is supported also by the found positive salts effect (Table I). A similar dependence was found also with alkaline hydrolysis of esters carrying a negative charge¹¹. In the presence of hydroxylamine (0.1M) at pH 12 the acetate *I* gives both benzohydroxamic and aceto hydroxamic acids (which were determined by chromatographic and spectral analysis). The hydroxylaminolysis is so rapid under these conditions, that practically no hydrolysis takes place. As a nucleophilic reagent hydroxylamine is somewhat less reactive than hydroxyl ion in a reaction with a neutral molecule⁸, however the attack on a negatively charged substrate is energetically more favourable for the neutral hydroxylamine. From the measurement of the hydrolysis rate of the acetate (*I*) in 1M-NaOH at 15 to 25°C the following thermodynamic parameters were computed: $E_{\text{act}} = 84600 \text{ J mol}^{-1}$, $\Delta H = 82400 \text{ J mol}^{-1}$ and $\Delta S = -2.09 \text{ J mol}^{-1} \text{ grad}^{-1}$. At pH 9.09 the rearrangement makes 90 per cent of the reaction, and the following parameters were obtained: $E_{\text{act}} = 119500 \text{ J mol}^{-1}$, $\Delta H = 115000 \text{ J mol}^{-1}$ and $\Delta S = 39 \text{ J mol}^{-1} \text{ grad}^{-1}$. Hence it is obvious that the change in the reaction mechanism makes itself felt also in the change of thermodynamic parameters. A positive activation entropy value can be expected for fragmentation monomolecular reactions (rearrangement), a negative entropy value is acceptable for bimolecular hydrolytic reaction¹⁰.

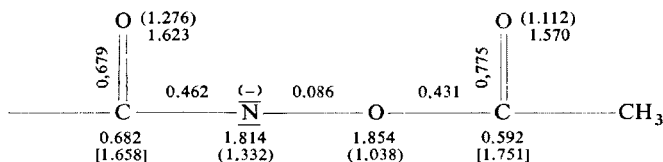


FIG. 2

HMO Diagram of Anion *Ib*

The superdelocalizability value of the electrophilic and the nucleophilic attacks are given in parenthesis and square brackets, respectively.

For the sake of comparison of the behaviour of the acetyl derivative (*I*) with that of O-benzoylbenzohydroxamate^{12,13} we followed also the reaction of the acetate in 0.1M ammonia at 30°C. The acetate is hydrolyzed ($k_{\text{obs}} = 5.7 \cdot 10^{-6} \text{ s}^{-1}$) whereas the benzoate gives 92% aniline under the same conditions ($k_{\text{obs}} = 1.3 \cdot 10^{-3} \text{ s}^{-1}$). The result agrees with the suggested mechanisms of hydrolysis and rearrangement. Benzoate ion is a better leaving group than acetate ion and, besides that, a carbonyl group in the vicinity of aromatic nucleus is less reactive to a nucleophilic attack (see Fig. 2 and ref.^{10,11}).

The results obtained in investigation of the reaction of O-acetyl-3-nitrobenzohydroxamate support the suggested mechanism, too. The maximum yield of 3-nitroaniline (the rearrangement product) was obtained at a lower pH (pH 7.2) (Table I) as compared to the reaction of the acetate (*I*), which stands in accord with the higher acidity of the 3-nitro derivative. In basic medium, only hydrolysis takes place, the reaction being faster than in the case of *I*. The estimated low reaction constant ($\rho \approx 0.5$) in 0.1M-NaOH at 25°C corresponds to the fact that the reaction centre is separated from the benzene nucleus by three atoms. The overall lower amount of 3-nitroaniline (rearrangement) agrees with the mechanism given, because the negative polar influence of 3-nitro group makes the leaving of acetate ion more difficult.

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Translated by J. Panchartek.