HYDROLYSIS KINETICS AND MECHANISM OF O-CARBAMOYL DERIVATIVES OF BENZOHYDROXAMIC ACID*

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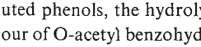
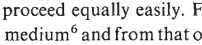
Hydrolysis rate constants of O-dimethylcarbamoyl- (*I*) ad O-monomethylcarbamoyl benzohydroxamate (*II*) have been determined in water in the pH region 0 to 14. Besides acid- and base-catalyzed hydrolysis in water also spontaneous hydrolysis takes place to give benzohydroxamic acid which is stable under the reaction conditions. The Lossen rearrangement also takes place as a competitive reaction in neutral (to about pH 5) and alkaline medium, being the only reaction of the compound *I* in the pH region 8 to 14, whereas in the case of the compound *II* it reaches its maximum (50%) at pH about 8 and decreases with increasing alkalinity. Mechanisms of the reactions in acid, neutral and alkaline media are suggested.

In a number of previous reports[1–4] we dealt with kinetics and mechanism of solvolyses of carbamic acid derivatives. The common feature of the studied compounds was that the molecules contained good leaving groups (phenolate ion), and the compounds underwent easily hydrolytic splitting. Now we have focused our attention on further carbamates having benzohydroxamic acid anion as the leaving group. With respect to that the conjugate acid of the leaving group is in its acidity (pK_a of benzohydroxamic acid in water at 20°C is 8·80; ref.[5]) comparable with negatively substituted phenols, the hydrolytic reactions should proceed equally easily. From the behaviour of O-acetyl benzohydroxamate in aqueous medium[6] and from that of O-benzoyl derivatives of benzohydroxamic acid[7] it can be inferred that the reaction mixture will possibly contain rearrangement products besides the hydrolysis products. For the study of solvolytic reactions we have chosen as the model substances N,N-dimethylcarbamoyl- (*I*) and N-methylcarbamoyl benzohydroxamates (*II*). The aim



I



II

of this work was to examine the behaviour of the mentioned compounds in aqueous media of various pH and suggest mechanism of the reactions taking place.

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EXPERIMENTAL

O-*Dimethylcarbamoyl benzohydroxamate* (I). Dimethylcarbamoyl chloride (0·2 mol) was added drop by drop to pyridine solution of 0·1 mol benzohydroxamic acid at room temperature. The mixture was left to stand for 24 hours and then heated to boiling for 20 minutes. A sample of the mixture did not give red colouration with ferric chloride solution. The mixture was diluted with 150 ml ether and extracted successively with 2 . 100 ml 10% HCl, 100 ml water, 2 . 100 ml 5% $NaHCO_3$ solution and 2 . 100 ml water. The ether solution was dried with anhydrous Na_2SO_4, ether was distilled off, and the residue was recrystallized from chloroform, yield 85·5%, m.p. 152—153°C agreed with ref.[8], and NMR spectrum confirmed the given structure, too.

O-*Methylcarbamoyl benzohydroxamate* (II). Methyl isocyanate (0·05 mol) and 2—3 drops of triethylamine were added to saturated solution of 0·04 mol benzohydroxamic acid in acetone. The mixture became warm spontaneously. After about four hours standing at room temperature the test with ferric chloride solution was negative. After evaporation in vacuum of a water pump the residue was recrystallized from tetrachloromethane, yield 76·7%, m.p. 146—148°C in accord with ref.[9]; NMR spectrum confirmed the structure of the prepared substance.

Kinetic measurements. Hydrolysis of the model substances was carried out in buffers[10] having constant ionic strength $I = 1$ under the conditions of a pseudomonomolecular reaction course. Both the hydrolysis and the rearrangement products were determined spectroscopically by the known method[11]. Concentrations of the compounds in the reaction mixture was determined with the use of calibration curves of the expected reaction products. The reaction half life was read from the dependence logarithm of the sum of the found concentration *vs* time, and the reaction rate constant was calculated therefrom ($k_{obs} = 0{\cdot}693\ t_{1/2}$). The determined rate constants (error less than ±5%) and the per cent aniline content in the final reaction mixtures of the studied compounds are given in Table I.

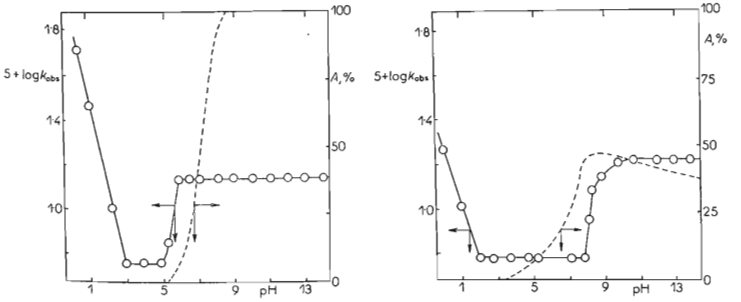


FIG. 1*a*, *b*

pH Dependence of log k_{obs} of Hydrolysis of O-Dimethylcarbamoyl-(*I*) (*a*) and O-Methylcarbamoyl Benzohydroxamates (*II*) (*b*) and Aniline Content (*A*) in the Reaction Mixture

RESULTS AND DISCUSSION

Fig. 1 gives the dependence log k_{obs} (Table I) of hydrolysis of the carbamoyl derivatives of benzohydroxamic acid in the pH range 0 to 14 along with the final per cent aniline content.

In the pH regions where the rearrangement takes place simultaneously, the ratio of aniline to benzohydroxamic acid remains constant during a kinetic run. Hence it can be presumed that the reaction products can be formed from the same intermediate. The reactions taking place during the hydrolysis are represented in Scheme 1 where R = CH_3, and R' = H or CH_3.

At higher conversions (over 50%), when aromatic amine was formed predominantly, diphenylurea (*V*) separated from the solution. In these cases the kinetic constants were calculated from the data obtained up to only 30% conversion. Carba-

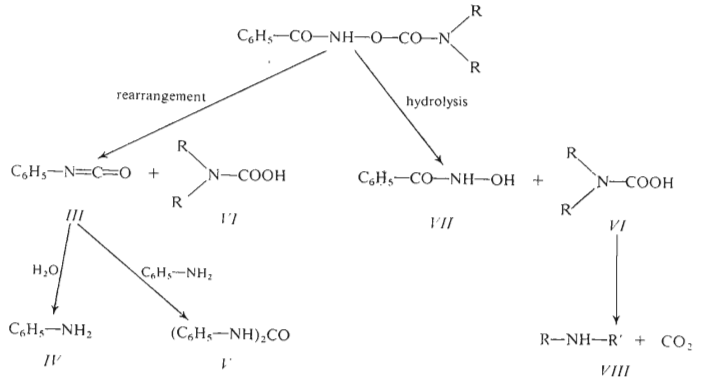
TABLE I

Hydrolysis Rate Constants (in s^{-1}) of O-Dimethylcarbamoyl- (*I*) and O-Monomethylcarbamoyl Benzohydroxamates (*II*) and Percentage of the Formed Aniline (*A*) at Various pH at 50°C at Ionic Strength 1·0

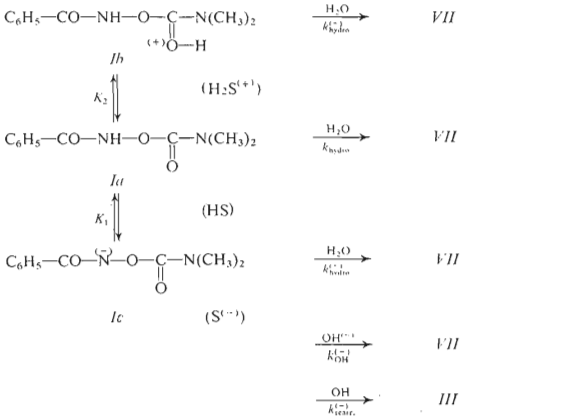
pH	$k_{obs} \cdot 10^4$	*A*, %	pH	$k_{obs} \cdot 10^4$	*A*, %
0·00	4·81	0	0·00	1·84	0
1·00	2·82	0	1·00	1·01	0
2·20	0·10	0	1·93	0·60	0
2·90	0·559	0	2·77	0·36	0
3·93	0·55	0	3·80	0·35	0
3·93	0·29[a]	0	4·78	0·40	5·6
5·00	0·56	0	5·29	0·43	11·1
5·20	0·55	0	6·23	0·40	15·6
5·50	0·71	0	7·24	0·40	24·0
5·90	1·35	6	7·62	0·40	48·7
6·50	1·34	18	7·96	0·40	48·5
7·00	1·30	38	7·99	0·55	43·4
8·10	1·35	100	8·30	0·88	42·8
9·00	1·34	100	8·97	1·32	39·0
10·05	1·39	100	9·80	1·58	38·8
11·00	1·35	100	10·77	1·60	38·0
12·10	1·39	100	12·22	1·44	40·0
13·00	1·38	100	13·00	1·49	39·5
14·00	1·36	100	14·00	1·49	38·5
14·37[b]		78	14·37[b]	1·47	38·1

[a] In D_2O; [b] in 2M-NaOH.

mic acid (*VI*) is evolved during the reactions, and it decomposes immediately into the amine *VIII* (Scheme 1). Besides the kinetic results, the discussion is also based on molecular diagrams calculated by the Hückel method (a mean value of the conjugation and the inductive models; Fig. 2).



SCHEME 1



SCHEME 2

Reaction of O-N,N-*dimethylcarbamoyl benzohydroxamate* (I). From the dependence log k_{obs} *vs* pH of the hydrolysis of substance *I* it follows that the reaction goes by several mechanisms which are given in Scheme 2. In the pH region 0 to 3 the constant k_{obs} is directly proportional to the hydroxonium ion activity. Benzohydroxamic acid is the reaction product, being not further hydrolyzed under the reaction conditions. Benzoic acid is not formed, which indicates that the reacting form consists of the substrate protonated at the carbonyl oxygen of its carbamate group (*Ib*), even though the alternative tautomer protonated at the other carbonyl oxygen can be present, too (Fig. 2*a*). After an attack by a water molecule (which is

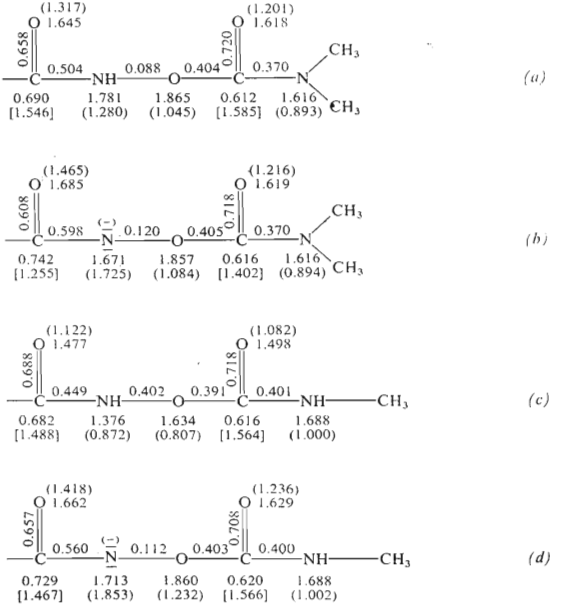
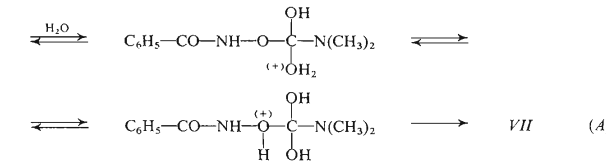


FIG. 2

HMO Diagrams of Compounds *I* and *II* and their Anions

(*a*) ——— bond order, (*b*) — ○ — electron density, (*c*) nucleophilic superdelocalizability, (*d*) electrophilic superdelocalizability.

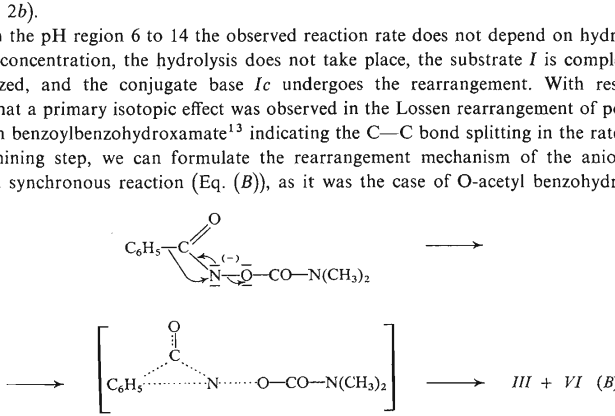
probably the rate-determining step) the tetrahedral intermediate decomposes into the products (Eq. (*A*)).



In the pH region 3 to 5 the reaction rate does not depend on the proton activity. The non-protonated substrate is the reacting form, giving the products by spotaneous solvolysis. The water molecule attacks on the carbonyl oxygen of the more reactive carbamoyl group (Fig. 2*a*). From the found kinetic isotopic effect it follows that a proton-transfer is involved in the rate-determining step (at 50°C at pH 3·94 it is $k_{obs}H_2O/k_{obs}D_2O = 1{\cdot}86$) (refs[12,13]).

From the dependence log k_{obs} *vs* pH of the medium (Fig. 1) it is possible to estimate the equilibrium constant of the equilibrium $I_a \rightleftarrows I_c$ (pK 5·8). Starting from pH 5·9 (Table I) the reaction products begin to contain also aniline beside benzohydroxamic acid. Simultaneously with the hydrolysis of the neutral substrate form there reacts obviously its conjugate base *Ic*, too. However, instead of the nucleophilic attack by solvent, the anion is split into phenyl isocyanate (*III*) and anion of dimethylcarbamic acid. The both instable intermediates undergo immediately further hydrolytic reactions. The easy splitting of N—O bond is due to low bond order (0·120; Fig. 2*b*).

In the pH region 6 to 14 the observed reaction rate does not depend on hydroxyl ion concentration, the hydrolysis does not take place, the substrate *I* is completely ionized, and the conjugate base *Ic* undergoes the rearrangement. With respect to that a primary isotopic effect was observed in the Lossen rearrangement of potassium benzoylbenzohydroxamate[13] indicating the C—C bond splitting in the rate-determining step, we can formulate the rearrangement mechanism of the anion *Ic* as a synchronous reaction (Eq. (*B*)), as it was the case of O-acetyl benzohydroxa-



mate[6]. The given equation is supported by the trapping of the reaction intermediate, *i.e.* phenyl isocyanate, in the form of diphenylurea (*V*) which is formed by its reaction with the aniline already present (Scheme 1). In strongly basic medium (pH > 14) the hydrolytic reaction is again significant (*i.e.* attack of hydroxyl ion on the more reactive carbamoyl group of the conjugate base of the substrate *Ic*; Fig. 2*b*).

According to Scheme 2 the relation (*1*) can be derived for the reaction rate (corresponding to the substrate *I* concentration decrease). The third term, $k^{-}_{hydro}[S^{-}]$,

$$v = k^{+}_{hydro}[H_2S^{+}] + k_{hydro}[HS] + k^{-}_{hydro}[S^{-}] + k^{-}_{OH}[S^{-}][OH^{-}] + k^{-}_{rearr}[S^{-}] \quad (1)$$

of Eq. (*1*) can be omitted, as no hydrolysis was observed in the pH region 6 to 13 where the concentration of the conjugate base of the substrate *Ic* is maximum. Introduction of the dissociation constants* (K_1 and K_2) in Eq. (*1*) gives Eq. (*2*) for the reaction rate. A very good agreement between experimental data and the

$$k_{obs} = k^{+}_{hydro}(1 + K_2[H^{+}]) + k_{hydro}(1 - 1/1 - K_2[H^{+}]) - 1/(1 + [H^{+}]/K_1)) + \\ + k^{-}_{OH}K_{H_2O}/([H^{+}](1 + [H^{+}]/K_1)) + k_{rearr}/(1 + [H^{+}]/K_1)$$

curve calculated from Eq. (*2*) (Fig. 1) is obtained with the use of the following values of coefficients of Eq. (*2*): $K_1 = 1{\cdot}59 \,.\, 10^{-6}$; $K_2 = 3{\cdot}16 \,.\, 10^{-2}$; $k^{+}_{hydro} = 4{\cdot}5 \,.\, 10^{-4}\ s^{-1}$; $k_{hydro} = 0{\cdot}55 \,.\, 10^{-4}\ s^{-1}$; $k^{-}_{OH} = 1{\cdot}9 \,.\, 10^{-4}\ s^{-1}\ mol^{-1}\ l^{-1}$; $k_{rearr} = 1{\cdot}36 \,.\, 10^{-4}\ s^{-1}$; $K_{H_2O} = 10^{-14}$. The obtained agreement supports the suggested reaction mechanisms.

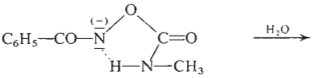
Reactions of O-*methylcarbamoyl benzohydroxamate* (II). The rate constant values (k_{obs}) of the substance *II* are given in Table I for various pH values. The dependence of log k_{obs} *vs* pH of the medium is given in Fig. 1b and is independent of the hydroxyl ion concentration in the pH range 2 to 8. We presume that the substrate *II* is practically completely dissociated in this pH region (*cf.* pK_a 5·9 of the compound *I*), being present in the form of anion *IIa*. If tautomer *IIb* is present in the solution, then also its concentration will be very low with respect to low acidity of the proton in HN group of N-methylcarbamoyl (see also the higher electron density at nitrogen of the carbamoyl group; Fig. 2*c*). In the reaction connected with rearrangement the N—O bond of the anion *IIa* is split analogously as that in O-acetyl benzohydroxamates and carbamate *I*. The phenyl isocyanate formed in the reaction was trapped as symmetrical diphenylurea, too (Scheme 1). In the given pH region the carbamate *II* is hydrolyzed into benzohydroxamic acid which is stable under the reaction conditions. Two indistinguishable hydrolysis mechanisms

* For the substrate deprotonation ($HS \rightleftarrows S^{-} + H^{+}$) it holds: $K_1 = [H^{+}][S^{-}]/[HS]$ and $[S^{-}] = 1/(1 + [H^{+}]/K_1)$. Similarly for deprotonation of the conjugate acid of substrate ($H_2S^{+} \rightleftarrows HS + H^{+}$) it is $K_2 = [H^{+}][HS]/[H_2S^{+}]$ and $[H_2S^{+}] = 1/(1 + K_2[H^{+}])$.

can be considered, *i.e.* attack of the conjugate base *IIa* by water or attack of the non-dissociated substrate *II* by hydroxyl ion. Another possible mechanism could be spontaneous decomposition of the tautomeric anion *IIb*. With respect to the acidity difference of the both protons in NH groups it is little likely that the observed hydrolysis could be ascribed to decomposition of the tautomer *IIb* (Eq. (*C*)). The kinetically

II ⇄ $C_6H_5-CO-\overset{(-)}{N}-O-CO-NH-CH_3$ (*IIa*) ⇄ $C_6H_5-CO-NH-O-CO-\overset{(-)}{N}-CH_3$ (*IIb*) (*C*)

equivalent attack of the nondissociated substrate *II* by hydroxyl anion is little likely. If pK_a of the compound *II* is estimated to be about 8 (Fig. 1), then at pH 14 concentration of the non-dissociated substrate is so low (about 10^{-6}) that the rate constant would have to be about 10^2 l mol^{-1} s^{-1}, should it agree with the observed rate constant $k_{obs} = 1{\cdot}5 \cdot 10^{-4}$ mol^{-1} s^{-1}. An acceptable mechanism of the hydrolysis starts from the anion *IIa* which could form an intramolecular hydrogen bond, the negatively charged nitrogen atom catalyzes intramolecularly the decomposition of the anion into products (Eq. (*D*)).



$C_6H_5-CO-\overset{(-)}{N}$ (O, C=O, H–N–CH_3) $\xrightarrow{H_2O}$ $CH_3NH_2 + CO_2 + C_6H_5-CO-\overset{(-)}{N}-OH$ (*D*)

About pH 9 the reaction rate of the compound *II* decreases as the amount of the dissociated substrate decreases, and it is independent of the proton activity in a broad pH region 2 to 8. Towards acidic region the amount of benzohydroxamic acid increases, and at pH 3·8 benzohydroxamic acid is the only product. It is presumed that the non-dissociated substrate reacts both in the spontaneous solvolysis and in the rearrangement. With respect to the presence of acid hydrogens and donor groups (carbonyl, amino) in the molecule it is likely that the substrate is connected by intramolecular hydrogen bond, which facilitates both the hydrolysis process and the rearrangement reaction. The increased intramolecular stabilization of the molecule *II* by hydrogen bonds (as compared with the dimethyl derivative *I*) is manifested in the dependence of the reaction velocity on pH (Table I, Fig. 1). Whereas in the case of the compound *I* the pH region, where the reaction is pH-independent, is relatively narrow (two pH units), for the compound *II* it is extended to six units. It can hardly be presumed that polar effects of a methyl group could cause such a great difference in the behaviour of the both substances. The both substrates differ in their acidity and basicity, the compound *II* being both protonated and deprotonated with greater

difficulty. Intramolecular hydrogen bonds block the basic centres of the molecule, which is manifested by the acid catalysis of the hydrolysis being observable at lower pH than that of the compound *I*. The intramolecular stabilization of the molecule is even more markedly seen in the base-catalyzed reaction of the compound *II*. The base-catalysis is observed first at pH > 8, *i.e.* three pH units higher than in the case of the compound *I*. The given explanation of the different behaviour of the both compounds is also supported by the fact that the rate of the reactions in individual pH regions is practically identical (Table I). The fact that the reaction rate does not change in the pH region 2 to 8, the composition of product being different, can, for present, only be stated.

In acid medium (pH < 2) the reaction rate again increases (the dependence log . . k_{obs} *vs* pH has the slope 1), benzohydroxamic acid being the hydrolysis product. The hydrolysis proceeds as an acid-catalyzed reaction, the attack of the protonated substrate by a water molecule being most probably the rate-limiting step (Fig. 2*d*).

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