KINETICS AND MECHANISM OF ALKALINE HYDROLYSIS OF (*E*)-O-(N-4-NITROPHENYLCARBAMOYL)BENZALDOXIMES IN 30% AQUEOUS ETHANOL*

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Alkaline hydrolysis of (*E*)-O-(N-4-nitrophenylcarbamoyl)benzaldoximes (*I*) gives 4-nitrophenyl carbamate (which is further decomposed to 4-nitroaniline) and (*E*)-benzaldoximates (which are hydrolyzed to benzaldehydes). The hydrolysis of (*E*)-O-(N-methyl-N-4-nitrophenylcarbamoyl)-benzaldoximes (*II*) gives directly N-methyl-4-nitroaniline and (*E*)-benzaldoximates. The hydrolysis velocities have been measured for a series of six compounds type *I* and three compounds type *II* in 30% aqueous ethanol at pH 7 to 14. The compounds *I* are hydrolyzed by ElcB mechanism; the respective rate constants (k_2) of the monomolecular reaction have been determined and compared with pK_a values of the corresponding leaving groups. The value $\beta = -1{\cdot}4$ has been found for the base catalyzed reaction, and the substituent effects have been estimated ($\varrho = 1{\cdot}4$). For the hydrolysis of the compounds type *II* the mechanism BAc2 has been suggested which is characterized by splitting of N–C bond in the decomposing tetrahedral intermediate. In these cases no substituent effects have been observed with respect to the reaction rate k_1.

The reaction of O(N-phenylcarbamoyl)benzaldoximes with aqueous sodium hydroxide was studied by Brady and coworkers[1,2]. Their aim was to find qualitative relations between structure of products and configuration of the starting compounds. It was found that alkaline hydrolysis of (*E*)-O-(N-phenylcarbamoyl)benzaldoxime gives predominantly the salt of benzaldoxime and aniline, whereas the *Z* isomer gives benzonitrile under similar conditions (Eqs (*A*)). Jordan and Hauser[3] found that benzaldoxime is hydrolyzed in alkaline medium very slowly to give finally benzaldehyde.

$$\underset{(E)}{Ar^1NHCO_2N{=}CHAr^2} \xrightarrow{H_2O,NaOH} Ar^1NH_2 + NaO{-}N{=}CHAr^2 \qquad (A)$$

$$\underset{(Z)}{Ar^1NHCO_2N{=}CHAr^2} \xrightarrow{H_2O,NaOH} Ar^1NH_2 + N{\equiv}CAr^2$$

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Our purpose was to find the hydrolysis mechanism of a chosen model of (*E*)-O--(N-4-nitrophenylcarbamoyl)benzaldoxime and its dependence on basicity of the leaving benzaldoximate in 30% aqueous ethanol. The 4-nitro substituent of the substrate was chosen with respect to easy spectrophotometric measurement of the reaction rate. For the sake of determination of the mechanism a series of six 3- or 4-substituted (*E*)-O-(N-4-nitrophenylcarbamoyl)benzaldoximes and three N-methyl derivatives have been studied.

EXPERIMENTAL

Reagents

Substituted (E)-O-(N-4-*nitrophenylcarbamoyl*)*benzaldoximes*: A solution of 0·05 mol 4-nitrophenyl isocyanate in 30 ml benzene was mixed with a solution of 0·05 mol substituted (*E*)-

TABLE I

Melting Points and Elemental Analyses of (*E*)-O-(N-4-Nitrophenylcarbamoyl)benzaldoximes

No Substituent	Formula (m.w.)	M.p., °C	Found/Calculated		
			% C	% H	% N
Ia (1) H	$C_{14}H_{11}N_3O_4$ (285·3)	167—168	58·81 58·94	4·13 3·89	14·50 14·73
Ib (9) 4-OCH_3	$C_{15}H_{13}N_3O_5$ (315·3)	174—175	57·42 57·14	4·17 4·15	13·85 14·05
Ic (8) 4-CH_3	$C_{15}H_{13}N_3O_4$ (299·3)	176—177	60·35 60·21	4·73 4·39	13·97 14·05
Id (3) 3-Cl	$C_{14}H_{10}ClN_3O_4$ (319·7)	164—165	52·60 52·59	3·46 3·15	13·19 13·14
Ie (6) 3-NO_2	$C_{14}H_{10}N_4O_6$ (330·2)	177—178	51·09 50·92	3·43 3·05	16·82 16·97
If (5) 4-NO_2	$C_{14}H_{10}N_4O_6$ (330·2)	182—184	50·65 50·92	3·30 3·05	16·60 16·97
IIa (2) H, N—CH_3	$C_{15}H_{13}N_3O_4$ (299·3)	136·5—137·5	60·29 60·20	4·51 4·39	14·08 14·05
IIb (4) H, 3-Cl, N—CH_3	$C_{15}H_{12}ClN_3O_4$ (334·6)	133—134	53·96 53·85	3·98 3·62	12·64 12·55
IIc (7) 4-NO_2, N—CH_3	$C_{15}H_{12}N_4O_6$ (344·3)	150—151	52·57 52·51	3·36 3·51	15·95 16·27

-benzaldoxime in 50 ml benzene. The mixture was heated to boil for 15 min. After cooling the product was filtered, recrystallized from ethanol, dried, and kept in dessiccator in dark. The yields of (*E*)-O-(N-4-nitrophenylcarbamoyl)benzaldoximes were 82 to 90%. The melting points and elemental analyses are given in Table I.

N-*Methyl*-4-*nitroaniline*: Solution of 15·7 g 4-nitrochlorobenzene in 50 ml dimethyl sulphoxide was mixed with 9 ml methylamine at −50°C. The mixture was heated at 50°C in a sealed ampoule for 48 hours and diluted with excess of water. The precipitated raw product (15·0 g) was recrystallized from ethanol. M.p. 150·5—151·5°C (ref.[4,5] gives 150—151°C).

N-*Methyl*-N-4-*nitrophenylcarbamoyl chloride*: Solution of 12·5 g 4-nitro-N-methylaniline in 50 ml dioxane was added to solution of 20 g phosgene in 50 ml toluene with stirring and cooling at 5°C within 20 min. The mixture was heated with stirring and introduction of phosgene for 1 hour. The solvent mixture was distilled off in vacuum. The precipitated N-methyl-N-4-nitrophenylcarbamoyl chloride (17·2 g; m.p. 100—102°C) was used in the next step without purification.

Substituted (E)-O-(N-*methyl*-N-4-*nitrophenylcarbamoyl*)*benzaldoximes*: Sodium 0·6 g was dissolved in 25 ml ethanol, and solution of 0,025 mol substituted (*E*)-benzaldoxime in 25 ml ethanol was added thereto. Ethanol was distilled off in vacuum and the evaporation residue was decanted with benzene. The suspension of sodium salt of (*E*)-benzaldoxime in 50 ml benzene was treated with solution of 4·4 g (0·025 mol) N-methyl-N-4-nitrophenylcarbamoyl chloride in 50 ml benzene. The mixture was heated to boil for 2 h. After cooling the precipitated sodium chloride was filtered, the benzene solution was washed with 100 ml water, dried with sodium sulphate and concentrated to crystallization. The raw products were crystallized from ethanol, dried and kept as the compounds *I*. The melting points and elemental analyses are given in Table I.

Analytical Methods

Uniformity of composition of the synthetized carbamates of *E* configuration was verified by thin layer chromatography using Silufol plates and chloroform–benzene (1 : 3) eluent system and by comparison with the model carbamates of *Z* configuration (which were prepared by the same way from *Z*-benzaldoximes). The spots were made visible by spraying with solutions of stannous chloride and the Ehrlich reagent.

The hydrolysis products of individual carbamates were analyzed in the following way: About 1 g carbamate (compounds *Ia, Ib, If* — Table I) was shaken with 100 ml 2M sodium hydroxide in 30% aqueous ethanol 10 min. In a sample withdrawn natrium N-4-nitrophenylcarbamate was identified by comparison of UV spectra with those of the standard sample prepared according to ref.[6]. The mixture was heated to boil for 1 h, cooled, and the precipitated substance was filtered, crystallized from ethanol and identified as 4-nitroaniline by spectra and melting points. The filtrate was neutralized and extracted by ether. The ether solution was concentrated chromatographed on Silufol with benzene–ethyl acetate[7] (5 : 1). Solutions of 2,4-dinitrophenylhydrazine and Pinacryptol Yellow were used for detection. In the ether solution were identified (by comparison with the model substances) the benzaldoximes of both *E* and *Z* configuration, their ratio being from 10 : 1 up to 7 : 1, and 4-nitroaniline. The hydrolysis products obtained from the compounds *IIa* and *IIc* were analyzed in the same way. Solution of natrium N-methyl-N-4-nitrophenylcarbamate (as a model substance) was prepared by mixing the dioxane solution of N-methyl-N-4-nitrophenylcarbamoyl chloride with 0·1M sodium hydroxide solution in 30% aqueous ethanol. The used chromatographical method allow to determine the individual components of the mixture with the accuracy of 2%. The hydrolysis of (*E*)-benzaldoximes to benzaldehydes was carried out in 2M sodium hydroxide in 30% aqueous ethanol in a sealed ampoule for 18 h.

Dissociation constants of benzaldoximes were determined spectrophotometrically in 30% aqueous ethanol in buffered media or in potassium hydroxide solutions in the region 280 to 300 nm. Dissociation constants of 4-nitrophenyl carbamates were determined graphically from kinetic dependences log k_{obs} *vs* pH.

Kinetic Measurements

The measurements were carried out in 30% aqueous ethanol using phosphate, borax and carbonate buffers or potassium hydroxide solutions. For the measurement about 10 μl ethanolic solution of the substrate was injected into 5 ml buffer solution in 30% aqueous ethanol. The measurements were carried out at 25 to 75°C. Concentration of the carbamates in the reaction mixtures was (1 to 2) . 10^{-5} mol l^{-1}. At chosen time intervals the reaction was stopped by acidification of the solution with sulphuric acid (pH 5 to 6). At these pH values the hydrolysis is very slow, and the natrium 4-nitrophenylcarbamate formed is quickly decarboxylated to give 4-nitroaniline[6] whose concentration was followed spectrophotometrically in UV region (385 nm for the compounds *Ia* to *If*; 415 nm for hydrolysis of *IIa* to *IIc* — formation of N-methyl-4-nitroaniline). The measurements were carried with a Zeiss VSU-2 spectrophotometer (Jena). Concentration of the hydrolysis products was followed within 6 to 7 reaction half-lives. pH of solutions was determined with the use of a pH-meter 4c (Radiometer, Copenhagen) at 25°C.

RESULTS AND DISCUSSION

Figures 1 and 2 give the dependences of logarithms of rate constants (k_{obs}) on pH values (pH 8 to 14) in 30% aqueous ethanol at 25°C for the series *Ia* to *If* and *IIa* to *IIc*, respectively.

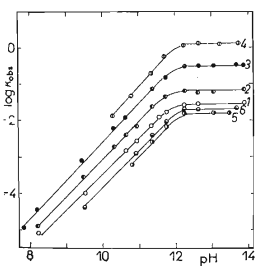


FIG. 1

pH Dependence of Hydrolysis Rate of Substituted (*E*)-O-(N-4-Nitrophenylcarbamoyl)-benzaldoximes in 40% Aqueous Ethanol at 25°C

The rate constant values are given in s^{-1}. *1* Parent substance, *2* 3-Cl, *3* 3-NO_2, *4* 4-NO_2, *5* 4-OCH_3, *6* 4-CH_3.

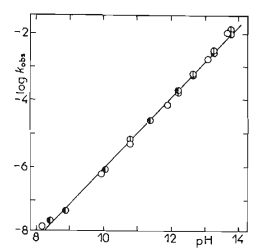
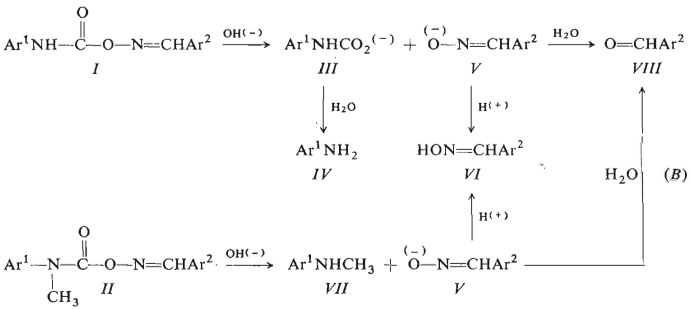


FIG. 2

pH Dependence of Hydrolysis Rate of Substituted (*E*)-O-(N-Methyl-N-4-nitrophenylcarbamoyl)benzaldoximes in 30% Aqueous Ethanol at 25°C

The rate constant value are given in s^{-1}. ○ the parent substance, ◐ 3-Cl, ◑ 4-NO_2.

Kinetic runs were carried out with carbamates of *E* configuration. It was found that isomerization in the carbamate phase does not take place during the hydrolysis. Scheme (*B*) can be suggested for the alkaline hydrolysis on the basis of analysis of the reaction products.



The hydrolysis of the carbamates type *I* involves splitting of O—CO bond, oximate *V* and carbamate *III* being formed. Aldehyde *VIII* was not found among the hydrolysis products; this aldehyde would be formed, if the reaction took place at N=CH bond or if the subsequent oximate hydrolysis were sufficiently rapid. The oximate *V* was stable enough against further hydrolysis (see Experimental), its acidification, however, gave *E* and *Z* isomers of the oxime *VI* (about 10–15% of the latter was found chromatographically); the isomerization does not affect the proper kinetic measurement. If carbamate *I* were subject to the isomerization, nitrile Ar^1CN would be formed as a reaction product[1,2]. Under the chosen experimental conditions nitrile was not found (within the accuracy of the used chromatographical method). Similar hydrolysis takes place with the carbamates of *II* series, too, as it was proved on the basis of analysis of the reaction products.

Hydrolysis of (E) O-(N-4-*Nitrophenylcarbamoyl*)*benzaldoximes* Ia *to* If

From analogy with analogous reactions of alkyl or aryl carbamates[8,9] it can be presumed that the bond O—CO will be split by addition-elimination (BAc2) or elimination-addition (ElcB) mechanism (Scheme (*C*)). We presume that the hydrolysis of the carbamates *Ia* to *If* proceeds by a mechanism characterized by splitting of the conjugate base of the substrate (ElcB). This suggested mechanism is supported by the following experimental findings.

$$\underset{I}{Ar^1NHCO_2N{=}CHAr^2} \xrightarrow[-Ar^2CH=N-O(-)]{k_1(HO(-))} \underset{III}{Ar^1NHCO_2^{(-)}} \xrightarrow{H_2O} \underset{IV}{Ar^1NH_2}$$

$$\begin{array}{ccc} H+ \uparrow\downarrow -H+ & & \uparrow HO(-) \\ \overset{(-)}{Ar^1{-}N{-}CO_2N{=}CHAr^2} & \xrightarrow[-Ar^2CH=N-O(-)]{k_2} & \underset{X}{Ar^1N{=}C{=}O} \\ \underset{IX}{} & & \end{array} \qquad (C)$$

Hydrogen atom at nitrogen is here sufficiently acidic, so that sufficient concentration of the conjugate base is present in the whole pH range investigated (8 to 14). From the break in the dependence $\log k_{obs}$ *vs* pH we can assess the pK_a of the compounds studied to be about 12, being not much affected by the substituents in the aromatic nucleus Ar^2 (Table II). The found value of the reaction constant $\varrho = 1{\cdot}42$ corresponds very well to the value $\varrho = 2{\cdot}9$ found for the hydrolysis of phenyl N-4-nitrophenylcarbamates[8], which is quite acceptable for a hydrolysis characterized by ElcB splitting, if the value of the transmission coefficient $\varepsilon = 0{\cdot}5$ is used for N=CH group (the value of transmission coefficient was calculated by comparison of the reaction constant $\varrho = 2{\cdot}11$ of ionization of phenols[10] with that of benzaldoximes, $\varrho = 1{\cdot}12$; see Table II). From Table II it is obvious that pK_a values of benzaldoximes are practically the same in 30% aqueous ethanol and in water media in contrast to phenols[10] (higher pK_a values in ethanolic media).

TABLE II

Ionization Constants of (*E*)-Benzaldoximes (pK_a^{ox}), (*E*)-O-(N-4-Nitrophenylcarbamoyl)benzaldoximes (pK_a^{carb}) and Rate Constants $\log k_2$ (or $\log k_1$) of Hydrolyses of (*E*)-O-(N-4-nitrophenylcarbamoyl)benzaldoximes in 30% Aqueous Ethanol at 25°C

No[a]	pK_a^{ox}	$(pK_a^{ox})^b$	$\log k_2$ ($\log k_1$)	pK_a^{carb}
Ia	10·80	10·68	−1·574	11·85
Ib	11·02	10·92	−1·827	12·05
Ic	10·83	—	−1·678	11·90
Id	10·50	—	−1·213	11·85
Ie	10·16	10·16	−0·507	11·95
If	9·95	9·97	−0·161	12·00
IIa	10·80	10·68	−1·944	—
IIb	10·50	—	−1·851	—
IIc	9·95	9·97	−1·851	—

[a] For numbers see Table I. [b] The values taken from ref.[12] (water).

The found reaction constant $\varrho = 1{\cdot}42$ obviously differs from that found for hydrolysis of the N-methyl derivatives *II* ($\varrho \approx 0$) where the reaction goes clearly by BAc2 mechanism.

The ElcB mechanism of the hydrolysis of this series of compounds is further supported by comparison of the rate constants log k_2 or those of their N-methyl derivatives *IIa* to *IIc* (log k_1) with the values pK_a^{ox} of the conjugate acid of the leaving group *i.e.* oximes *VI* (Fig. 3). Slope of the dependence log k_1 *vs* pK_a^{ox} ($\varrho = -1{\cdot}4$) reflects the sensitivity of the reaction centre of the conjugate base of (*E*)-O-(N-4-nitrophenylcarbamoyl)benzaldoximes to monomolecular decomposition and is close to the data for hydrolysis of N-phenyl carbamates ($\beta = -1{\cdot}17$, ref.[9]; $\beta = -1{\cdot}36$, ref.[8]). On the contrary, the β value of hydrolysis of (*E*)-O-(N-methyl-N-4-nitrophenylcarbamoyl)benzaldoximes *II* approaches zero (Fig. 3) and does not much differ from the corresponding data for hydrolysis of phenyl N-methyl-N-phenylcarbamates ($\beta = -0{\cdot}23$, ref.[9]; $\beta = -0{\cdot}20$, ref.[8]).

The values σ^- were used for calculation of the reaction constant of hydrolysis of (*E*)-O-(N-4-nitrophenylcarbamoyl)benzaldoximes, which also supports the ElcB mechanism characterized by splitting of C—O bond of the conjugate base in the rate-limiting step (the rate constants obtained at pH 13 were used for the correlation).

Hydrolysis of (*E*)-O-(N-4-*nitrophenylcarbamoyl*)*benzaldoximes* IIa *to* IIc

From Fig. 2 its is obvious that the N-methyl derivatives differ from the carbamates type *I* in their hydrolysis at pH 8 to 14. The dependence has no break, and substituents in Ar[2] have no effect on the hydrolysis rate ($\varrho \approx 0$). The value $\varrho \approx 1$ was found[11] for the hydrolysis of phenyl N,N-dimethylcarbamates, and attack of carbonyl carbon atom by hydroxyl ion was presumed to be rate-limiting. If the same should be true for alkaline hydrolysis of the carbamates *IIa* to *IIc*, too, then the magnitude

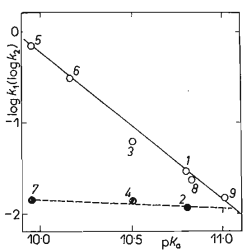
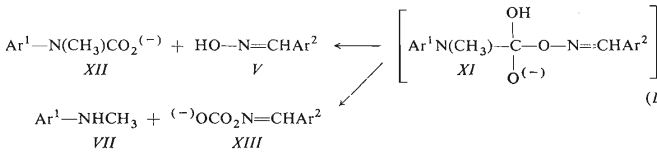


FIG. 3

Dependence of log k_1 (log k_2) on pK_a^{ox} of Leaving Groups in 30% Aqueous Ethanol at 25°C

For numbers see Table I.

of the reaction constant calculated with the use of the transmission coefficient of N=CH group $\varepsilon = 0{\cdot}5$ would have to be at least 0·5. Therefore, it is pressumed that the rate-limiting step consists in decomposition of the tetrahedral intermediate formed by addition of hydroxyl ion to carbonyl carbon atom (Scheme (*D*)). The tetrahedral intermediate (*XI*) can be decomposed into products by two ways (by splitting off of N-methyl-4-nitroaniline (*VII*) or N-methyl N-4-nitrophenylcarbamate



(*D*)

(*XII*)). From the found value $\varrho \approx 0$ it is inferred that the tetrahedral intermediate is decomposed into N-methyl-4-nitroaniline (*VII*) and carbonate (*XIII*) which is further split into oxime (*VI*). In this case the substituent effects from Ar^2 on the formation of the tetrahedral intermediate are compensated by opposite effects of the same substituent on splitting of C—N bond. If the decomposition of the tetrahedral intermediate proceeded according to the second alternative (Scheme (*D*)), then the presumed magnitude of the reaction constant would be greater than 0. (Concordant substituent effects in the first and the second steps of the hydrolytic reaction.) Besides that we could not prove the presence of the carbamate (*XII*) among the reaction products, although (according to analogy with the compounds type *I*) it should be sufficiently stable.

From the study carried out it follows that the ElcB mechanism characterized by decomposition of the conjugate base of substrate is not limited to phenols in the carbamate series[8,9,11], but it operates in the cases of other O-carbamoyl compounds, too.

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