KINETICS AND MECHANISM OF HYDROLYSIS OF ARYL N-METHOXYCARBAMATES AND THEIR DERIVATIVES

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Hydrolysis kinetics have been studied of 3- and 4-substituted phenyl N-methoxycarbamates and their N-methyl derivatives in aqueous buffers at 60°C. The N-methyl derivatives show linear dependence of the rate constants on concentration of hydroxyl ion in the pH range measured. Hydrolysis of aryl N-methoxycarbamates is independent of hydroxyl ion concentration at higher pH values. Logarithms of the rate constants have been correlated with the substituent constants σ. The calculated values 0·9 for N-methyl derivatives, 4·5 and 3·3 for aryl N-methoxy-carbamates in the regions of linear pH-dependency and pH-independency, respectively, suggest that the hydrolysis follows the $B_{Ac}2$ and ElcB mechanisms in the case of the N-methyl derivatives and aryl N-methoxycarbamates, respectively. Difference between the two ϱ constants for the hydrolysis of aryl N-methoxycarbamates agrees with the found value $\varrho = 1\cdot2$ for dissociation constants of these compounds. The elimination mechanism has been confirmed by reaction of the isocyanate formed with added aniline to give the respective urea.

Derivatives of N-alkoxycarbamic acid exhibit insecticidal, fungicidal and acaricidal activity[1]. As these compounds are decomposed by action of water, their application is limited by their stability in nature. So far no data on rates and mechanism of their hydrolysis have been published. In this communication hydrolysis kinetics and mechanism of this type of compounds is studied with phenyl N-methoxycarbamates and their N-methyl derivatives as model compounds.

EXPERIMENTAL

Reagents

O-Methylhydroxylamine was prepared from O-methylhydroxylamine hydrochloride[2] by reaction with solid potassium hydroxide and by rectification of the obtained mixture of O-methyl- and O,N-dimethylhydroxylamines as a fraction boiling at 48·5—49·0°C.

Substituted phenyl N-methoxycarbamates were prepared by addition of solutions of 5 mmol substituted phenyl chloroformate in 5 ml ether to 12 mmol O-methylhydroxylamine in 5 ml ether. After 20 min O-methylhydroxylamine hydrochloride was filtered off, the solvent was evaporated, and the product was distilled in vacuum and recrystallized from heptane. Yield 65—88%. Physical properties and elemental analyses are given in Table I.

Substituted phenyl N-*methoxy*-N-*methylcarbamates*: 10 mmol substituted phenyl chloroformate in 20 ml ether was treated with aqueous solutions of 10 mmol O,N-dimethylhydroxylamine hydrochloride and saturated aqueous solution of 10 mmol potassium carbonate added simultaneously with stirring and cooling at 0—5°C during 15 min. The mixture was left to stand 20 min. where-upon organic layer was separated and dried. The solvent was evaporated and raw product was distilled *in vacuum* and recrystallized from heptane. Yields 70—80%. Physical constants and elemental analyses are given in Table I.

Identification of Hydrolysis Products

Mixture of 3 g phenyl N-methoxycarbamate and 70 ml carbonate buffer (pH 10·8) was heated at 100°C 10 min and then steam distilled 3 h. The distillate was acidified with hydrochloric acid and evaporated *in vacuum*. The evaporation residue was mixed with 2 g powdered potassium hydroxide and gently heated to distil off O-methylhydroxylamine, b.p. 48—49°C, 0·7 g (83%). The alkaline solution after the steam distillation was acidified and extracted with ether. Evaporation of ether gave 1·2 g (72%) phenol, m.p. 35—40°C. The two products were compared with the

TABLE I
Physical constants and elemental analyses of aryl N-methoxycarbamates $X—C_6H_4O—CO—NR—OCH_3$

No	X R	Formula (mol.mass)	B.p., °C/pressure, kPa m.p., °C (n_D^{20})	Calculated/Found		
				% C	% H	% N
I	H CH₃	$C_9H_{11}NO_3$ (181·0)	131—132/2·0 (1·5069)	59·40 59·67	5·75 6·08	7·98 7·73
II	3-Cl CH₃	$C_9H_{10}ClNO_3$ (215·5)	159—162/2·4 (1·5218)	49·68 50·10	4·60 4·65	6·27 6·51
III	4-CH₃ CH₃	$C_{10}H_{13}NO_3$ (195·0)	149—150/2·4 40·0—41·0	61·28 61·52	7·02 6·66	7·32 7·18
IV	4-Cl CH₃	$C_9H_{10}ClNO_3$ (215·5)	130—136/2·3 41·0—42·5	49·79 50·10	4·99 4·65	6·80 6·51
V	H H	$C_8H_9NO_3$ (167·0)	— 54·0—55·0	57·71 57·48	5·20 5·39	8·15 8·38
VI	3-Cl H	$C_8H_8ClNO_3$ (201·5)	— 43·0—44·5	47·51 47·76	4·20 3·98	6·66 6·97
VII	4-CH₃ H	$C_9H_{11}NO_3$ (181·3)	— 92·5—93·5	59·40 59·67	6·20 6·08	7·98 7·73
VIII	4-Cl H	$C_8H_8ClNO_3$ (201·5)	— 83·0—84·0	47·42 47·76	4·11 3·98	6·66 6·97

authentic substances by means of a gas chromatograph Carlo Erba Model GV using 2 m column with Chromosorb A, SE-52.

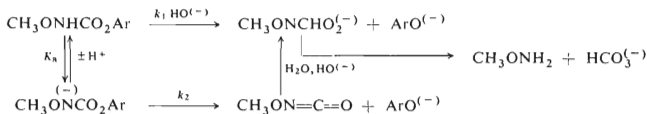## Evidence of Methoxyisocyanate

Solution of 0·25 g 4-chlorophenyl O-methoxycarbamate in 5 ml dioxane was added to 1 ml aniline in 10 ml dioxane, 25 ml borax buffer (pH 8·25), and 25 ml 10% KCl solution with stirring. The solution formed was heated at 100°C 1 h. After cooling the organic products were extracted with 50 ml ether, the extract was washed with 50 ml water, twice with 50 ml 10% sodium carbonate solution, again with water, with 50 ml 2M-HCl and finally with water. Evaporation of ether gave 0·1 g (47%) N-phenyl-N'-methoxyurea, m.p. 117—118·5°C. The sodium carbonate solution from the previous operation was mixed with 25 ml ether and acidified with hydrochloric to acid pH about 2. The organic phase gave 0·05 g (31%) 4-chlorophenol, m.p. 43·0—45·0°C. The two products were compared chromatographically with authentic 4-chlorophenol and N-phenyl--N'-methoxyurea[3].

Hydrolysis Kinetics

The hydrolysis rates of the substituted phenyl N-methoxycarbamates and their N-methyl derivatives were measured at 60°C in borate, carbonate, and phosphate buffers and sodium hydroxide solutions with pH range from 7·5 to 13·7 using spectrophotometry at 285 nm (Zeiss VSU-2, Specord UV VIS, and Unicam SP 800 apparatus). The pH values of the individual buffers were determined with a Radiometer pHM 62 apparatus at 25°C.

RESULTS AND DISCUSSION

The hydrolysis rates of substituted phenyl N-methoxycarbamates and their N-methyl derivatives followed pseudo-first order kinetics in all the cases. pH-Dependences of $\log k_{obs}$ are given in Figs 1 and 2. Two mechanisms can be considered for the hydrolysis of phenyl N-methoxycarbamates (Scheme 1).

$$CH_3ONHCO_2Ar \xrightarrow{\ k_1\ HO^{(-)}\ } CH_3ONCHO_2^{(-)} + ArO^{(-)}$$

$$K_A \updownarrow \pm H^+$$

$$\xrightarrow{\ H_2O,\ HO^{(-)}\ } CH_3ONH_2 + HCO_3^{(-)}$$

$$CH_3ONCO_2Ar \xrightarrow{\ k_2\ } CH_3ON{=}C{=}O + ArO^{(-)}$$

SCHEME 1

The hydrolysis *via* $B_{Ac}2$ mechanism involves direct attack of carbonyl group of the neutral substrate by hydroxyl ion with simultaneous splitting off of phenoxide ion. The ElcB mechanism involves decomposition of conjugated base of the substrate into phenoxide ion and methoxy isocyanate in the rate-limiting step. In subsequent rapid step methoxy isocyanate reacts with water or (at higher pH values) hydroxyl

ion to give carbamate ion. With the N-methyl derivative the $B_{Ac}2$ mechanism is only possible. The both mechanisms involve carbamate ion as the intermediate. Its decarboxylation can be presumed to be acid catalyzed (as it is the case with substituted phenylcarbamates[4]), hence its rate decreases with increasing pH value, and at sufficiently high pH values the carbamate ion is accumulated in the reaction mixture. As absorbances of both methoxycarbamate ion and O-methylhydroxyl-amine are negligible at 278 nm, the decarboxylation rate has no effect on the k_{obs} value.

Three criteria were used for determination of the hydrolysis mechanism: *a*) Comparison of the hydrolysis rate with that of N-methyl derivatives, *b*) substituent effects in phenyl ring on the reaction rate, *c*) determination of the reaction products in the presence of aniline which can trap the little stable intermediate — methoxy isocyanate. The hydrolysis rate of the substituted phenyl N-methoxycarbamates is (at low pH values) faster by $1-2$ orders of magnitude than that of the corresponding N-methyl derivatives. This fact could suggest different mechanisms[5] in the two series of compounds, but the difference could be interpreted as steric or inductive effect of the methyl group. From Scheme 1 Eqs (*1*) and (*2*) can be derived for the two reaction paths:

$$k_{obs} = k_1 \cdot K_v/(K_a + a_H) \tag{1}$$

$$k_{obs} = k_2 \cdot K_a/(K_a + a_H) ; \tag{2}$$

if it is $a_H \ll K_a$, then in the first case it is $k_{obs} = k_1/K_a$, whereas in the second case it is $k_{obs} = k_2$. The K_a, k_1, and k_2 values increase with increasing σ constant of the substituent in benzene ring, but the substituent effect on k_1 is slight. By optimization of parameters the values k_{obs} and Eq. (*2*) were used for calculation of the pK_a and k_2 values (Table II) which were correlated with σ constants. The value 3·3 of the ϱ constant indicates unambiguously the ElcB mechanism. The dependence of log K_a

TABLE II
Dissociation and hydrolysis rate constants of substituted phenyl N-methoxycarbamates

Substituent	pK_a	$k_2 \cdot 10^3$, s^{-1}
H	9·15	0·22
3-Cl	8·60	7·60
4-CH$_3$	9·30	0·30
4-Cl	8·95	1·90

on σ constant has the value $\varrho = 1.2$. Comparison of hydrolysis of phenyl N-methoxy-carbamates with that of phenyl N-methylcarbamates[6], N-phenyl-[7] and N-(4-nitro-phenyl)carbamates[8] shows that methoxy group increases strongly the dissociation constants and decreases even more strongly the k_2 values. N-Methoxycarbamates are much more stable than the above-mentioned compounds, this phenomenon being especially distinct at higher pH values where the hydrolysis rate becomes constant (Fig. 1), whereas in the other cases it increases linearly with increasing
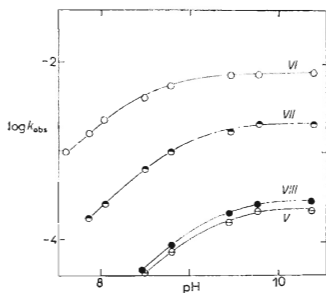

FIG. 1

pH Dependence of log k_{obs} of hydrolysis of substituted phenyl N-methoxycarbamates at 60°C. For numbers of the compounds see Table I

FIG. 2
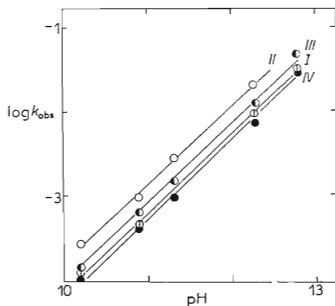
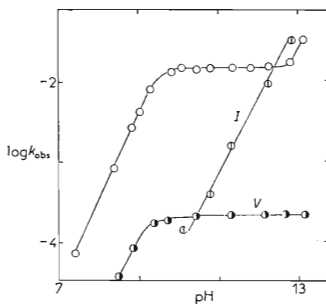pH Dependence of log k_{obs} of hydrolysis of substituted phenyl N-methoxy-N-methyl-carbamates at 60°C

FIG. 3

Comparison of pH dependences of log k_{obs} of hydrolysis of N-methoxycarbamates I and V with that of phenyl N-hydroxycarbamate (○) at 60°C

hydroxyl ion concentration. Their behaviour resembles somewhat that of aryl N-trichloroacetylcarbamates[9] which have about the same acidity and are hydrolyzed at 25°C about ten times faster than N-methoxycarbamates are hydrolyzed at 60°C. The value 3·3 of ϱ constant is higher than that of the other mentioned carbamates, which suggests that the C—O bond splitting is rather advanced in the transition state.

The attempt to trap methoxy isocyanate in the form of N-methoxy-N'-phenylurea by reaction with aniline was carried out at pH 8·25. At lower pH values the hydrolysis is too slow, whereas at high pH values isocyanate reacts preferably with $OH^{(-)}$ ions. Isolation of N-methoxy-N'-phenylurea in the yield 47% presents another support for the ElcB mechanism.

The hydrolysis rates of N-methoxy-N-methylcarbamates increase linearly with increasing $OH^{(-)}$ ion concentration in the whole range investigated (Fig. 2). Slope of the dependence of log k_{obs} on σ constants is 0·7 in accordance with $B_{Ac}2$ mechanism. Dependence of log k_{obs} on pH is given in Fig. 3 for the both non-substituted carbamates and for phenyl N-hydroxycarbamate. The pK_a values of N-hydroxy- and N-methoxycarbamates are comparable, but the hydrolysis rate of N-hydroxycarbamate is higher by almost two orders of magnitude. The increase of k_{obs} at pH 13 is obviously due to elimination of phenoxide ion from the dianion $^{(-)}O—N=$.$(OC_6H_5)O^{(-)}$; the kinetically equivalent reaction of the monoanion with hydroxyl ion cannot be considered, because it is not likely that the rate of this reaction would be comparable with that of N-methoxy-N-methylcarbamate with hydroxyl ion (see Fig. 3).

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