HYDROLYSIS KINETICS AND MECHANISM
OF SOME N-METHYLBISCARBAMATES*

J.ŠTOHANDL and M.VEČEŘA

Organic Chemistry Department,
Institute of Chemical Technology, 532 10 Pardubice

pH Dependence (pH profile) of hydrolysis rate constants of six carbamates having two functional groups —OCONHCH$_3$ on one or two separated aromatic rings has been studied in alkaline region, the first and the second step of the reaction being followed. In acid and neutral region the kinetics have been measured with 1,3-N-methyl-1,3- and 1,4-phenylbiscarbamates. General base catalysis has been followed at pH 6·88. The hydrolysis mechanism is discussed.

In our previous papers[1−3] it was shown that N-alkylcarbamates with a good leaving group (phenolate anion) are hydrolyzed by ElcB mechanism, *i.e.* the conjugated base of carbamate decomposes into products in the rate-determining step. From the kinetical point of view the hydrolysis of biscarbamates is interesting, the substances being important by their ability of cholineesterase inhibition[4]. As the model substances N-methylbiscarbamates from hydroquinone (*I*), resorcinol (*II*) and pyrocatechol (*III*) were chosen. A greater distance of the reaction centres was achieved by using the biscarbamates derived from 2,2-bis(4-hydroxyphenyl)propane (*IV*) and its 3,3′,5,5′-tetrachloro (*V*) and tetrabromo derivatives (*VI*).

The aim of this work was to study the behaviour of the carbamates *I* -- *VI* in hydrolyzing aqueous media, try to separate the respective hydrolysis rate constants to the first and the second degrees, and obtain thus information about the ratio of the both constants with respect to the structure. The problem of general base catalysis was given attention, too.

EXPERIMENTAL

Model Substances

1,4-*Bis*(N-*methylcarbamoyloxy*)*benzene* (I) was prepared by reaction of hydroquinone with 2·4-molar excess of methyl isocyanate in tetrahydrofurane with the catalysis by triethylamine, the yield being almost quantitative. M.p. 187−189°C (benzene–dioxane). For C$_{10}$H$_{12}$N$_2$O$_4$ (224·1) calculated: 53·10% C, 5·31% H, 12·39% N; found: 53·39% C, 5·59% H, 12·51% N.

The structures at the top of the page:

I — 1,4-bis(N-methylcarbamoyloxy)benzene with OCONHCH₃ groups

II — 1,3-bis(N-methylcarbamoyloxy)benzene

III — 1,2-bis(N-methylcarbamoyloxy)benzene

I   *II*   *III*

Structure IV/V/VI:
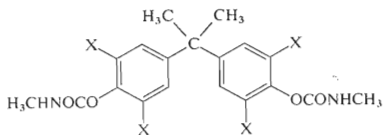
$$H_3C \quad CH_3$$
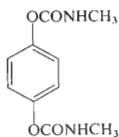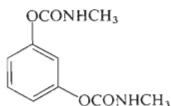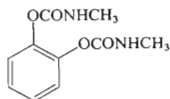
IV, X = H   *V*, X = Cl   *VI*, X = Br

1,3-*Bis*(N-*methylcarbamoyloxy)benzene* (II) was prepared from resorcinol and methyl isocyanate in the same way. The reaction was finisshed after six hours boiling, yield 75%. The product was recrystallized from benzene until constant melting point 154—155°C. For $C_{10}H_{12}N_2O_4$ (224·1) found: 53·79% C, 5·63% H, 12·82% N.

1,2-*Bis*(N-*methylcarbamoyloxy)benzene* (III) was prepared from pyrocatechol and methyl isocyanate by eight hours boiling in tetrahydrofurane, m.p. 142°C (tetrahydrofurane), yield 60%.

Carbamate IV was prepared from commercial Dian (Progil) and methyl isocyanate (1 : 2·2mol) with catalysis by triethanolamine by boiling in toluene for eight hours, yield 50%. M.p. 160—162°C (toluene). For $C_{19}H_{22}N_2O_4$ (342·2) calculated: 69·50% C, 6·93% H, 7·05% N; found: 69·90% C, 6·91% H, 7·32% N.

2,2-*Bis*(3,5-*dichloro*-4-N-*methylcarbamoyloxyphenyl)propane* (V) was prepared in the same way (the required 2,2-bis-(3,5-dichloro-4-hydroxyphenyl)propane was synthetized according to ref.[5]). M.p. 219—220°C (benzene), yield 70%. For $C_{19}H_{18}Cl_4N_2O_4$ (479·8) calculated: 47·50% C, 4·75% H, 29·68% Cl, 5·30% N; found: 47·90% C, 4·41% H, 30·19% Cl, 5·50% N.

Tetrabromo derivative IV was obtained by reaction of 2,2-bis(3,5-dibromo-4-hydroxyphenyl)-propane (Spolek pro chemickou a hutní výrobu, Ústí nad Labem) and methyl isocyanate with catalysis by dibutyltinlaurate (in dioxane), yield 65%. M.p. 180—182°C (benzene). For $C_{19}H_{18}$ . . $Br_4N_2O_4$ (657·6) calculated: 34·65% C, 2·74% H, 48·63% Br, 4·26% N; found: 33·95% C, 2·98% H, 47·90% Br, 4·10% N.

2-(4-*Hydroxyphenyl*)-2-(4′-N-*methylcarbamoyloxyphenyl)propane* was prepared from commercial Dian (Progil) and methyl isocyanate (1 : 0·9 mol) in dioxane by standing overnight. The resulting mixture of the parent phenol, its monomethylcarbamate, and bismethylcarbamate was separated on an alumina column (Voelm, activity V). The chromatographically homogeneous fraction of 2-(4-hydroxyphenyl)-2-(4′-N-methylcarbamoyloxyphenyl)propane was evaporated and recrystallized from benzene. M.p. 125—127°C. For $C_{17}H_{19}NO_3$ (285·1) calculated: 4·91% N; found: 5·18% N.

Kinetic Measurements

The measurements were carried out at 25°C at the ionic strength 0·04 in the medium of 5% aqueous dioxane using a Specord UV VIS and a Unicam SP 800 spectrophotometers. A cell with 1·9 ml buffer was placed in the tempered cell compartment of the apparatus, and, after 5 minutes, 0·1 ml stock solution of the carbamate in dioxane was added. The resulting concentration of the substrate was within $9 . 10^{-5}$ to $1 . 10^{-5}$ mol/l. In neutral region, where the half lives are several hours, the kinetics was measured discontinuously with a VSU 2 spectrophotometer. In strongly alkaline medium the half lives are below 20 s, and the kinetics was measured by the stopped-flow method using a Durrum Gibson apparatus. 0·03 ml 0·1M-NaHSO$_3$ was added in the cell to prevent oxidation of the reaction products of the compounds $I-III$ in alkaline medium (formation of quinones).

At the wavelength 292 nm it is possible to follow both the rapid hydrolysis of the carbamates $I-III$ to the first degree and the hydrolysis to the second degree in alkaline medium which is slower by about two orders of magnitude. Separation of the rate constants to the second degree was carried out with sufficient accuracy for the carbamates $I-III$ where 4- or 3- or 2-hydroxyphenyl-N-methylcarbamate is formed and further completely hydrolyzed. The hydrolysis to the second degree was measured at pH above 10 when the intermediate is almost completely ionized. Under these conditions the both combined reaction constants $k_{obs,1}$ and $k_{obs,2}$ were obtained (Scheme 1). From the measurements it follows that the ratio $k_{obs,1}^I / k_{obs,2}^I$ equals $1·45 . 10^2$, so that the calculation from the kinetic relation of the subsequent reaction need not be done. The same accuracy of results was achieved by evaluation of the reaction rate constant of the first step from the time dependence of the first half life of the first reaction, and the rate constant of the second step was obtained from the second half life of the second reaction when the conversion of the first step is minimum 99%. In this way the rate constants of the second step were evaluated in the pH region 10 to 14.

Separation of the rate constants of the carbamates $IV-VI$ was carried out by means of the optimization program Bard[6] for non-linear regression using the computer EC 1040. However, it turned out that the spectral change of the absorbance in the first step is 10 to 20 times greater than that of the hydrolysis of the intermediate to the second degree to bisfenol, *i.e.* the experimental values of the second step are within experimental error of those of the first step. Accuracy of this iterative method is not sufficient, and the evaluations cannot be done simultaneously in this case. Therefore, the hydrolysis intermediate of the carbamate *IV*, *i.e.* 2--(4-hydroxyphenyl)-2-(4'-N-methylcarbamoyloxyphenyl)propane, was prepared, too, and its separate hydrolysis (using the more sensitive spectrophotometer VSU 2) gave the kinetic picture of the second reaction step. In the neutral region the measurements were carried out at 60 and 90°C and the constants found were extrapolated to 25°C according to the Arrhenius relation.

## RESULTS AND DISCUSSION

Alkaline Hydrolysis

The alkaline hydrolysis mechanism will be discussed in terms of Scheme 1 representing the reaction course which involves rapid reversible dissociation equilibria to the first and the second degrees and further decomposition of the conjugated bases to phenolate ion and methyl isocyanate, the latter being in alkaline medium rapidly hydrolyzed to methylamine and carbon dioxide[7]. The dianion is supposed
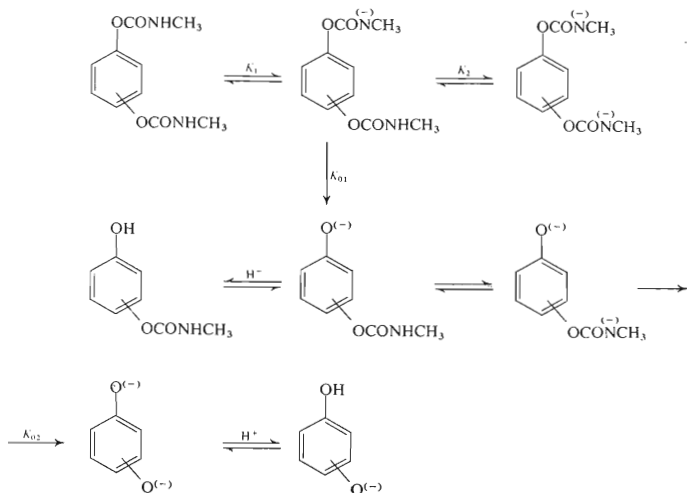
SCHEME 1

FIG. 1

Dependence of Logarithm of the Observed Hydrolysis Rate Constant on pH for Carbamates *I—III* at 25°C

The data for the carbamates *I* and *II* in neutral region were obtained by extrapolation of the measurements carried out at 60 and 90°C according to the Arrhenius relation. Meaning of the points: *3 — I, 2 — II, 1 — III* to the first degree; *6 — I, 5 — II, 4 — III* to the second degree.
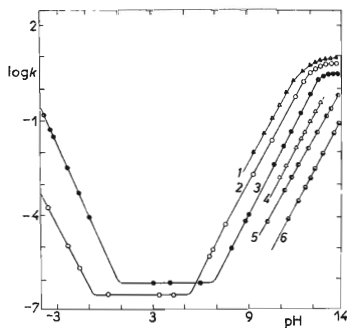
to be present in slight concentration only, so that the reaction path involving it is not considered. In the case of carbamates $I-III$ it was possible to measure the solvolysis rate in strongly alkaline region, where the rate is pH-independent confirming thus the ElcB mechanism (*cf.* ref.[2]). The measurement enabled also an estimate of the equilibrium constant K_1 and a calculation of the constant of spontaneous solvolysis (k_{01}) of the anion from the combined rate constants $k_{obs,1}^{I,II}$ (Table I).

Fig. 1 and Table II give the experimental results for the carbamates $I-III$ and $IV-VI$, respectively. In alkaline region (about pH $6-13$) the hydrolysis of the carbamates I and II is 1. order in OH^-. In this region the *m*-isomer II is hydrolyzed faster than the *p*-isomer I by about one order of magnitude (Fig. 1). It can be presumed that polar effects of methylcarbamoyl group are practically the same as those of acetoxy group, *i.e.* $\sigma_m = 0.39$, $\varkappa_p = 0.31$ (ref.[8]). Their influence on the acid–base equilibrium (dissociation of the substrate to the first degree) is almost the same from *meta* and *para* positions. The small difference in the estimated equilibrium constants ($pK^I = 13.30$, $pK^{II} = 13.65$; Table I) along with the reaction constant of hydrolysis of methylcarbamates ($\varrho = 2.80$; ref.[9]) cannot explain the hydrolysis rate difference of one order of magnitude. We suggest that the faster hydrolysis of *m*-isomer is due to phenolate ion of the carbamate II being a better leaving group than that of the carbamate I ($+M$ effect of p-OCONHCH$_3$ group).

In neutral region the carbamates I and II exhibit a plateau in their pH profiles within pH 1 to 6·5 and 1·5 to 5, respectively. As the rate constants were extrapolated to 25°C, the experimental measurements being carried out at 60 and 90°C, the difference in the rate constants of spontaneous solvolysis cannot be discussed with respect to lower accuracy of the mentioned method.

The same explanation as in the above case can be used also for the difference in hydrolysis rates of the carbamates I and II to the second degree which is constant in the pH region 9 to 14, the ratio $k_2^{II}/k_2^{I} = 9$. As in the given pH region hydroxyl group is ionized, it is presumed that in this case $-O^-$ group exhibits $+M$ effect from *para* position, making thus the leaving of dianion more difficult. Ratio of the

Table I

Ionization Constants K_1 of the first Step and Constants of Spontaneous Solvolysis of Monoanions for Carbamates $I-III$

Carbamate	pK_1	k_{01}, s^{-1}
I	13.30 ± 0.02	2.07 ± 0.02
II	13.65 ± 0.02	4.60 ± 0.05
III	12.99 ± 0.02	8.09 ± 0.06

first and the second step rate constants is the same for I and II isomers $(1.45 \cdot 10^2)$ and equals 72·5 after statistical correction (attack of a bifunctional substrate by OH^- ion[10]). It means that the difference in the substituent constants of $—OCONHCH_3$ and $—O^-$ groups is the same in *meta* and in *para* positions $(\sigma_{m-OCONHCH_3} - \sigma_{m-O^-} = \sigma_{p-OCONHCH_3} - \sigma_{p-O^-})$.

In acid medium the hydrolysis of the carbamates I and II is acid-catalyzed. The dependence $\log k_{obs}$ vs H_R function is linear with the slope 1. If H_0 function is used for this dependence (which we do not give), the curve obtained is analogous to that found[1,2] for the acid-catalyzed hydrolysis of m- and p-substituted phenylcarbamates (maximum about H_0 -5 corresponding to solvation change of the activated complex due to H_2O activity decrease). From Fig. 1 it is obvious that the reactivity order in the acid medium is reversed with respect to that in alkaline region. We presume p-isomer to be more basic $(+M$ effect of $—OCONHCH_3^-$ group). *I.e.* at a given proton activity concentration of the protonated substrate I in the reaction mixture is greater. The relatively great difference in reactivities of the both isomers (about 2·5 orders of magnitude) is obviously due to the sum of the polar substituent effects in the two reaction steps. We presume that, besides the protonation of the substrate, in the case of the carbamate I there is a relatively greater concentration of the tautomer of the protonated tetrahedral intermediate the decomposition of which is rate limiting.

Hydrolysis of carbamate III. Dependence of the hydrolysis rate on pH was investigated in the pH region 7·60 to 14·20 where the reaction can be followed spectroscopically. The dependence $\log k_{obs,1}^{III}$ vs pH is linear, the slope being unity. The corresponding velocity is, however, about 8 times higher than that of the carbamate II. This led to a supposition that the hydrolysis rate increase is due to interaction of two

TABLE II

Rate Constants of Hydrolysis (in s^{-1}) to the First Degree for Carbamates $IV—VI$ at Various pH (carbamate concentrations $1 \cdot 10^{-5}M$)

IV		V		VI	
pH	$k_{obs} \cdot 10^2$	pH	$k_{obs} \cdot 10^3$	pH	$k_{obs} \cdot 10^3$
12·69	6·93	8·60	3·50	8·60	3·30
13·07	12·5	9·70	34·7	9·70	30·8
13·41	21·6	10·80	528	10·80	248
14·02	110	13·99	1 370	13·00	1 200
14·20	106	14·20	1 440	13·99	1 540

neighbouring groups $OCONHCH_3$ by means of hydrogen bonds (*ortho*-effect). We also verified that the two groups did not undergo ring closure − elemental analysis confirmed unambiguously the structure *III*. At pH close to 14 it is possible to measure the hydrolysis rate in the second step. The ratio $k_{obs,1}^{III}/k_{obs,2}^{III} = 113$ gave the value 56·6 after statistical correction (interaction of OH^- with two groups)[10], which is similar to that of the carbamates *I* and *II*. The rate constant $k_{obs,2}^{III}$ of the separate second step is three times higher than the value $k_{obs,2}^{II}$ of the derivative *II*.

General Base Catalysis

Dependence of the reaction rate of the compound *I* on concentration of phosphate buffer was followed in neutral region at pH 6·88, the constant ionic strength being maintained by addition of 1M-KCl. However, no marked dependence of $\log k_{obs}$ on buffer concentration was found, as it was the case in the work[7]. The measured deviations $\pm 5\%$ (in the buffer concentration range 0·1 to 0·9 mol/l) are insignificant.

Hydrolysis of biscarbamates IV − VI. In these systems mutual interactions of the both N-methylcarbamoyl groups are strongly restricted as a consequence of separation by two rings and one more C atom. In hydrolysis the both groups can be considered almost equivalent. Here the graphical separation of the first and the second step rate constants is impossible, since the both velocities are very close. It was possible to follow the kinetic dependence of hydrolysis of the carbamates *IV − VI* to the intermediate (the first step) (Table II) and that of the separately prepared intermediate, 2-(4-hydroxyphenyl)-2-(4′-N-methylcarbamoyloxyphenyl)propane, to 2,2′-bis(4-hydroxyphenyl)propane:

pH	10·20	10·80	12·00	12·20	13·00	13·41	13·71
$k_{obs,2}^{IV} \cdot 10^4 (s^{-1})$	0·651	2·56	42·0	57·6	462	780	2 070

Dependence $\log (E - E_\infty)$ vs time t is linear up to more than three half-lives and agrees with the course of a pseudomonomolecular reaction. The same results were obtained by measurements at several chosen wavelengths.

Dependence $\log k_{obs,1}$ vs pH is linear in alkaline region, the reaction being 1. order in OH^-. At pH above 14 the rate does not increase, see discussion of the mechanism ElcB. Table II gives the $k_{obs,1}$ values of the carbamates *IV − VI* at various pH. Dependence $\log k_{obs,2}$ (the second step) vs pH is also linear, indicating the 1. order in OH^-. The ratio $k_{obs,1}^{IV}/k_{obs,2}^{IV}$ is 2·7; introduction[10] of the statistical correction 0·5 gives the ratio 1·35, which indicates a small change between the influence of $p\text{-}CH_3NHCOOC_6H_4C(CH_3)_2$ group and that of $p\text{-}O^-C_6H_4C(CH_3)_2$ group, considering $\varrho = 2·80$ for alkaline hydrolysis of N-methylcarbamates[9].

REFERENCES

1. Vontor T., Večeřa M.: This Journal *38*, 3139 (1973).
2. Vontor T., Socha J., Večeřa M.: This Journal *37*, 2183 (1972).
3. Vontor T., Drobilič J., Socha J., Večeřa M.: This Journal *39*, 281 (1974).
4. Woss G.: Anz. Schaedlings *40*, 5/73 (1967).
5. Hurdis E. G., Petras J. F.: U.S. 2,902.518; Chem. Abstr. *54*, 8732 (1960).
6. Bard Y.: *A Function Maximization Method with Application to Parameter Estimation.* Scientific Center Report 322.0902 IBM, New York (May) 1967.
7. Bender M. L.: Homer R. B.: J. Org. Chem. *30*, 3875 (1965).
8. Ritchie C. D., Sager W. F. in the book: *Progress in Physical Organic Chemistry* (S. G. Cohen, A. Streitwieser, R. V. Taft, Eds). Wiley, New York 1964.
9. Vontor T., Večeřa M.: This Journal *38*, 516 (1973).
10. Charton M.: Chem. Tech. (Leipzig) *5*, 245 (1975).

Translated by J. Panchartek.