

KINETICS AND MECHANISM OF HYDROLYSIS  
OF SUBSTITUTED PHENYL CARBAMATES

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The hydrolysis rate constants of *m*- and *p*-substituted phenyl N-methylcarbamates have been determined in the pH and  $-H_0$  ranges 0–13 and 0–4 respectively. The Hammett reaction constant ( $\rho$  2.8) found in alkaline region supports the splitting mechanism suggested. The reaction mechanism changes in neutral medium. A mechanism of spontaneous hydrolysis of carbamates have been suggested explaining the break in the Hammett dependence. General catalysis and influence of ionic strength of medium have been determined, the latter having an opposite direction. In acid medium the hydrolysis rate of carbamates increases, reaches a maximum in the range of  $H_0$  –0.5 to –2.5, and again decreases on further increasing sulphuric acid concentration.

In order to gather further knowledge about the hydrolysis mechanism of carbamates<sup>1</sup>, we followed in this work the hydrolysis kinetics of eleven substituted phenyl N-methylcarbamates I–XI. Such substituents were chosen to cover as broad region of the Hammett  $\sigma$  constants as possible and to enable a decision as to whether there is any conjugation with the reaction centre in the activated complex. The aqueous reaction medium and acidity ranges of pH 0–13 and  $-H_0$  0–4 were chosen so that it might be possible to link on the results of the preceding study.

## EXPERIMENTAL

*Reagents.* The carbamates used were prepared by mixing a solution of 0.05 mol of the respective substituted phenol in minimum amount of tetrahydrofuran with a solution of 0.06 mol methyl isocyanate in 20 ml tetrahydrofuran and 1 ml triethylamine (catalyst). After several days standing at the room temperature the crystals of the product separated and were collected by suction. If not, the product was precipitated by addition of light petroleum. The products were purified by crystallization from tetrachloromethane. The following substituted phenyl N-methylcarbamates were prepared: 4-OCH<sub>3</sub> (I) (m.p. 94–96°C, calculated/found % C 59.65; 59.51, % H 6.12, 6.21, % N 7.73; 7.55), 4-CH<sub>3</sub> (II), 3-CH<sub>3</sub> (III), H (IV), 4-Cl (V), 3-Cl (VI), 3-NO<sub>2</sub> (VII), 4-COCH<sub>3</sub> (VIII) (m.p. 111–112°C, calculated/found % C 62.16; 62.24, % H 5.74; 5.71, % N 7.25; 7.33), 4-CN (IX) (m.p. 118–120°C, calculated/found % C 61.36; 61.43, % H 4.58; 4.66, % N 15.90; 15.98), 4-SO<sub>2</sub>CH<sub>3</sub> (X) (m.p. 109–110°C, calculated/found % C 47.16; 47.23, % H 4.80; 4.78, % N 6.11; 6.08), 4-NO<sub>2</sub> (XI). The melting points of all the known carbamates agreed with those of ref.<sup>2</sup>.

*Kinetic measurements* were carried out in the same way as in our previous work<sup>1</sup>.

## RESULTS AND DISCUSSION

All the hydrolysis kinetics of the carbamates *I–XI* (Fig. 1) were measured in acid and alkaline media under the conditions of pseudomonomolecular course. Fig. 1 gives the pH profile of the hydrolyses of all the 11 carbamates and includes the acidity region expressed by  $H_0$  scale, too. The hydrolysis kinetics can be described by Eq. (1) where  $k_0$ ,  $k_{OH}$ ,  $k_H$ ,  $k_{BH}$  and  $k_B$  are the rate constants of non-catalyzed,  $OH^-$ -catalyzed, proton-catalyzed, nonlyate acids and bases catalyzed hydrolysis, respectively.

$$k_{obs} = k_0 + k_{OH}K_w/a_H + k_H a_H + k_{BH}a_{BH} + k_B a_B \quad (1)$$

*Hydrolysis in Alkaline Medium*

The values  $k_{OH}$   $2.3 \cdot 10^2$  and  $7.6 \cdot 10^5$   $l \text{ mol}^{-1} \text{ s}^{-1}$  of the hydrolyses (at  $120^\circ\text{C}$ ) of the carbamates *II* and *XI*, respectively, were estimated from the slope of the dependence  $k_{obs}$  vs  $k_w/a_H$ , the last three terms of Eq. (1) being neglected; an acid catalysis can be excluded in the given pH region, and general base catalysis was not found experimentally. With respect to the lower accuracy of extrapolation of the dependence  $k_{obs}$  vs  $K_w/a_H$  the estimate was not carried out for further carbamates so far.

The hydrolysis of carbamates *I–XI* in alkaline region can be expressed schematically by Eq. (A). As the acid–base equilibrium is established very quickly, the reaction rate can be expressed by Eq. (2), where  $K$  gives the position of the equilibrium between the respective carbamate and its conjugate base. The determined values  $k_{OH}$  of hydrolysis of the carbamates *II* and *XI* represent thus a product  $Kk_2$ . The dissociation equilibrium constant is not accessible by direct measurement and, with

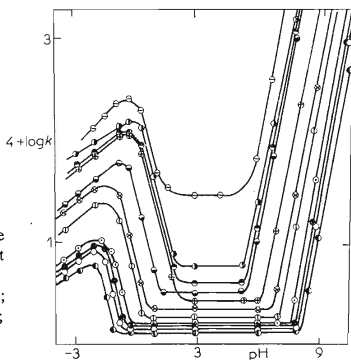
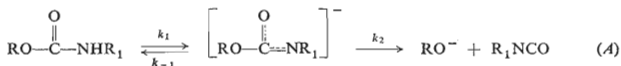


FIG. 1

Dependence of Logarithm of Hydrolysis Rate Constants of Carbamates *I–XI* on pH at  $120^\circ\text{C}$

Compound *I* ●; *II* ○; *III* ●; *IV* ⊙;  
*V* ⊕; *VI* ⊗; *VII* ⊙; *VIII* ⊕; *IX* ⊙; *X* ⊙;  
*XI* ⊙.

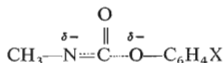


$$v = k_2 K [\text{carbamate}] [\text{OH}^-] \quad (2)$$

respect to the reaction velocity, the experimental values of the rate constants can be determined only in the pH regions differing from the estimated p*K* value by more than 5 units.

Fig. 2 gives the dependence of  $k_{\text{obs}}$  on  $\sigma^-$  at pH 8.2. The reaction constant  $\rho_{\text{obs}}$  equals to the sum  $\rho_1 + \rho_2$ , where  $\rho_1$  reflects the influence of substituents on the splitting of carbamate anions. The value  $\rho_{\text{obs}}$  found for the alkaline hydrolysis of the carbamates I–XI in aqueous medium is 2.8. As the proton is split off from the third atom (counting from the carbon one of the benzene nucleus) we can estimate  $\rho_1$  0.5 for this dissociation according to analogy with the dissociation of similar models (e.g. phenylacetic acids, 0.489, ref.<sup>3</sup>). The reaction constant of the proper splitting is then  $\rho_2 = 2.8 - 0.5 = 2.3$ .

The Hammett correlation is very good when using the exalted values of substituent constants  $\sigma^-$ . Therefrom it follows that the C–O bond is strongly split in the activated complex:



The reaction constant  $\rho = 2.8$  found by us is higher than that of hydrolysis of carboxylic esters (e.g. in 60% acetone  $\rho$  1.05 for hydrolysis of substituted phenyl benzoates going *via* tetrahedral intermediate). From our results it follows that the reaction centre is more sensitive to substituent effects, if the leaving group is split off from an anion formed by ionization at the nitrogen atom next to carbonyl group (mechanism  $E_1\text{cB}$ , ref.<sup>4,5</sup>) than in a hydrolysis going by usual mechanism *via* tetrahedral intermediate.

#### Hydrolysis in Neutral Medium

Hydrolysis of the carbamates I–XI at 120°C is independent of hydroxyl ion resp. proton concentrations in a wide range of pH and  $H_0$  functions (Fig. 1). The  $k$ 's involve besides the terms of spontaneous solvolysis by water an eventual contribution of general base resp. acid catalysis. In the case of the carbamates V and XI we could not find any general base catalysis by usual method of changing buffer concentration at a constant pH and ionic strength 0.1. However, when studying the influence of ionic strength using sodium chloride, sulphate and perchlorate we found a salt effect: the reaction rate markedly dropped with increasing electrolyte

concentration in all cases (Table I). From this phenomenon we conclude that the presence of salts during spontaneous solvolysis results in immobilization of water molecules. This influence is most pronounced in the presence of  $\text{NaClO}_4$ . Therefore, it is not excluded that the special effect of salts makes itself felt even during the testing of the reaction with respect to general base catalysis, and it masks the effect of ions in the sense of general base catalysis.

If we suppose that the bivalent anion  $\text{HPO}_4^{2-}$  forming the main part of the buffer used in the pH range studied behaves analogously to  $\text{SO}_4^{2-}$ , we may try to eliminate the salt effect by using phosphate buffers. We increased the buffer concentration without adjusting ionic strength and corrected the rate constants found to zero ionic strength. A graphical estimate of  $k_0$  and  $k_B$  was carried out for the carbamate II ( $k_0 = 1 \cdot 10^{-6} \text{ mol}^{-1} \text{ s}^{-1}$ ;  $k_B = 7 \cdot 10^{-1} \text{ s}^{-1}$ ).

In Fig. 2 there are the values of  $\log k$  of the spontaneous solvolysis (not corrected with respect to eventual contribution of general catalysis) plotted against the substituent constants  $\sigma$ . It is obvious that there is a sharp break in the dependence. Whereas in the region of low sensitivity of the reaction centre towards the substituent effects ( $\rho$  0.36) the normal  $\sigma$  constants comply with the correlation, the carbamates carrying the substituents capable of conjugation with the reaction centre are almost 8 times more sensitive towards the substituent effects ( $\rho$  3.04) and the correlation is well fulfilled with the  $\sigma$ -values. From the dependence it follows that a change of mechanism of spontaneous solvolysis occurs in the series studied. In order that we might better characterize the both reaction mechanisms in the series studied, we have followed the activation parameters (Table II), influence of the polarity of medium (ionic strength, solvolysis in mixtures water-ethanol; Table I), and kinetic isotopic effect (Table III). The  $E_a$  values (Table II) increase regularly from the 4-nitro derivative up to the 4-methoxy derivative, and there is a marked difference of the entropic

TABLE I

Influence of Salts and Ethanol on Hydrolysis Rates of Carbamates *V* and *XI* at pH 2.94 and Temperatures 120° and 70°C, respectively

Carbamate	$\text{NaClO}_4$ mol/l	$k \cdot 10^4$ $\text{s}^{-1}$	$\text{NaCl}$ mol/l	$k \cdot 10^4$ $\text{s}^{-1}$	% EtOH	$k \cdot 10^4$ $\text{s}^{-1}$
<i>XI</i>	1.0	2.39	1.0	2.09	10.0	4.88
	3.0	1.67	2.0	1.75	20.0	3.41
	6.0	0.599	4.0	1.03	30.0	1.68
<i>V</i>	1.0	2.76	1.0	1.60	10.0	2.20
	3.0	2.06	2.0	1.50	20.0	1.95
	6.0	1.04	4.0	1.30	30.0	1.50

TABLE II  
Activation Parameters of Hydrolysis of Carbamates  $RC_6H_4OC(O)NHCH_3$

R	$E_a$ , kcal mol <sup>-1</sup>	$\Delta S$ , e.u.	$k^a$ , s <sup>-1</sup>
4-NO <sub>2</sub>	15.21	-37.93	$3.22 \cdot 10^{-6,b}$
4-SO <sub>2</sub> CH <sub>3</sub>	16.18	-34.28	$4.02 \cdot 10^{-5,c}$
4-CN	17.24	-32.25	$2.36 \cdot 10^{-5,c}$
4-COCH <sub>3</sub>	19.01	-27.56	$1.86 \cdot 10^{-5,c}$
3-NO <sub>2</sub>	22.14	-22.18	$3.36 \cdot 10^{-5,c}$
3-Cl	23.01	-20.04	$2.19 \cdot 10^{-4}$
4-Cl	25.18	-14.97	$1.84 \cdot 10^{-4}$
H	27.01	-10.55	$1.59 \cdot 10^{-4}$
3-CH <sub>3</sub>	28.14	- 5.88	$1.53 \cdot 10^{-4}$
4-CH <sub>3</sub>	29.04	- 0.99	$1.41 \cdot 10^{-4}$
4-OCH <sub>3</sub>	31.00	- 0.22	$1.29 \cdot 10^{-4}$

<sup>a</sup> pH 2.94; 120°C; <sup>b</sup> 40°C; <sup>c</sup> 70°C.

TABLE III  
Kinetic Isotopic Effect in Hydrolysis of Carbamates  
t 70°C, pH 3.43, pD 3.42.

R	$k_D$ , s <sup>-1</sup>	$k_H$ , s <sup>-1</sup>	$k_D/k_H$
4-Cl	$2.397 \cdot 10^{-7}$	$1.038 \cdot 10^{-6}$	0.283
H	$2.560 \cdot 10^{-7}$	$8.859 \cdot 10^{-7}$	0.289
4-NO <sub>2</sub>	$3.606 \cdot 10^{-5}$	$2.520 \cdot 10^{-5}$	1.431
4-CN	$3.277 \cdot 10^{-5}$	$2.359 \cdot 10^{-5}$	1.389

factor between the both series. From the results we conclude that the spontaneous solvolysis of carbamates having substituents capable of conjugation with the reaction centre (VIII–XI) is more exacting as to the sterical arrangement of the activated complex. Accordingly, the *p*-nitro derivative XI is more sensitive to the change of ionic strength of the medium (immobilization of water molecules) than the *p*-chloro derivative. The same trend can be observed with the abovementioned carbamates when lowering the water concentration in water–ethanol mixtures (Table I). The both compounds differ markedly in their behaviour in D<sub>2</sub>O, too (Table III). Kinetic isotopic effect  $k_D/k_H = 1.4$  was found for the solvolysis of the carbamate XI and about the same value for the carbamate X. The carbamates IV and V have, however, a reverse kinetic isotopic effect  $k_D/k_H = 0.29$ .

From the results given we conclude that, in the case of the carbamates *VIII–XI* having the reaction centre more sensitive to substituent effects ( $\rho = 3.04$ ), the C—O bond is split in the rate-determining step of their spontaneous hydrolysis. In the case of the carbamates *I–VI*, which have lower value of the reaction constant ( $\rho = 0.36$ ) and behave as esters as far as the kinetic isotopic effects is concerned<sup>4,6</sup>, we consider a hydrolysis through the tetrahedral intermediate.

In accord with experimental data we could suggest the cyclic activated complex *XII*, which is noted for an advanced splitting of the C—O bond and splitting of N—H bond, for the spontaneous solvolysis of the carbamates *VIII–XI*. In contrast to this it seems that, during the spontaneous solvolysis of the carbamates *I–VII*, the bond between water molecules and the carbonyl carbon atom is partially formed in the activated complex, a participation of further water molecules eventually bases present (*B* can also be water) in the reaction being not excluded (*XIII*).

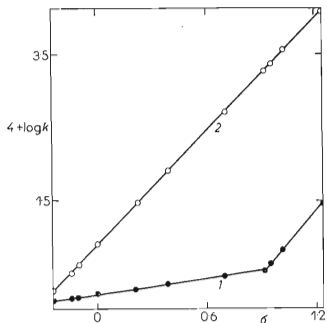
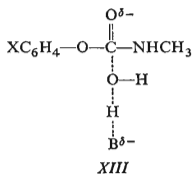
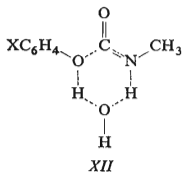


FIG. 2  
Hammett Correlation of Solvolysis of Carbamates *I–XI* at pH 4 and 8 (Curves 1 and 2 respectively)

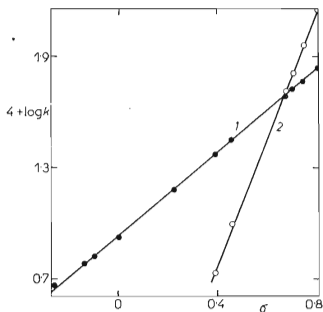


FIG. 3  
Hammett Correlation of Solvolysis of Carbamates *I–XI* at pH 0.5 (Curve 1) and at  $H_0 - 3.0$  (Curve 2)

*Hydrolysis in Strongly Acid Medium*

From the pH profile of hydrolysis of the carbamates I—XI it follows that the reaction rate steeply increases and, after reaching the maximum, it slowly decreases. The maximum of the hydrolysis rate increases with increasing electronegativity of the substituent and shifts towards less acidic medium. In Fig. 3 there are the hydrolysis rate constants\* (water medium, pH 0.5) plotted against the substituent constants  $\sigma$ . It is obvious that the reaction centre is highly sensitive to the substitution influence ( $\rho$  3.3). The substituent effects in carbamate hydrolysis have not yet been studied in acid region, for comparison there are available the values of substituted phenyl acetates ( $\rho = -0.2$  in 60% acetone<sup>3</sup>). We ascribe the enhanced sensitivity of the reaction centre of carbamates towards the substituent effects to the C—O bond being greatly split in the activated complex of the rate-determining step. The value  $\rho_{\text{obs}}$  is composed of  $\rho_1$  of the acid base equilibrium between the protonated and non-protonated substrate,  $\rho_2$  of the attack of the carbonyl carbon atom of the protonated substrate by the nucleophile, *i.e.* water, and  $\rho_3$  of splitting of the tetrahedral intermediate. Electronegative substituents shift the protonation equilibrium in behalf of the non-protonated form (negative  $\rho_1$ ), but they facilitate the attack of the protonated substrate by nucleophile as well as the splitting of the tetrahedral intermediate (positive  $\rho_2$  and  $\rho_3$ ).

The sensitivity of the reaction centre towards the substituent effects gradually decreases in media of higher values of  $-H_0$  function. The  $\rho$  constant drops to 1.1 at  $H_0 - 3.0$ , the normal substituent constants  $\sigma$  being satisfactory for the correlation. We suppose that a change of the reaction mechanism can occur in the region of low activity of nucleophile (water). The attack of the protonated substrate by water becomes the rate-determining step. Our results cannot decide whether the reaction goes through a tetrahedral intermediate or by a direct nucleophilic substitution<sup>1,7</sup>.

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\* The values  $k_{\text{obs}}$  not corrected with respect to eventual spontaneous solvolysis were used for the correlation. This solvolysis is not significant at the pH chosen.