

CARBAMATES. IV.*

KINETICS AND MECHANISM OF HYDROLYSIS OF SUBSTITUTED PHENYL N-METHYLCARBAMATES IN STRONGLY ALKALINE AND ACID MEDIA

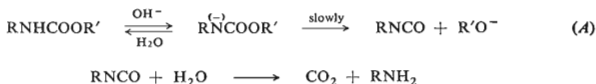
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Dependence of hydrolysis rate constants of carbamates IX–XI on pH has been determined in alkaline medium. The acid–base equilibrium constants have been determined from kinetic data, and the decomposition rate constant of the anion into products has been computed. The reaction intermediate, methyl isocyanate, has been trapped as urethan. The hydrolysis rate constants of carbamates I–XI have been determined in acid region at pH 0.5, and their pK_a values have been obtained spectrophotometrically. From the values obtained the equation has been derived enabling calculation of k_{obs} in the range of pH 14 to $H_0 - 3$.

Ester hydrolysis usually takes a two-step course in alkaline medium. The hydroxyl ion adds to the carbonyl group, and the tetrahedral intermediate formed decomposes into products (mechanism B Ac2, ref.¹). Alkaline hydrolysis of N,N-dialkylcarbamates takes a similar course. However, alkaline hydrolysis of phenyl carbamates having a hydrogen atom at nitrogen was found to proceed *via* ElcB mechanism, *i.e.* the conjugated base of the carbamate was decomposed into products in the rate-limiting step^{2,3}. This new mechanism was established in the case of hydrolysis of phenyl esters of the carboxylic acids having electron-withdrawing groups at α -position, too⁴.



The following are the basic experiments supporting the ElcB mechanism of hydrolysis of phenyl carbamates: *a*) the exchange of hydrogen at nitrogen for deuterium is much faster than the proper hydrolysis², *b*) substitution of the hydrogen atom by methyl group slows down the alkaline hydrolysis by more than three orders of magnitude, *c*) the Hammett reaction constant is substantially greater for CH_3NHCOOR ($\text{R} = \text{aryl}$) than for the ester hydrolysis going *via* the B Ac2 mechanism², *d*) the reaction is subject to specific base catalysis and the hydrolysis rate is greater in deuterium oxide than that in water^{2,3}.

* The following are considered to be the preceding reports of this series: Part I: This Journal 37, 2183 (1972); Part II: This Journal 38, 516 (1973); Part III: This Journal, in press.

The mechanism given in Scheme (A) could be confirmed directly by following the hydrolysis rate up to the pH range in which the carbamate was present practically only as anion. The results could make it possible to determine, with sufficient accuracy, the pK_a of the carbamate and the rate of the spontaneous decomposition of the anion (and to determine the ρ value of this reaction step). These reactions are, however, very fast and cannot be followed by usual methods^{1,3,5}. The stopped-flow method enabled the necessary measurements for the selected carbamates in strongly alkaline aqueous medium.

According to the mechanism suggested the phenyl N-methylcarbamate anion decomposes into phenolate and methyl isocyanate in alkaline medium (Scheme (A)). However, methyl isocyanate is not the final product of the reaction, being hydrolyzed quickly into methylamin and carbon dioxide. In order to be able to support this reaction course *via* methyl isocyanate, we tried to trap this intermediate as urethan by carrying out the reaction in methanol.

Acid hydrolysis of carbamates proceeds by AAC2 mechanism most frequently (the reaction rate is limited by the attack of the protonated substrate by a water molecule), a change to the AAC1 mechanism being possible in strongly acidic medium (the reaction is limited by decomposition of the protonated substrate⁶⁻⁸). The determination of protonation equilibria of esters, which is necessary for separation of rate constants, is very difficult experimentally. However, the preliminary experiments showed that these values of phenyl N-methylcarbamates could be determined spectrophotometrically, which enables the separation of rate constants.

The aim of this work was to carry out the abovementioned designs and, on the basis of the results obtained, discuss the substituents effects in terms of the mechanism suggested.

EXPERIMENTAL

Reagents. Phenyl N-methylcarbamates carrying the following substituents were used: 4-OCH₃ (I), 4-CH₃ (II), 3-CH₃ (III), H (IV), 4-Cl (V), 3-Cl (VI), 3-NO₂ (VII), 4-COCH₃ (VIII), 4-CN (IX), 4-SO₂CH₃ (X), 4-NO₂ (XI). Their physical properties and methods of preparation are given in our previous paper².

Ethyl N-phenylcarbamate. 1 ml triethylamine (catalyst) was added to 9.2 g (0.1 mol) ethanol, and 11.9 g (0.1 mol) phenyl isocyanate was added thereto drop by drop with vigorous stirring and cooling. After finishing the reaction the mixture was cooled and the product collected by suction. It was purified by vacuum distillation, b.p. 152°C/14 Torr, m.p. 51–52°C (*cf.*^{9,10}).

Base catalyzed methanolysis of carbamate XI. The solution formed by dissolving 0.5 g (0.2 mol) sodium in 15 ml methanol was added to 1 g (5.1 mmol) carbamate XI. The reaction mixture was heated 30 min under reflux, cooled, and the presence of methylurethan was proved by gas-liquid chromatography using a Carlo Erba apparatus.

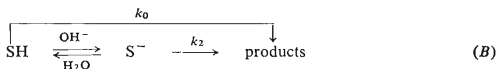
Kinetic measurements. In alkaline region spectral method was used as in ref.². In strongly alkaline region, where the reaction is very fast, the kinetic measurements were carried out by the stopped-flow method using a Durrum Stopped-Flow Spectrophotometer. Aqueous $5 \cdot 10^{-5}M$ solutions were used for the measurements; the pH being maintained by buffers in the range 10–14 at a constant ionic strength 0.02 (the buffers used had twofold concentration of components as compared to those used in ref.¹¹). The measurement was carried out at the wavelength of the longwave absorption band of phenolate ion. The time dependence of extinction was determined after mixing equal amounts of carbamate and buffer solutions at 25°C. The half-life, $t_{1/2}$, of the reaction was read directly from the curve on the screen of the apparatus, and the

pseudomonomolecular rate constant was calculated therefrom according to the relation $k = 0.692/t_{1/2}$ for the given pH. The values given are average values of at least three measurements each. From the dependence $\log k$ vs pH the ionization constants were determined by the known method⁴.

In acid region the decomposition of the protonated form of carbamates is slow, and spectrum of the substances does not practically change for at least 15 minutes, so that the classic spectral method¹² could be used for pK_a determination. In acid region the hydrolysis rate was measured as in ref.².

RESULTS AND DISCUSSION

Hydrolysis of carbamates can be expressed by Scheme (B) where $k_0 = k_{H_2O} + k_H[H^+]$ represents an expression of spontaneous and acid-catalyzed solvolyses



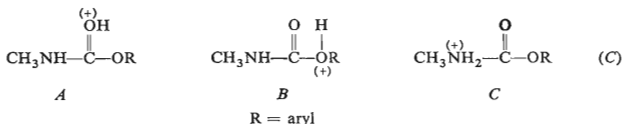
at low pH values. Previously² it was found that the k_0 value of carbamate solvolyses was negligible at $\text{pH} > 7$, the equilibrium between the substrate and the conjugated base was established rapidly in the case of *p*-nitrophenyl *N*-methylcarbamate³, and the same should apply for other *N*-methylcarbamates, too. By applying these conclusions in the case of the studied carbamates IX–XI the expression (1) can be derived for k_{obs} of the hydrolysis in the alkaline medium, K_a and k_2 representing the equilibrium constant of the carbamate dissociation and the rate constant of the spontaneous decomposition of the conjugated base into products (Scheme (B)), respectively.

$$k_{\text{obs}} = k_2 K_a / (K_a + a_{\text{H}}) \quad (1)$$

At high pH values $a_{\text{H}} \ll K_a$ and $k_{\text{obs}} = k_2$. Hence, the reaction rate is independent of pH. The experimental results of alkaline hydrolysis of carbamates IX–XI agree with this presumption; from Fig. 1 it is obvious that, in the pH range 7–11, the dependence of $\log k_{\text{obs}}$ vs pH is linear, the slope being unity, and over pH 11 the reaction order with respect to OH^- ion decreases. Both these findings are in accord with the suggested mechanism ElcB for alkaline hydrolysis of the carbamates studied. From the dependence pH vs k_{obs} it is possible to estimate the values K_a and k_2 of carbamates IX–XI with sufficient accuracy (Table I) by using the expression (1). In the case of hydrolyses of carbamates carrying less electronegative substituents the pH region suitable for a K_a estimate could not be reached even at pH 14 (Fig. 1). The values K_a and k (Table I) enable a determination of influence of substitution on both the position of the acid–base equilibrium of carbamates ($q_1 = +0.3$) and the splitting rate of the conjugated base of carbamates into products ($q_2 = +2.5$; the values σ^- were used for the estimate). The low value

of $\rho_1 = -0.3$ agrees with that the dissociation takes place at the nitrogen atom which is separated from the benzene nucleus by two atoms. The high value of $\rho_2 = +2.5$ stands in accord with the carbamate C—O bond being split in the rate-limiting step and this bond fission being considerably advanced in the activated complex of the rate-limiting step. Also this fact supports the ElcB mechanism of alkaline hydrolysis of carbamates. This mechanism obviously necessitates the presence of a good leaving group (e.g. aryloxy group) in addition to a hydrogen atom at the nitrogen atom of the molecule. The pK_a value 13.8 was found for ethyl N-phenylcarbamate by spectral method. The hydrolysis rate was determined at pH 14 when more than one half of the substrate was present as the conjugated base; nevertheless, the hydrolysis is by more than three orders of magnitude slower than that of the carbamate which has the good leaving group OC_6H_5 . It is obvious that the carbamates, which have a hydrogen atom at nitrogen but have a bad leaving group, are hydrolyzed by a different mechanism, most probably *via* a tetrahedral intermediate having one or two negative charges.

Base-catalyzed methanolysis of phenyl N-methylcarbamate gave N,O-dimethylurethan as the final reaction product, which stands in accord with the ElcB mechanism expressed in Scheme (A). Carbamate hydrolysis in acid medium involves protonation of the substrate at nitrogen or one of the two oxygen atoms:



In $\text{SO}_2\text{—SbF}_5\text{—FSO}_3\text{H}$ at -60°C it was found¹³⁻¹⁶ that the protonation took place at the carbonyl oxygen atom irrespective of the substituents attached to nitrogen or oxygen atoms. We presume the tautomer A to be present in greatest concentration even in aqueous medium. The experimental pK_a values of conjugated acids of carbamates I—XI determined in aqueous sulphuric acid medium at 25°C are summarized in Table II. The correlation of the pK_a values with the Hammett substituent constants is very good ($pK_a = 1.29 + 1.41\sigma$; $r = 0.999$; the Exner test $\psi = 0.0452$), and the successful applicability of normal substituent constants stands in accord with that there is no direct conjugation between the reaction centre and substituents at the nucleus. The ρ value found (1.4) is somewhat higher than that of protonation of substituted benzoic acids¹⁴ (1.09), even though the reaction centre is farther from the nucleus in the case of carbamates. The found pK_a values of the carbamates I—XI differ from the corresponding values of benzoic acids by about 6 units. The enhanced basicity of carbamates is ascribed to the presence of nitrogen atom.

TABLE I
Rate and Equilibrium Constants of Carbamates IX–XI at 25°C

Value	IX	X	XI
$k_{OH} \text{ l mol}^{-1} \text{ s}^{-1}$	9.89	10.50	17.60
$k_0 \cdot 10^7, \text{ s}^{-1}$	6.57	15.80	27.60
$K_B k_H \cdot 10^5$	2.06	4.29	22.20
$K_{a_1} \cdot 10^{13} \text{ }^a$	4.48	5.50	6.31
$K_A \cdot 10^{-2} \text{ }^b$	1.85	2.17	2.70

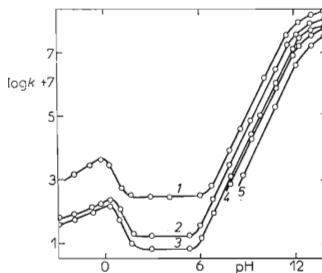
^a For dissociation of carbamates; ^b for dissociation of the conjugated acids of carbamates.

TABLE II
Protonation of Substituted Phenyl N-Methylcarbamates at 25°C

Carbamate	pK_{a_1}	Carbamate	pK_{a_1}
<i>I</i>	-0.938 ± 0.005	<i>VII</i>	-2.279 ± 0.008
<i>II</i>	-1.099 ± 0.008	<i>VIII</i>	-1.924 ± 0.009
<i>III</i>	-1.164 ± 0.007	<i>IX</i>	-2.266 ± 0.007
<i>IV</i>	-1.304 ± 0.006	<i>X</i>	-2.337 ± 0.008
<i>V</i>	-1.593 ± 0.006	<i>XI</i>	-2.432 ± 0.006
<i>VI</i>	-1.857 ± 0.007		

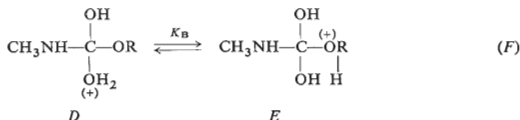
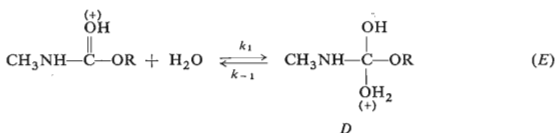
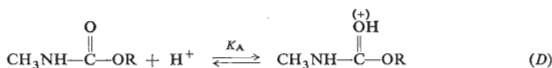
FIG. 1
pH Dependence of Logarithm of Carbamate Hydrolysis Rate Constants at 25°C

Specification of experimental points: carbamate *VII* (5), *VIII* (4), *IX* (3), *X* (2), *XI* (1).



Kinetics of acid-catalyzed hydrolyses of carbamates IX–XI were followed in the $-H_0$ range 0–3. In this region the hydrolysis catalyzed by hydroxyl ions and spontaneous solvolysis can be neglected. The dependence of experimental rate constants on acidity of medium and water activity obeys the relation (2), where A and B are constants, and a_{H^+} and a_{H_2O} are the proton and water activities, respectively. The reaction scheme of the acid-catalyzed hydrolysis can be expressed as follows:

$$k_{\text{obs}} = ABa_{H_2O}a_{H^+}/(Ba_{H^+} + 1) \quad (2)$$



Assuming that the tetrahedral intermediates D and E are present in low steady concentrations, the steady state treatment can be applied to give Eq. (3) for the observed rate constant.

$$k_{\text{obs}} = k_H K_A K_B a_{H_2O} a_{H^+} / (k_{AH^+} + 1) \quad (3)$$

Comparison of Eqs (3) and (2) shows that the suggested Scheme (D)–(G) agrees with the experimental k_{obs} values. The presumption of the decomposition of the tetrahedral intermediate protonated at the ether oxygen atom corresponds to the principle of microscopic reversibility.

The reaction constant $\rho = 4.7$ was estimated from the slope of the dependence $\log k_H$ vs σ . The data of the carbamates IX–XI are given in Table II, the rest of the k_H were obtained in an analogous way from the pK_a values given in Table II and the k_{obs} values given in our previous report⁵. From the high value of reaction constant it can be judged that the rate-limiting step consists in decomposition of the tetrahedral intermediate.

From the found equilibrium constants and the calculated rate constants of alkaline, acid and spontaneous hydrolysis Eq. (4) can be derived under the assumption that no acid, base and general catalyses make themselves felt.

$$k_{obs} = k_0 + k_{OH} \frac{K_{a1}}{K_{a1} + a_{H^+}} + k_H K_B \frac{1}{1 + (1/K_A a_{H^+})} a_{H_2O} \quad (4)$$

The coefficients of this equation are given in Table I. Eq. (4) makes it possible to calculate the hydrolysis rates of carbamates IX–XI in the range pH 11 to $H_0 - 3$. The values measured agree very well with those calculated from Eq. (4) using the coefficients given in Table I (see the experimental points and the calculated curve in Fig. 1).

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