

KINETICS AND MECHANISM OF HYDROLYSIS OF ARYL
N-TRICHLOROACETYL CARBAMATES

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pH Dependence of hydrolysis rate constants of seven substituted phenyl and 1-naphthyl N-trichloroacetyl carbamates has been investigated in aqueous medium. General acid catalysis has been found for 4-nitrophenyl N-trichloroacetyl carbamate at pH 5.3, the respective activation parameters have been obtained at pH 10.3. For the same carbamate the influence of ionic strength at pH 13.5 and 11.6 and that of the polarity of medium in mixtures water-ethanol and water-acetone have been studied. The hydrolysis mechanism is discussed.

Phenyl N-alkyl carbamates having good leaving groups (phenolate anion) are hydrolysed in alkaline medium by Elcb mechanism, *i.e.* the conjugate base of the carbamate is spontaneously split in the rate determining step to give phenolate anion and substituted isocyanate. The conjugate bases of the types of phenyl N-alkyl carbamates studied so far are decomposed, however, very rapidly (the reaction half-life is of the order of 10^{-2} s)¹, and it is difficult to reach such a pH value where the substrate is present in its dissociated form (phenyl N-ethyl carbamate, pK_a 13.8)¹. Therefore, we introduced an acidifying group (trichloroacetyl) in the carbamate molecule, whereby the pK_a value was lowered by about five orders of magnitude, and the hydrolysis kinetics could be experimentally followed in pH regions of fully ionized substrate.

EXPERIMENTAL

Model Substances

The studied phenyl N-trichloroacetyl carbamates *II* to *VIII* were prepared by mixing the solution of 0.05 mol of the respective phenol dissolved in minimum amount of benzene with 0.06 mol trichloroacetyl isocyanate². The crystals separated on standing at room temperature for several days were collected by suction, and the product was crystallized from benzene (Table I); yield 70 to 80%. 1-Naphthyl N-trichloroacetyl carbamate (*I*) was prepared by the same procedure from 1-naphthol. M.p. 158–159°C (ref.³ m.p. 160–162°C). Yield 82%. 1-Naphthyl carbamate (*IX*) was prepared from 1-naphthyl chloroformate⁴ and aqueous ammonia. M.p. 156°C (ref.⁵ 158°C). Yield 63%. Trichloroacetamide (*X*) was prepared according to ref.⁶. M.p. 141°C (ref.⁶ m.p. 139–141°C). Yield 75%.

Kinetic Measurements

Buffer solution (2.9 ml) was placed in the thermostated cell compartment of a spectrophotometer Unicam SP 800 or Specord UV VIS. After five minutes 0.1 ml 10^{-3} M carbamate solution in dioxane was added. In alkaline region the kinetics was followed by the absorbance increase of the formed phenolate anion, whereas in neutral and acid regions it was followed by the absorbance decrease of the substrate. The buffers were prepared from chemicals of *p.a.* purity grade and re-distilled water⁷. The pH values were determined with a pH-meter PHM 4 (Radiometer, Copenhagen). Chloroform was determined in the reaction mixture by gas-liquid chromatographical analysis using a Carlo Erba apparatus with a 4 mm \times 2 m column packed with chromosorb A with 20% methylphenylsilicone elastomer SE-52 at 120°C. Detection was carried out with a ionisation flame detector.

The hydrolysis kinetics of the carbamates *I* and *VIII* was measured in the pH region 5 to 14, the other substances were measured at pH 9.6 under the conditions of pseudomonomolecular reaction (phosphate and carbonate buffers with constant ionic strength 0.05 and sodium hydroxide solutions). Experimental error of the obtained rate constant did not exceed $\pm 10\%$.

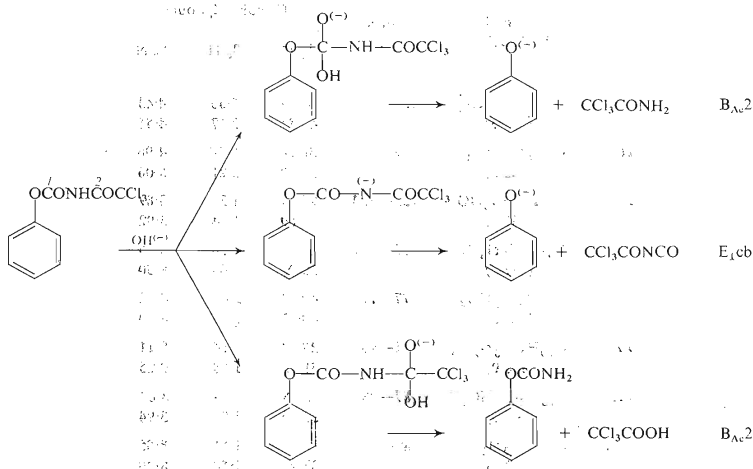
TABLE I
Properties of Compounds *I* to *VIII*

Compound	Formula (Mol. weight)	M.p. °C	Calculated/Found		
			% C	% H	% N
<i>I</i>	$C_{13}H_8Cl_3NO_3$ (224.3)	158—159	49.32	2.55	4.43
			49.41	2.67	4.55
<i>II</i>	$C_9H_6Cl_3NO_3$ (282.5)	96—97	38.24	2.14	4.96
			38.40	2.21	5.06
<i>III</i>	$C_9H_5BrCl_3NO_3$ (361.4)	132—133	29.89	1.39	3.87
			29.80	1.34	3.92
<i>IV</i>	$C_9H_5Cl_3N_2O_5$ (327.5)	106—107	32.99	1.54	8.55
			33.08	1.60	8.50
<i>V</i>	$C_{11}H_8Cl_3NO_4$ (324.5)	77—79	40.69	2.49	4.32
			40.62	2.38	4.40
<i>VI</i>	$C_{10}H_5Cl_3N_2O_3$ (306.0)	94—95	39.04	1.64	9.11
			38.95	1.58	9.25
<i>VII</i>	$C_{10}H_8Cl_3NO_5S$ (360.5)	87—88	33.38	1.96	3.89
			33.20	1.89	3.94
<i>VIII</i>	$C_9H_5Cl_3N_2O_5$ (327.5)	82—83	32.99	1.54	8.55
			33.20	1.58	8.70

RESULTS AND DISCUSSION

The hydrolysis of phenyl N-trichloroacetylcarbamates can be expressed by Scheme 1 taking into account both the hydrolysis *via* Elcb mechanism (spontaneous decomposition of the conjugate base) and that by $B_{Ac}2$ mechanism (nucleophilic attack at the carbonyl carbon atom of the non-ionized substrate). The nucleophilic attack can take place at carbon 1 or 2.

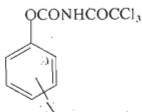
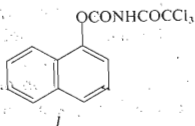
In pH region 9 to 13 the hydrolysis rate of the carbamate *VIII* is independent of pH of the medium (Fig. 1). In this pH region the substrate is practically completely ionized, and spontaneous decomposition of the conjugate base of the substrate into phenolate ion and trichloroacetyl isocyanate is presumed (Elcb mechanism). The observed rate constants determined from the concentration increase of phenolate ion correspond to the rate-limiting decomposition of the conjugate base (Scheme 1). In the given pH region the intermediate trichloroacetamide (*X*) is accumulated (Fig. 1), being hydrolyzed more slowly than the carbamate *VIII*. The mechanisms Elcb and $B_{Ac}2$ cannot be differentiated by identification of the hydrolysis products, as the both paths give the same final products. It can be shown that the hydrolysis of carbamate *VIII* *via* $B_{Ac}2$ mechanism would have the same kinetics course, as far as the attack of hydroxyl ions on the non-ionized substrate is considered rate-limiting. However, this mechanism is little likely, the rate constant of the reaction of the



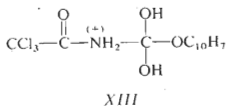
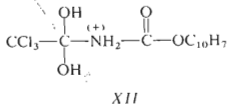
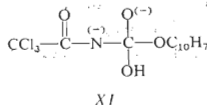
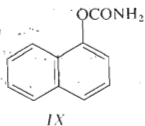
SCHEME 1

undissociated substrate *VIII* with hydroxyl ion having the value $10^4 \text{ mol}^{-1} \text{ s}^{-1}$ at pH 9.0 ($k = k_{\text{obs}}/[\text{OH}^-]$). This value is by more than seven orders of magnitude greater than the hydrolysis rate constant of 4-nitrophenyl N,N-dimethylcarbamate which is hydrolyzed by $B_{\text{Ac}2}$ mechanism⁸.

When investigating the solvent effect on the spontaneous hydrolysis of the conjugate bases of carbamates *I* and *VIII*, such pH of aqueous medium was chosen that any change in concentration of the conjugate base of the substrate due to addition of organic solvent was prevented. Lowering of polarity of medium due to addition of both ethanol and acetone caused an obvious reaction rate increase in the case of the carbamate *VIII* (Table II), which stands in accord with the Ingold rule⁹ and



- II*, X = H
III, X = 4-Br
IV, X = 3-NO₂
V, X = 4-CH₃CO
VI, X = 4-CN
VII, X = 4-CH₃SO₂
VIII, X = 4-NO₂



supports the Elcb mechanism. The carbamate *I* is solvolyzed in the same way as *VIII* in water-acetone medium, although the acceleration of the reaction in less polar media is smaller; in the water-ethanol system the solvent polarity effect on the hydrolysis rate was slight (Table II). Effect of ionic strength on the decomposition rate of the conjugate base of carbamate *VIII* at pH 11.6 is small but perceptible. The dependence of $\log(k_{\text{obs}}/k_0)$ vs $(I)^{1/2}$ was found to have the slope 0.35 corresponding to the reactions which are characterized by a charge dispersion in the transition state and differing fundamentally from the slope value of reactions resulting from collisions of equally charged particles¹⁰. The found value of activation entropy change in the

spontaneous decomposition of the conjugate base of carbamate *VIII* ($\Delta S^\ddagger = 3.39 \text{ J} \cdot \text{K}^{-1} \text{ mol}^{-1}$ at pH 10.3) is similar to those given for monomolecular reactions¹¹. The found value of activation enthalpy change $\Delta H^\ddagger = 83.3 \text{ kJ} \cdot \text{mol}^{-1}$.

The Hammett correlation of $\log k_{\text{obs}}$ of the hydrolyses of carbamates *II* to *VIII* (Fig. 2) (substituent in the benzene ring) at pH 9.6 (corresponding to the plateau in the pH-profile, Fig. 1) shows a marked break indicating a change in the reaction mechanism of the solvolytic reaction. For the carbamates *V* to *VIII* the fragmentation reaction is more sensitive to the substituent effects ($\rho = 2.6$). We presume the C—O bond to be extensively split in the transition state of the rate-limiting step of the spontaneous decomposition of the conjugate base of carbamates (*cf.* the magnitude of the ρ constant; the correlation is better when using σ^- constants).

The splitting produces trichloroacetyl isocyanate which is further hydrolyzed to trichloroacetamide (*X*) and carbon dioxide. The other fragment is phenolate ion which is sufficiently stable in the given medium, and its splitting obviously does not need any assistance by water (general catalysis). So far the participation of water in fragmentation reaction of the carbamates *V* to *VIII* can be hardly assessed in this case.

Splitting of the anions of carbamates *II* to *IV* is less sensitive to substituent effects in the benzene ring ($\rho = 1.6$). This lower value of the reaction constant suggests that C—O bond is not split in the transition state of the rate-limiting step. Water, being neutral hard nucleophile, can easily attack the carbonyl carbon atom of carbamate anion. The molecular diagram calculated by the HMO method¹² (Fig. 3) shows the

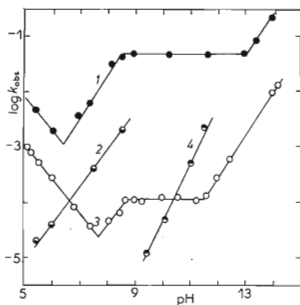


FIG. 1

pH Dependence of Logarithms of Hydrolysis Rate Constants of Carbamates at 25°C

I (○), *VIII* (●), *IX* (●), *X* (●).

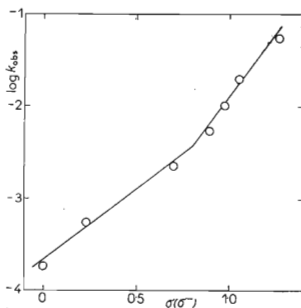


FIG. 2

Hammett Correlation of Solvolysis of Carbamates *II* to *VIII* at 25°C at pH 9.6

preference of the attack at the carbonyl carbon atom 1. This finding agrees with the found value $\rho = 1.6$ which is much too high for an attack at the carbonyl carbon atom 2 isolated by three atoms from the benzene ring. Therefore, we suppose that the spontaneous solvolysis of the carbamate anions *II* to *IV* involves bond formation between oxygen atom of water molecules or other bases present and carbonyl carbon atom in the rate-limiting step. However, participation of a further water molecule is not excluded.

The results obtained from the study of splitting of the carbamates anions correspond to spontaneous decomposition with possible assistance by water and give unambiguous evidence for Elcb mechanism of hydrolytic splitting of phenyl N-trichloroacetylcarbamates. In accordance with the hydrolysis mechanism of carbamates in the pH region 9 to 12 it can be presumed that the chloroform found after hydrolysis of the carbamate *VI* at pH 10.3 was formed by a subsequent hydrolysis of trichloroacetic acid which is very smooth. In strongly alkaline medium the hydrolysis rate of the carbamates *I* and *VIII* increases with increasing hydroxyl ion concentration, the slope being unity (Fig. 1). Therefrom it follows that the activated complex of the rate-limiting step involves OH^- ion. Therefore, it is presumed that in this pH region the conjugate base of the substrate is hydrolyzed by $\text{B}_{\text{Ac}2}$ mechanism involving the attack

TABLE II
Hydrolysis Rate Constants of Carbamates *I* and *VIII* in Mixed Solvents at 25°C

Ethanol vol. %	pH	$k_{\text{obs}} \cdot 10^4$ s^{-1}	Acetone vol. %	pH	$k_{\text{obs}} \cdot 10^4$ s^{-1}
Carbamate <i>I</i>					
0	9.07	0.748	0	10.66	0.752
10	9.36	0.751	10	10.66	2.28
20	9.64	0.766	20	10.82	2.75
30	9.90	0.764	30	10.98	2.86
40	10.19	0.748	40	11.15	3.11
50	10.46	0.806	50	11.21	3.36
Carbamate <i>II</i>					
0	9.07	344	0	10.66	342
10	9.36	375	10	10.66	877
20	9.64	505	20	10.82	1 480
30	9.90	1 040	30	10.98	1 970
40	10.19	1 540	40	11.15	—
50	10.46	3 190	50	11.21	—

of the carbonyl carbon atom 1 (see the molecular diagram, Fig. 3) by hydroxyl ion to give the tetrahedral intermediate *XI*. In accord with the suggested hydrolysis mechanism in strongly alkaline medium the found dependence of $\log(k_{\text{obs}}/k_0)$ vs $(I)^{1/2}$ had the slope 1.15 (hydrolysis of the carbamate *VIII* at pH 13.5) which agrees well with the value given for reactions involving a collision of two equally charged particles¹⁰.

From pH 9 down to acid region the hydrolysis rate of the carbamates *I* and *VIII* decreases, the slope being unity (Fig. 1), which is obviously due to decreasing concentration of the reacting form i.e. the conjugate base of the substrate. Therefore, it is presumed that conjugate base of the substrate is spontaneously solvolyzed in this pH region, too, the non-ionized form being relatively stable. Further decrease in pH below the value 7.5 (carbamate *I*) resp. 6.0 (carbamate *VIII*) causes no further change,

TABLE III

General Acid Catalysis in Hydrolysis of Carbamate *VIII* at 25°C in Phosphate Buffer pH 5.4

Buffer, mol l ⁻¹	pH	$k_{\text{obs}} \cdot 10^2, \text{s}^{-1}$	Buffer, mol l ⁻¹	pH	$k_{\text{obs}} \cdot 10^2, \text{s}^{-1}$
0.079	5.375	2.70	0.474	5.325	5.54
0.158	5.385	3.40	0.632	5.320	6.51
0.237	5.380	3.94	0.790	5.340	8.85
0.395	5.380	4.78			

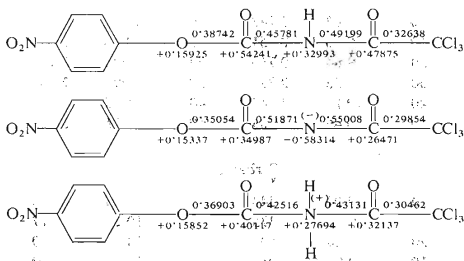


FIG. 3

Molecular Diagram of Carbamate *VIII* — Non-Dissociated Molecule, Conjugate Base and Acid

i.e. practically all substrate is present in its non-dissociated form, and if spontaneous solvolysis of the non-ionized substrate took place, the pH profile would show another plateau. However, in the pH region 6.5 to 5.0 an increase in the hydrolysis rate of the carbamate *VIII* was found experimentally, the slope being unity again. This break in the pH-profile can be ascribed to a change in the reaction mechanism. The matter is an acid catalyzed hydrolysis. The hydrolysis of the carbamate *VIII* shows general acid catalysis in this pH region (Table III). The carbamate *I* behaves similarly in the pH region 5.0 to 7.5 (Fig. 1). Its acid catalyzed hydrolysis is observed already at higher pH values in accord with the carbamate *I* being more basic than *VIII*. The mechanism of acid catalyzed hydrolysis is characterized by primary splitting of trichloroacetyl group, which was proved by spectroscopic detection of 1-naphthyl carbamate (*IX*) in the reaction mixture after hydrolysis of the carbamate *I*, the identity of *IX* being confirmed kinetically, too. At a suitable pH value (5.47), when the difference between the hydrolysis rate constants of the carbamate *I* and 1-naphthyl carbamate (*IX*) is about two orders of magnitude (Fig. 1), the carbamate *I* was hydrolyzed for a period of six half-lives (98.5% hydrolysis); then a sample of the reaction mixture was transferred into a buffer with a higher pH value (8.52), and the hydrolysis kinetics of the accumulated 1-naphthyl carbamate (*IX*) was followed. The hydrolysis rate constant of 1-naphthyl carbamate thus obtained ($k_{\text{obs}} = 2.33 \cdot 10^{-3} \text{ s}^{-1}$) agrees with the value found for hydrolysis of a reference sample ($k_{\text{obs}} = 2.30 \cdot 10^{-3} \text{ s}^{-1}$). From quantum-chemical calculations it follows, that the substrate will be protonated preferentially at the nitrogen atom. The protonated substrate can be attacked by water again at the carbonyl carbon atoms 1 or 2 (Fig. 3). From the molecular diagram it follows that the carbon atom 1 of the protonated substrate is more reactive. However, on the basis of the experimental data the attack at the carbonyl carbon atom 2 must be considered leading to formation of the carbamate *IX*. Even though the tetrahedral intermediate *XII* is formed less easily than *XIII*, the reaction course is obviously controlled by that the $\text{C}_{10}\text{H}_7\text{OCONH}_2$ group is a better leaving group than the anion $\text{C}_{10}\text{H}_7\text{O}^-$ in acid medium.

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