Kinetics of alkaline hydrolysis of substituted esters of phenylcarbamic acid

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The presented paper deals with the kinetics of alkaline hydrolysis of substituted basic esters of phenylcarbamic acid. ΔH^{+} and ΔS^{+} were calculated by Eyring equation from the temperature dependence of the rate constants. The extent of the influence of spectral parameters and the Taft substituent constants upon the rate constants of the studied substances was examined using a polynomial function with several variables.

There are several different groups of biologically active compounds among the esters of phenylcarbamic acid. Kinetic studies of their hydrolysis represent one of the possibilities of examining their chemical reactivity and stability. Molecular orbitals determining the reactivity of the substances are also important to their binding on the receptor in an organism. Several works on kinetics of the hydrolysis of phenylcarbamates appeared in literature. *Dittert* [1] proposed the reaction mechanism of the alkaline hydrolysis of aromatic carbamates assuming the formation of isocyanate as an intermediate in the second step of the reaction

$$\mathrm{R{-}O{-}\overset{\overset{\mathrm{O}}{\|}}{C}{-}NHR' + OH^- \underset{k_{-1}}{\overset{k_1}{\rightleftarrows}} R{-}O{-}\overset{\overset{\mathrm{O^-}}{|}}{C}{=}NR' + H_2O \xrightarrow{k_2} RO^- + R'N{=}C{=}O,}$$

$$\mathrm{R'{-}N{=}C{=}O + H_2O \xrightarrow{k_3} R'{-}NH{-}COOH,}$$

$$\mathrm{R'{-}NH{-}COOH \xrightarrow{k_4} CO_2 + R'{-}NH_2,}$$

$$\mathrm{CO_2 + 2OH^- \xrightarrow{quickly} CO_3^{=} + H_2O.}$$

Bender [2] found that it is the second step, *i.e.* the formation of isocyanate, which is slowest and therefore rate-determining step of the total hydrolysis. Other intermediates react so quickly that they cannot be detected by simple analytical methods. The results of *Christenson* [3] and *Vontor* [4] are in conformity with the above-stated mechanism.

In the presented work, some local-anaesthetically active phenylcarbamates are studied from the standpoint of the influence of *o*-substitution on the aromatic ring and the changes in the aliphatic part of the molecule upon the rate of their alkaline hydrolysis.

Experimental

Chemicals

The studied compounds were synthesized by a group of authors at the Department of Pharmaceutical Chemistry of the Faculty of Pharmacy. Their preparation and pharmacologic evaluation have been already reported [5, 6]. A survey of the chemical structures of the studied compounds is in Table 1. Other chemicals used in experiments were anal. grade.

Kinetics of hydrolysis

The studied compounds were hydrolyzed in alkaline medium at 36.0, 40.0, 50.0, 60.0, and 70.0°C. Since the aqueous solubility of their basic forms is relatively low ($10^{-5}-10^{-4}$ M), we used 0.1 M alcoholic solution of NaOH with 50% (v/v) of ethanol for the hydrolysis. Concentrations of phenylcarbamates varied from 3×10^{-4} to 1×10^{-3} M. The prepared solutions were tempered in closed flasks in an ultrathermostat U 10 and temperature was maintained with the precision ± 0.2°C. In definite time intervals, concentrations of aniline liberated from the phenylcarbamate molecule by the alkaline hydrolysis were determined photometrically [7] in the drawn off samples.

The rate constants of the reaction were calculated employing the second order kinetic equation by the least squares technique

$$\log \frac{b(a - x)}{a(b - x)} = f(t).$$

The possible influence of the ethanol concentration on the rate of the hydrolysis was checked with the compound *IX*.

Instruments

A spectrophotometer MOM 202 (Budapest) with 1-cm glass or quartz cells was used both for the aniline determination and for the spectral measurements of the studied compounds.

Spectra

The measured u.v. spectra of the aqueous solutions of the studied compounds were resolved into individual bands by an empirical method of *Jaffé* [8]. The band with λ_{max} in the region 219—233 nm was used for calculations corresponding to the $\pi \rightarrow \pi^*$ transition connected with the intramolecular charge transfer. The oscillator force f which is a measure of the probability of an electron transition, was calculated from relationship (*1*) [9]

$$f = 10^3(\ln 10)\,(m\,c^2/\pi\,e^2\,N_A) \int_{\tilde{\nu}_1}^{\tilde{\nu}_2} \varepsilon\,d\tilde{\nu}, \qquad (1)$$

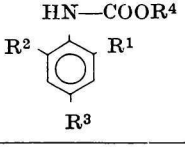
where e is the electron charge, m its mass, N_A the Avogadro number, ε the molar absorptivity, $\tilde{\nu}$ the wavenumber, and c the speed of light in vacuum. An approximate relationship (*2*) [10] was used for calculating the angle Θ of the distortion of the plane of the benzene ring with respect to the other fragment of the molecule represented by the carbamate group

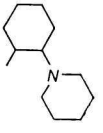
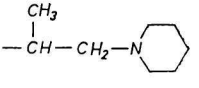
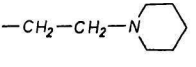
$$\cos^2 \Theta = \frac{f_x}{f_0}. \qquad (2)$$

Here f_0 and f_x are the oscillator forces of the unsubstituted and substituted compound respectively.

Table 1

Chemical structure of the studied compounds



Compound	R1	R2	R3	R4
I	Cl	H	H	
II	Cl	Cl	H	
III	Cl	CH_3	H	
IV	CH_3	H	H	
V	CH_3	CH_3	H	
VI	CH_3	CH_3	CH_3	
VII	H	H	H	
VIII	H	H	H	
IX	H	H	H	

Calculations

Coefficients of the linear functions and those of the polynomial function with several variables

$$y = a_1 x_1 + a_2 x_2 + \cdots + a_n x_n + a_{n+1} \qquad (3)$$

were calculated by the least squares technique on a CDC 3300 computer at the Computing Research Centre, Program UN, Bratislava. The method of the calculations and the relationships for the correlation coefficient r and the standard deviation s were the same as in the structure-activity studies [6].

Results and discussion

The course of the alkaline hydrolysis of the studied compounds corresponds to the second order reaction. Kinetic parameters, *i.e.* the activation enthalpy ΔH^{+} and activation entropy ΔS^{+} were calculated from the Eyring equation. The experimental rate constants k determined at various temperatures, values of ΔH^{+} and ΔS^{+} are summarized in Table 2. They are mean values of three parallel determinations, with the relative standard deviation always lower than 4.5%.

The acidic hydrolysis was examined with compounds *VII*, *VIII*, and *IX* in 2 M-HCl at 20°C. However, no traces of aniline, as a decomposition product of the hydrolysis, were analytically detected in the solutions even after three months' treatment.

The study of the effect of the ethanol concentration in the reaction solution upon the rate of the alkaline hydrolysis of the compound *IX* resulted in the following values of k determined at 70.0°C and at constant concentration of NaOH: 10% ethanol $k = 1.01 \times 10^{-3}$, 30% ethanol $k = 8.21 \times 10^{-4}$, and 70% ethanol $k = 5.39 \times 10^{-4}$ (s^{-1} l mol^{-1}). The acceleration of the reaction in the solutions with lower content of ethanol, *i.e.* with higher content of water, follows from the above-stated reaction mechanism.

The differences in the rate constants as well as in the activation enthalpies of the substances *I*—*VI* may be explained especially by the +I effect of the methyl substituent and the —I effect of chlorine. Methyl increases the electron density in the carbamate functional group, decreasing thus the probability of the bond formation with a negatively charged hydroxyl ion. This is in conformity with the results of *Christenson* [3]. Differences between mono- and disubstitution in the *o*-positions of benzene ring are connected with the steric effect representing a disarrangement of the coplanarity of the benzene ring with the carbamate group (Table 3). It again results in changes of the electron density since in the unsubstituted compound, the conjugation of π-electrons may be theoretically extended as far as to the carbonyl oxygen.

Variations in the aliphatic part of the molecule are demonstrated by a different degree of the induction effect and, eventually, also by steric factors. Both the effects increase with the increasing size of the alkyl substituent on C_α, thus decreasing the rate of the hydrolysis.

Polar effects of the substituents can be characterized by the Taft σ^* constants. Tabular values of σ_B^* were used for seeking a relation between the hydrolysis rate and the parameters characterizing the substituents on the benzene ring. The values of σ_B^* are based on hydrogen: for methyl $\sigma_B^* = -0.17$, for chlorine $\sigma_B^* = 0.20$. The substitution on C_α in the aliphatic segment of the molecule is characterized by a coefficient σ_A^* [11], calculable from eqn (*4*)

$$\sigma_A^* = 0.45\,\sigma^*. \qquad (4)$$

For methyl in the aliphatic part $\sigma_A^* = 0.00$, for hydrogen $\sigma_A = 0.49$. An approximate value of $\sigma_A^* = -0.052$, corresponding to the propyl substituent was used for other compounds with cyclohexylene in the linking chain.

The resulting spectral data are summarized in Table 3. For *o*-monosubstitution, values of ε_{max} are about one half of this value for the unsubstituted compound. In the spectral curve of the *o*-disubstituted compound, a submerged band is examined so that the precision of the calculated f is lower. The plane of the more bulky sub-

Table 2

Experimental values of k and calculated ΔH^+ and ΔS^+

Compound	k [s^{-1} l mol^{-1}]					ΔH^+ [kcal mol^{-1}]	ΔS^+ [cal K^{-1} mol^{-1}]
	70.0°C	60.0°C	50.0°C	40.0°C	36.0°C		
I	$4.51 \times 10^{-}$	$1.50 \times 10^{-}$	5.11×10^{-5}	$1.63 \times 10^{-}$	7.62×10^{-6}	24.0 ± 0.8	−4 ± 2
II	1.66×10^{-4}	$4.40 \times 10^{-}$	$1.00 \times 10^{-}$	$2.28 \times 10^{-}$	$1.30 \times 10^{-}$	29.6 ± 0.3	10 ± 1
III	$1.46 \times 10^{-}$	3.39×10^{-5}	$8.30 \times 10^{-}$	$1.55 \times 10^{-}$	$1.01 \times 10^{-}$	30.6 ± 0.7	13 ± 2
IV	8.97×10^{-5}	2.61×10^{-5}	5.78×10^{-6}	$1.36 \times 10^{-}$	7.23×10^{-7}	29.4 ± 0.5	8 ± 2
V	$7.66 \times 10^{-}$	1.35×10^{-5}	$2.42 \times 10^{-}$	3.90×10^{-7}	1.75×10^{-7}	36.8 ± 0.5	30 ± 1
VI	5.14×10^{-5}	1.26×10^{-5}	2.23×10^{-6}	3.70×10^{-7}	1.73×10^{-7}	34.9 ± 1.2	23 ± 4
VII	8.50×10^{-5}	2.25×10^{-5}	$6.71 \times 10^{-}$	1.82×10^{-6}	$1.00 \times 10^{-}$	26.5 ± 0.4	0 ± 1
VIII	1.99×10^{-4}	5.11×10^{-5}	1.42×10^{-5}	$4.09 \times 10^{-}$	$1.87 \times 10^{-}$	27.5 ± 0.7	4 ± 2
IX	7.22×10^{-4}	$2.34 \times 10^{-}$	8.86×10^{-5}	2.82×10^{-5}	1.54×10^{-5}	22.7 ± 0.5	−7 ± 2

stituent represented by the carbamate group is turned with respect to the plane of the benzene ring. A possibility of the mesomeric effects is therefore limited and higher values of the electron densities may be assumed in the area of the hydrolyzed group. This effect is numerically evaluated by means of $\cos^2 \Theta$.

Table 3

Spectral characteristics of the $\pi \rightarrow \pi^*$ electron transition

Compound	λ_{max}^{a} [nm]	ε^{b}	f^{c}	Θ^{d}	$\cos^2 \Theta$
I	232	8 080	0.152	44°10′	0.515
II	226	4 250	0.050	65°50′	0.169
III	224	3 600	0.047	66°30′	0.159
IV	226	6 180	0.142	46°10′	0.481
V	219	3 200	0.047	66°30′	0.159
VI	222	5 600	0.077	66°30′	0.159
VII	233	15 300	0.295	0°	1.000
VIII	233	13 700	0.242	0°	1.000
IX	233	12 600	0.232	0°	1.000

a) Wavelength;
b) molar absorptivity;
c) oscillator force;
d) angle of distortion of the plane of the benzene ring towards the carbamate group.

The individual parameters σ_B^*, σ_A^*, f, and $\cos^2 \Theta$ do not correlate with the rate of the hydrolysis. It means that none of them itself reflects sufficiently the effect brought about especially by the simultaneous substitution in position 2 and 6 of the benzene ring. Values of the correlation coefficients are $|r| = 0.4$—0.6. However, a combination of the mentioned parameters makes it possible to calculate $\log k$ at 40.0°C or ΔH^+ and ΔS^+ using a polynomial function with several variables

$$-\log k = -1.376 \sum \sigma_B^* - 4.117 \sum \sigma_A^* - 3.403 f + 0.565 \cos^2 \Theta + 5.706, \qquad (5)$$

$$r = 0.910 \qquad s = 0.37$$

$$\Delta H^+ = -10.442 \sum \sigma_B^* - 25.206 \sum \sigma_A^* - 75.726 f + 13.954 \cos^2 \Theta + 31.862, \qquad (6)$$

$$r = 0.941 \qquad s = 2.23$$

$$\Delta S^+ = -27.121 \sum \sigma_B^* - 62.058 \sum \sigma_A^* - 226.128 f + 42.014 \cos^2 \Theta + 16.992. \qquad (7)$$

$$r = 0.944 \qquad s = 5.67$$

The symbol r denotes the multiple correlation coefficient and s is the standard deviation of the calculated function. The increased values of r confirm the importance of examining the secondary steric effect together with the polar σ^* constants. Eqns (*5*—*7*) also enable preliminary calculations of the kinetic parameters for other *o*-derivatives providing the values of the σ^* constants and the spectral characteristics are known. The substituent constants and the regression analysis were

analogously used in the studies of an enzymatic reaction mechanism of the hydrolysis of several compounds [12].

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