Kinetics of alkaline hydrolysis of the 2-piperidinoethyl esters of *o*-, *m*-, and *p*-alkoxyphenylcarbamic acids

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The rate constants of alkaline hydrolysis have been determined at 60°C for a series of the basic esters of alkoxyphenylcarbamic acids. The values of $\Delta\Delta G$ have been calculated and the relationships $\log k = \mathrm{f}(\sigma)$ and $\Delta\Delta G = \mathrm{f}(\sigma)$ have been determined for some *m*- and *p*-derivatives.

В серии щелочных эфиров алкоксифенилкарбамовых кислот определились константы скорости их щелочного гидролиза при 60°С. У некоторых *м*- и *п*-производных вычислились величины $\Delta\Delta G$ и определились зависимости $\log k = \mathrm{f}(\sigma)$, $\Delta\Delta G = \mathrm{f}(\sigma)$.

In the preceding paper [1] dealing with the kinetics of alkaline hydrolysis of the basic esters of phenylcarbamic acid the probable mechanism of this reaction had been drawn. That paper is concerned with the effect of *o*-substitution in aromatic ring as well as with the change in the aliphatic part of molecule on the rate of alkaline hydrolysis. The aim of this study is to investigate the effect of the change in the position of alkoxy substituents in the aromatic ring of molecule on the rate of alkaline hydrolysis at equal temperature for a series of the piperidinoethyl esters of *o*-, *m*-, and *p*-alkoxyphenylcarbamic acids, which are used as local anaesthetics. The synthesis, u.v., and i.r. spectra of these substances have been published [2].

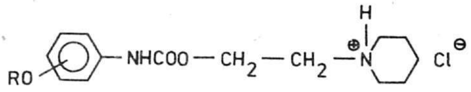
Experimental

Kinetics of hydrolysis

The substances studied (Table 1) were hydrolyzed at 60°C. As their basic solubility in water is small (10^{-5}—10^{-4} M), the hydrolysis was carried out with an alcoholic (50% (v/v) of ethanol) 0.1 M solution of NaOH. The concentration of substituted phenylcarbamates varied in the range 5×10^{-4}—1×10^{-3} M. The solutions prepared were thermostated in closed flasks accurate to ±0.1°C (ultrathermostat U 10). In certain time intervals after taking a sample from the reaction mixture, the concentration of aniline arising in the reaction was estimated by spectrophotometric method (spectrophotometer MOM 202 (Budapest), 1-cm quartz cells).

Table 1

Investigated substances and rate constants of their alkaline hydrolysis at 60°C



No.	R	$k\cdot10^4$ s^{-1} l mol^{-1}
I	2-CH_3	2.490
II	3-CH_3	2.552
III	4-CH_3	1.294
V	3-C_2H_5	2.497
VI	4-C_2H_5	1.307
VII	2-C_3H_7	1.874
VIII	3-C_3H_7	2.275
IX	4-C_3H_7	1.285
X	2-C_4H_9	1.789
XI	3-C_4H_9	2.089
XII	4-C_4H_9	1.292
XIII	2-C_5H_{11}	1.746
XIV	3-C_5H_{11}	2.085
XV	4-C_5H_{11}	1.127
XVI	2-C_6H_{13}	1.880
XVII	3-C_6H_{13}	2.214
XVIII	4-C_6H_{13}	1.185
XIX (Heptacaine)	2-C_7H_{15}	1.684
XX	3-C_7H_{15}	1.632
XXI	4-C_7H_{15}	1.240
XXII	2-C_8H_{17}	1.626
XXIII	3-C_8H_{17}	1.580
XXIV	4-C_8H_{17}	1.262
Nonsubstituted species	H	2.340

Calculation

The concentration of the substance at the time moment t was calculated according to the following equation

$$c_1 = \frac{A - \varepsilon_2 c}{\varepsilon_1 - \varepsilon_2} \tag{1}$$

where the symbols A, c, c_1, ε_1, and ε_2 stand for the absorbance of solution measured at a certain wavelength, initial concentration of the substance, concentration of the substance at the time moment t, molar absorptivity of the substance, and molar absorptivity of aniline, respectively. The wavelengths were so chosen that the difference between the absorptivities of the substance and corresponding aniline was large as possible. The wavelengths used were 295 nm for o- and m-derivatives and 307 nm for p-derivatives. The rate constants of alkaline hydrolysis k were calculated from eqn (*2*) valid for reactions of the second order [3]

$$\log \frac{a - x}{b - x} = \log \frac{a}{b} + t\, k\, \frac{(a - b)}{2.303} \tag{2}$$

For all calculations, a computing programme KIN 1 was set up. The calculations were carried out on a computer SIEMENS 4004 in the Institute of Computing Technique, Komenský University, Bratislava.

Results and discussion

The rate constants of alkaline hydrolysis calculated for a series of substances at 60°C are listed in Table 1. The standard deviation of the values of rate constants is less than 1% in all cases. The rate constants of the substances with a substituent in *para* position are not much different. Only the substances with an alkoxy substituent containing 7 and 8 carbon atoms show higher rate constants. The hydrolysis of the substances with an alkoxy substituent in *ortho* or *meta* position proceeds more rapidly than the hydrolysis of *para* derivatives. An alkoxy substituent in *ortho* and *para* position raises the electron density in the carbamate functional group. For this reason, the reactivity with hydroxyl ion is decreased. The major effect of an alkoxy substituent in *ortho* position of the benzene ring is due to its steric influence. The secondary steric effect reduces the result of an induction effect. In the series of the substances investigated, the *para* derivatives react most slowly, then the *ortho* derivatives follow whereas the *meta* derivatives are hydrolyzed most rapidly. That is especially obvious for the substances containing alkoxy substituents with the number of carbon atoms 1—5. The esters of o-, m-, and p-nonyloxyphenylcarbamic and o-, m-, and p-decyloxyphenylcarbamic acids which also belong to this series were not subjected to hydrolysis because of their low solubility in reaction solution.

The Hammett equation

$$\log \frac{k_{\mathrm{R}}}{k_{\mathrm{H}}} = \varrho\, \sigma \tag{3}$$

Table 2

Values of log k, substituent constants σ and $\Delta\Delta G$

No.	log k	$\Delta\Delta G$ J mol^{-1}	σ
II	−3.593	−240	0.115
III	−3.888	1640	−0.270
V	−3.620	−180	0.100
VI	−3.884	1620	−0.240
VIII	−3.643	78	0.100
IX	−3.891	1660	−0.250
XI	−3.686	314	0.100
XII	−3.889	1650	−0.320
XIV	−3.654	320	0.100
XV	−3.948	2020	−0.340
Nonsubstituted species	−3.631	—	—

which expresses the relationship between the reaction rate constant and the character of the substituent in aromatic ring for substances with equal functional group, was used to determine the relationship between the tabulated values of the substituent constants σ for *meta* and *para* alkoxy substituents and the rate constants of hydrolysis [4]. In Table 2 the values of log k and the substituent constants σ [5] are presented. Fig. 1 represents the relation log $k = \mathrm{f}(\sigma)$. The value of the correlation coefficient is $r = 0.975$ [6].

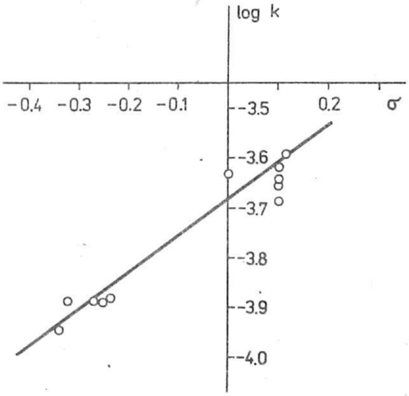


Fig. 1. log $k = \mathrm{f}(\sigma)$.

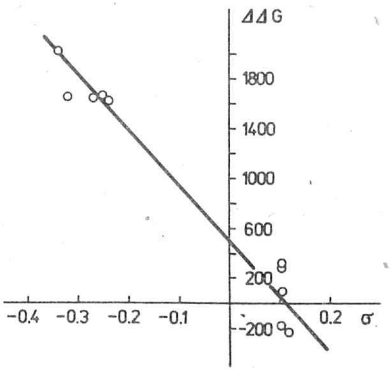


Fig. 2. $\Delta\Delta G = \mathrm{f}(\sigma)$.

As known from thermodynamics and the theory of absolute reaction rates, ΔG^0 and ΔG^{+} characterize the difference between the Gibbs energy of final reaction products and that one of transition state or of starting substances, respectively. These values define the ability of substances to take part in a certain reaction. ΔG^0 and ΔG^{+} are in linear relation with log k [7], which enables us to give a simple thermodynamic interpretation of the following equations.

By inserting into the Hammett equation, we obtain

$$\log k_{\mathrm{R}} - \log k_{\mathrm{H}} = \frac{1}{2.303\ RT}(\Delta G_{\mathrm{R}} - \Delta G_{\mathrm{H}}) \qquad (4)$$

$$\log \frac{k_{\mathrm{R}}}{k_{\mathrm{H}}} = -\frac{1}{2.303\ RT}\Delta\Delta G \qquad (5)$$

The second difference Δ characterizes the change in the Gibbs energy of the reaction, or the activation of the substituted compounds (R) in comparison with the nonsubstituted compound, *i.e.* it expresses the effect of substituent in units of the Gibbs energy. As $\Delta\Delta G$ is a linear function of log $k_{\mathrm{R}}/k_{\mathrm{H}}$ which is a linear function of σ, there must exist a linear relation between $\Delta\Delta G$ and the substituent constant. That is a result of the rule of linear free energies (LFE). This principle enables to establish a mathematical formulation of the relationship between structure and reactivity. The real expression of LFE is the Hammett equation [8]. The calculated values of $\Delta\Delta G$ are given in Table 2. Fig. 2 shows the relationship $\Delta\Delta G = \mathrm{f}(\sigma)$. The correlation coefficient is $r = -0.987$. The change in the value of rate constants, especially of the higher derivatives, may be due to the steric effect of longer alkoxy substituent as well as the induction effect. A possible association and formation of aggregates of the phenylcarbamate molecules [9] must also be taken into consideration. Only the monomers participate in the reaction with the OH^- ion, which distorts the resulting value of the rate constant. On the basis of these facts, it can be understood that the m-derivatives show a different rate constant though their substituent constants σ are equal.

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