Kinetics of alkaline hydrolysis of heptacaine chloride basic analogues

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Received 3 April 1989

Dedicated to Professor P. Hrnčiar, DrSc., in honour of his 60th birthday

Kinetics of alkaline hydrolysis have been studied with a series of six basic analogues of heptacaine chloride (*N*-{2-[*N*-(2-heptyloxyphenyl)carbamoyloxy]ethyl}piperidinium chloride) in aqueous-ethanolic solution of 0.1 M-NaOH at 40, 50, and 60 °C. The rate constants and the activation parameters E_A, $\Delta H^{\neq}$, and $\Delta S^{\neq}$ have been calculated. pK_a Values of the studied substances have been determined titrimetrically and have been correlated with the obtained rate constants.

Кинетика щелочного гидролиза шести основных аналогов хлорида гептакаина (хлорида *N*-{2-[*N*-(2-гептилоксифенил)карбамоилокси]этил}пиперидиния) была изучена в водно-этанольном растворе 0,1 M-NaOH при 40, 50 и 60 °C. Рассчитаны константы скоростей и активационные параметры E_A, $\Delta H^{\neq}$ и $\Delta S^{\neq}$. Значения pK_a изучаемых соединений были определены с помощью титрации и затем сопоставлены с полученными величинами констант скоростей.

Heptacaine chloride (*N*-{2-[*N*-(2-heptyloxyphenyl)carbamoyloxy]ethyl}piperidinium chloride) is a substance with considerable local anaesthetic [1] and expressive antiarrhythmic activity [2]. During the study of relation between chemical structure and activity there were prepared also its basic analogues, presenting high local anaesthetic activity [3]. The basic analogues of heptacaine chloride have a piperidine ring in the molecule replaced by other alkyl group or by a heterocycle — dimethylamino and diethylamino groups, pyrrolidine, morpholine, methylpiperazine, perhydroazepine.

The goal of the present paper is to study the effect of described variations in the basic part of heptacaine chloride molecule on the alkaline hydrolysis rate.

Experimental

Chlorides of studied substances (Table 1), their preparation and pharmacologic evaluation have been published in Ref. [3].

Registration spectrophotometer Specord UV VIS and spectrophotometer VSU-2 (Zeiss, Jena), digital pH-meter OP-208/1, glass and calomel electrodes, and automatic

burette OP-930 (Radelkis, Budapest), microcomputer PMD 85-2A (Tesla, Czechoslovakia) were used for measurements.

Studied substances were hydrolyzed in aqueous-ethanolic solution of 0.1 M-NaOH at 40, 50, and 60 °C. The ethyl alcohol content in the reaction medium was 50 vol. %. Concentration of studied substances was 1×10^{-3} mol dm^{-3}. The processing method and rate constants calculation have been described in Ref. [4].

pK_a Values of studied substances were determined by titration of 0.1 M-NaOH from an automatic burette controlled by microcomputer PMD 85-2A [5], connected to the digital pH-meter OP-208/1. pK_a Values of substances were calculated using the Henderson—Hasselbach equation.

Results and discussion

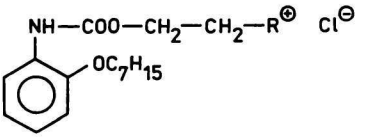
As reported in Refs. [4, 6—9] the kinetics of alkaline hydrolysis of phenylcarbamates with local anaesthetic activity were studied by our team. These substances are in alkaline medium decomposed to final products — substituted aniline, basic alcohol, and carbon dioxide. Studied were the effect of the character of connecting chain between basic and aromatic part of molecule and *o*-substitution [4], the effect of alkoxy substituents in *o*-, *m*-, and *p*-position of the aromatic ring and their magnitude on the hydrolysis rate of basic phenylcarbamates [6]. In more detail were studied the kinetics of alkaline hydrolysis of three most active substances of this series: heptacaine chloride [7, 8], carbisocaine chloride, and pentacaine chloride [8]. The validity of Hammett's and Swain—Lupton's equation [10, 11] has been confirmed on the series of *m*- and *p*-substituted piperidinoethyl phenylcarbamates [9].

Substances studied in the present paper are different in the character of basic part of the molecule, it is demonstrated by different pK_a values. Values of negative logarithm of dissociation constants of the studied substances are given in Table 1. Expressively are different pK_a values for morpholinoethyl (*III*) and 4-methyl-1-piperazinylethyl (*IV*) 2-heptyloxyphenylcarbamates, the second one has two pK_a values, owing to the presence of two nitrogens in basic part of the molecule. Dimethylammonioethyl 2-heptyloxyphenylcarbamate (*II*) has pK_a value higher when compared to the above mentioned. Nearly the same pK_a values can be found for pyrrolidino-, perhydroazepin-1-yl, diethylammonio-, and piperidinoethyl esters.

Resulting values of the rate constants of the second-order alkaline hydrolysis at temperatures 40, 50, and 60 °C are presented in Table 2. It follows from k values that the rate of hydrolysis of substances *III* and *IV* is higher. Activation energy values E_A (Table 3) were calculated from the Arrhenius equation, using the relation $\log k = f(1/T)$, mean values of activation enthalpy $\Delta H^{\neq}$ and activation entropy $\Delta S^{\neq}$ were calculated from Eyring's equation, from the relation $-\ln(kh/\boldsymbol{k}T) = f(1/T)$ (h is Planck's constant, $\boldsymbol{k}$ is Boltzmann's constant).

Table 1

Review of chemical structure of studied substances and pK_a values



Compound	R	pK_a
I	pyrrolidinio	8.2
II	dimethylammonio	7.3
III	morpholinio	5.0
IV	4-methyl-1-piperazinyl	2.2 6.2
V	diethylammonio	8.1
VI	perhydroazepin-1-yl	8.1
VII (Heptacaine)	piperidinio	7.9

Activation enthalpy was calculated from the slope a of this relation and activation entropy from the intercept b on the y axis [12].

Activation energy values E_A and activation enthalpy values ΔH^* in this series of *o*-substituted derivatives are lower than the values of *m*- and *p*-substituted piperidinoethyl phenylcarbamates [9].

Activation entropy values ΔS^* were different compared to [9] (*e.g.* for *p*-Cl substituted piperidinoethyl phenylcarbamate $\Delta S^* = -30.0$ J K^{-1} mol^{-1} whilst values of *o*-alkyloxy substituted derivatives varied from $\Delta S^* = -70.0$ to -110.0 J K^{-1} mol^{-1}). A higher drop of entropy is probably caused by different structure of these derivatives. Structural difference is due to the presence of *o*-heptyloxy substituent near the reaction centre — carbamate group, which is affecting molecules arrangement during the reaction of OH^- ions with the carbamate functional group. At the same time it is also a reason for different physicochemical properties (solubility, lipohydrophilicity). In bimolecular reactions the activated complex is created by connection of two separate molecules and thus ΔS^* is mostly negative.

The rate of alkaline hydrolysis for substance *III* is the highest in comparison to the rest of studied substances (Fig. 1). This substance has also the lowest pK_a value. The black point on the straight line belongs to heptacaine, its rate constants of alkaline hydrolysis and activation parameters have been determined in Refs. [7, 8]. Coefficients of $\log k = f(pK_a)$ relation at all studied temperatures are in Table 4. Slope of the straight line a is equal to the value β

Table 2

Resulting values of the second-order rate constants k from alkaline hydrolysis of studied substances

Compound	$k/(\mathrm{dm^3\ mol^{-1}\ s^{-1}})$		
	40 °C	50 °C	60 °C
I	$3.66 \times 10^{-5} \pm 1.60 \times 10^{-6}$	$9.07 \times 10^{-5} \pm 1.6 \times 10^{-6}$	$2.20 \times 10^{-4} \pm 4.6 \times 10^{-6}$
II	$4.20 \times 10^{-5} \pm 9.0 \times 10^{-7}$	$1.10 \times 10^{-4} \pm 6.0 \times 10^{-7}$	$2.76 \times 10^{-4} \pm 3.0 \times 10^{-6}$
III	$5.81 \times 10^{-5} \pm 1.9 \times 10^{-6}$	$1.33 \times 10^{-4} \pm 3.0 \times 10^{-6}$	$3.02 \times 10^{-4} \pm 1.1 \times 10^{-5}$
IV	$5.33 \times 10^{-5} \pm 2.2 \times 10^{-6}$	$1.20 \times 10^{-4} \pm 3.6 \times 10^{-6}$	$2.66 \times 10^{-4} \pm 3.6 \times 10^{-6}$
V	$3.51 \times 10^{-5} \pm 7.0 \times 10^{-7}$	$7.82 \times 10^{-5} \pm 1.1 \times 10^{-6}$	$2.14 \times 10^{-4} \pm 5.3 \times 10^{-6}$
VI	$3.34 \times 10^{-5} \pm 1.7 \times 10^{-6}$	$8.59 \times 10^{-5} \pm 2.5 \times 10^{-6}$	$2.13 \times 10^{-4} \pm 5.7 \times 10^{-6}$

Rate constants and activation parameters from alkaline hydrolysis of heptacaine chloride are presented in Ref. [8].

in Brönsted's relation [13] and is negative. Brönsted's relation was examined by authors [14—16] in the studies of alkaline hydrolysis kinetics of carbamates with the aim to explain a mechanism of this reaction. *Williams* [14] determined values $\beta = -1.15$ for phenyl and alkyl phenylcarbamates, pK_a values by hydrolysis of departing alcohols were 12.2—16, or $\beta = -0.250$ for alkyl *N*-methyl-*N*-phenylcarbamates with values $pK_a = 7$—16. *Hegarty* and *Frost* [15] for alkyl and aryl *N*-(*p*-nitrophenyl)carbamates determined $\beta = -1.34$, pK_a values by hydrolysis of alcohols were 9.1—15.1. *Bergon* and *Calmon* [16] determined $\beta = -1.56$ for substituted phenyl 3,4-dichlorophenylcarbamates, pK_a values 7—12.2. For alkyl esters $\beta = -0.31$, pK_a values by hydrolysis of departing alcohols were 14.8—16. Changes in β values are according to authors [14, 16] due to the change in the mechanism of alkaline hydrolysis of studied substances, according to *Dittert* [17] there are two possible mechanisms of this change, $B_{AC}2$ for aliphatic carbamates through carbamate anion and E1cB for aromatic carbamates through isocyanate.

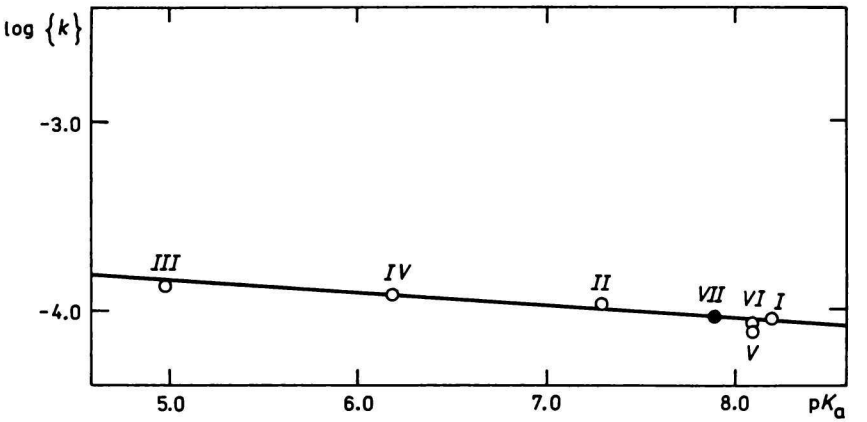


Fig. 1. Dependence of $\log k$ of alkaline hydrolysis at 50 °C on pK_a values.

Table 3

Activation parameters from alkaline hydrolysis of studied substances

Compound	E_A / kJ mol^{-1}	ΔH^* / kJ mol^{-1}	ΔS^* / J K^{-1} mol^{-1}
I	77.8 ± 0.9	75.1 ± 0.9	−90.4 ± 2.7
II	81.6 ± 0.3	78.9 ± 0.2	−77.2 ± 0.8
III	71.4 ± 0.9	68.7 ± 0.9	−107.0 ± 2.7
IV	69.8 ± 1.1	67.1 ± 1.0	−112.9 ± 3.2
V	78.2 ± 6.6	75.5 ± 6.6	− 89.8 ± 20.4
VI	80.2 ± 0.5	80.0 ± 2.1	−75.2 ± 6.5

Table 4

Coefficients of the dependence of $\log k$ values from alkaline hydrolysis at 40, 50, and 60 °C on pK_a values of studied substances

θ/°C	a	b	n	r	F	s
40	−0.0714	−3.86	7	0.953	48.9	0.0305
50	−0.0655	−3.52	7	0.929	31.3	0.0350
60	−0.0453	−3.28	7	0.906	23.0	0.0282

The values of the second-order rate constants k of studied substances are close to each other. Determined β values are low (−0.05 to −0.07), the reason is probably that pK_a values, which are similar, range from 5.0 to 8.2, depending on the character of the hydrolysis of departing basic alcohols. Differences in the character of basic part of the molecule in these substances have probably no dominant effect on the rate of their alkaline hydrolysis.

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Translated by V. Bachratý