KINETICS OF ALKALINE HYDROLYSIS AND CORRELATION STUDIES OF *m*- AND *p*-SUBSTITUTED PIPERIDINOETHYL PHENYLCARBAMATES

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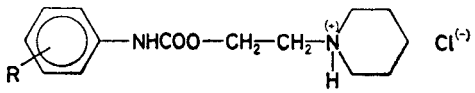
Received October 18, 1988
Accepted December 12, 1988

Kinetics of alkaline hydrolysis have been studied with a series of 15 *m*- and *p*-substituted piperidinoethyl phenylcarbamates. The rate constants have been determined at 70, 60, 50, and 40°C and the activation parameters have been calculated. These values have been correlated with the substituent constants σ, $\mathscr{F}$, $\mathscr{R}$, F, R, π. Validity of the Hammett equation and the Swain–Lupton equation has been confirmed in the series studied and for the *p*-derivatives, respectively. The lipophilicity parameter π does not correlate with the values found.

The basic esters of substituted phenylcarbamic acids, which mostly are local anesthetics and affect cardiovascular system, belong among themes of our long-term studies[1]. These studies also involve physico-chemical investigation of kinetics of alkaline hydrolysis of the compounds studied[2-5]. This present communication represents a continuation of these studies with the aim of estimation of rate constants of the alkaline hydrolysis and verification of validity of the Hammett[6] and Swain–



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–Lupton[7] equations for a series of fifteen *m*- nad *p*-substituted piperidinoethyl esters of phenylcarbamic acid (Table I) with local anesthetic activity. Moreover, the kinetic parameters have been correlated with the inductive and mesomeric constants F, R and lipophilic parameters π, π^- taken from refs[8-11].

EXPERIMENTAL

Syntheses of the investigated hydrochlorides of compounds *Ia* to *Io* (Table I) are described elsewhere[12,13]. Ethanol for UV spectroscopy as well as the substituted aniline derivatives were distilled before use.

TABLE I

A survey of the compounds studied, of the rate constant values (k, s^{-1} l mol^{-1}) of alkaline hydrolysis and the activation parameters (E_A and $\Delta H^{\neq}$ in kJ mol^{-} , $\Delta S^{\neq}$ in J K^{-1} mol^{-1}, $\Delta G^{\neq}$ in kJ mol^{-1})

Compound	R	$k_{40} \cdot 10^5$	$k_{50} \cdot 10^5$	$k_{60} \cdot 10^4$	$k_{70} \cdot 10^4$	E_A	$\Delta H^{\neq}$	$\Delta S^{\neq}$	$\Delta G^{\neq}$
Ia	H	2·54	8·43	2·22	6·27	94·7 ± 1·9	91·9 ± 1·9	−39·6 ± 3·9	105·5
Ib	3-F	3·92	13·3	3·60	10·7	97·6 ± 2·0	94·8 ± 2·0	−26·8 ± 6·2	104·0
Ic	4-Cl	3·43	12·9	3·74	8·80	96·8 ± 4·7	94·0 ± 4·9	−29·9 ± 15·	104·3
Id	4-C_2H_5	1·69	6·24	1·66	4·01	93·8 ± 4·4	91·0 ± 4·5	−45·3 ± 14·	106·6
Ie	4-CH_3	1·62	5·20	1·89	4·54	101· ± 4·1	98·2 ± 4·1	−23·3 ± 12·	106·2
If	3-OCH_3	2·84	7·98	2·47	7·17	96·5 ± 2·6	93·8 ± 2·6	−33·3 ± 8·8	105·2
Ig	4-OCH_3	1·77	4·87	1·29	3·52	88·9 ± 1·6	86·1 ± 1·5	−61·6 ± 4·7	107·2
Ih	3-OC_2H_5	2·66	7·42	2·28	6·84	97·0 ± 3·0	94·2 ± 3·0	−32·5 ± 9·2	105·4
Ii	4-OC_2H_5	1·62	4·52	1·41	3·50	92·7 ± 2·2	89·9 ± 2·2	−50·5 ± 6·7	107·1
Ij	3-OC_3H_7	2·68	7·81	2·28	7·08	97·3 ± 2·9	94·5 ± 2·8	−31·5 ± 8·6	105·3
Ik	4-OC_3H_7	1·64	4·63	1·29	3·21	88·8 ± 0·6	86·1 ± 0·6	−62·2 ± 2·0	107·4
Il	3-(OC_3H_7-*i*)	2·43	6·53	2·06	5·74	94·9 ± 3·0	92·2 ± 3·0	−39·7 ± 9·1	105·8
Im	4-(OC_3H_7-*i*)	1·44	3·26	1·08	2·95	91·5 ± 5·7	88·8 ± 5·7	−55·5 ± 1·7	107·8
In	4-F	2·49	10·5	3·24	8·50	105· ± 4·7	102· ± 4·8	−6·5 ± 14·	105·4
Io	3-CF_3	—	9·69	3·13	7·28	93·1 ± 7·1	90·3 ± 7·1	−42·7 ± 27·	104·6

The spectrophotometry was carried out with a Specord UV VIS (Zeiss Jena, G.D.R.) and Spektromom MOM 203 (Budapest, Hungary) apparatus in 0·1 dm quartz cells using an ultrathermostat U-15 (Prüfgeräte Werk, Dresden, G.D.R.). An analytical balance type WP-11 (Poland) was used for weighing.

The alkaline hyrolysis of all the compounds with $c = 0{\cdot}001$ mol l^{-1} proceeded in aqueous-ethanolic solution of sodium hydroxide with $c = 0{\cdot}1$ mol l^{-1}, the ethanol concentration being 50% v/v. The solutions were heated in closed flasks in the ultrathermostat at the temperature of 70, 60, 50, and 40°C with the accuracy of $\pm 0{\cdot}2$°C. The reaction course was followed by estimating the concentration of the compound investigated by means of UV spectrophotometry at definite time intervals. The optimum wavelength was determined experimentally from the differences of the values of molar absorption coefficients of the compound hydrolyzed and the respective substituted aniline: the wavelength used corresponded to the maximum difference between these values. The hydrolysis kinetics of the compounds investigated was evaluated with application of the overall 2nd order equation[14]. The procedure used and the formula for calculation of the concentration of the compounds during the reaction are given in ref.[3]. The rate constants and the activation parameters E_A, $\Delta H^{\neq}$, $\Delta S^{\neq}$, and $\Delta G^{\neq}$ were calculated according to ref.[14]. The parameters of the linear dependences

$$y = a_0 + a_1 x_1 + a_2 x_2 + \ldots . \qquad (1)$$

were calculated by the least squares treatment[15] using an RPP 16 S computer in the Institute of Applied Mathematics and Computer Technique, Comenius University, Bratislava.

RESULTS AND DISCUSSION

According to several reports published so far[2-5,16-29] dealing with alkaline hydrolysis of aliphatic and aromatic carbamates under various conditions it can be presumed that in the case of the compounds studied the alkaline hydrolysis also proceeds by the scheme suggested by Dittert[16]. In the case of heptacainium chloride it was found[4] by means of the half-life method that the overall rate equation of the hydrolysis with sodium hydroxide is of the 2nd order. The derivatives of phenylcarbamic acid are hydrolyzed to give the respective substituted aniline, basic alcohol, and carbon dioxide. The decomposition products from this hydrolysis (the substituted aniline and basic alcohol) were proved by TLC[5,30].

Table I gives the resulting values of rate constant k, the values of activation energy E_A calculated from the Arrhenius equation, the values of activation enthalpy $\Delta H^{\neq}$ and activation entropy $\Delta S^{\neq}$ calculated from the Eyring equation[14], and the values of activation free (Gibs) energy $\Delta G^{\neq}$ for $T = 343{\cdot}15$. Figure 1 presents the dependence $\log k = f(T^{-1})$: not all the straight lines are given, since the points are close to each other and some straight lines would be overlapped.

Compounds *Ib*, *Ic*, *If*, *Ih*, *Ij*, *In* exhibit faster hydrolysis courses as compared with that of the parent compound *Ia* as well as *Id*, *Ie*, *Ig*, *Ii*, *Ik*, *Im*, which follows from the values of rate constants and from the values of $\Delta G^{\neq}$. The substituents 3-F, 4-Cl, and 4-F in the aromatic ring of compounds *Ib*, *Ic*, and *In*, respectively, have strong negative inductive effects due to which the electron density at the carbamate group

is decreased and the reaction with OH^- is accelerated. Within the series investigated the slowest reaction is observed with the derivatives carrying alkyl groups at para position (4-CH_3, 4-C_2H_5; predominating +I effect) and alkoxyl goups (4-OCH_3 through 4-OC_3H_7; predominating +M effect): these substituents increase the electron density at the carbamate group and retard the course of alkaline hydrolysis. This fact is distinctly expressed by the dependence of experimental log k values on the σ substituent constants given in Fig. 2. The coefficients of the function are given in Table II for all the four temperatures, Eqs (*2*) through (*5*).

Compound *Io* was excluded from the correlation because of its slight solubility in the reaction solution; in this case the substrate amount was reduced and the proportion of ethanol in the reaction system was increased whereby the reaction conditions were considerably different from those used for the other substrates.

Using the *p*-derivatives of the compound series studied it was possible to verify the presumption by Swain & Lupton[7] that the σ values can be reproduced as linear combinations of the inductive constants $\mathscr{F}$ and mesomeric constants $\mathscr{R}$. The authors suggested these constants as more precisely defining and physically more significant independent variables serving for predictions of substituent effects on reaction rates or for correlation studies. Table II gives Eqs (*6*)–(*9*) for log k values at four temperatures.

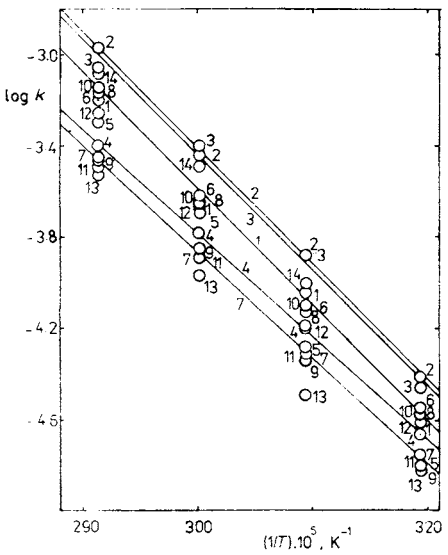

FIG. 1

Dependence of log k on $1/T$. 1 *Ia*, 2 *Ib*, 3 *Ic*, 4 *Id*, 5 *Ie*, 6 *If*, 7 *Ig*, 8 *Ih*, 9 *Ii*, 10 *Ij*, 11 *Ik*, 12 *Il*, 13 *Im*, 14 *In*

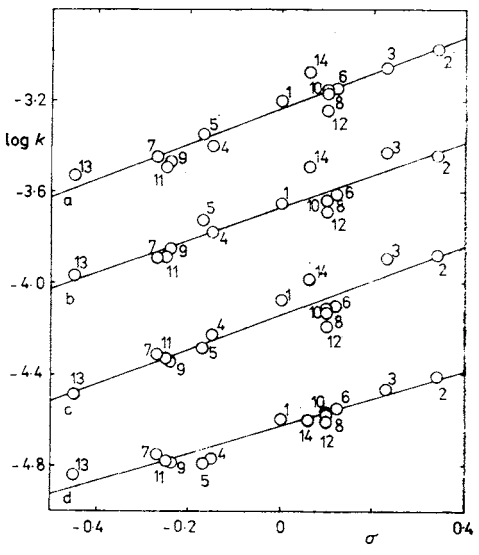

FIG. 2

Dependence of log k on σ at a 70°C, b 60°C, c 50°C, d 40°C

Hansch et al.[8] modified the $\mathscr{F}$ and $\mathscr{R}$ constants to obtain different values which, however, correlate with the values of $\mathscr{F}$ and $\mathscr{R}$ by Swain & Lupton[7]. In Eqs (*10*)–(*13*) we used the $\mathscr{F}$ and $\mathscr{R}$ values by Hansch et al.[8] and arrived at almost the same r values. The same results were also obtained when using the scales of constants F and R by Swain et al.[9] (see Table II, Eqs (*14*)–(*17*)). Hence it follows that the reactivity within the series investigated can be expressed by the polar effects of substituents as well as by the combination of their inductive and mesomeric effects involved in the values of constants $\mathscr{F}$ and $\mathscr{R}$ or F and R.

Equations (*18*)–(*21*) of Table II correlate the log k values of the whole set with the constants F and R, suggested by Williams & Norrington[10], in order to make

TABLE II

The regression coefficients of equations of the dependences of log k on the parameters σ, $\mathscr{F}$, $\mathscr{R}$, F, R, and the activation parameters on σ

Equation	Function	n	r	F	s	a_0	a_1	a_2
2	$\log k_{70} = f(\sigma)$	14	0·961	144·2	0·052	−3·236	0·7827	—
3	$\log k_{60} = f(\sigma)$	14	0·937	86·94	0·061	−3·668	0·7128	—
4	$\log k_{50} = f(\sigma)$	14	0·937	86·05	0·065	−4·139	0·7496	—
5	$\log k_{40} = f(\sigma)$	14	0·967	172·6	0·036	−4·630	0·5921	—
6	$\log k_{70} = f(\mathscr{F}, \mathscr{R})^a$	9	0·954	30·32	0·059	−3·238	0·5245	0·8298
7	$\log k_{60} = f(\mathscr{F}, \mathscr{R})^a$	9	0·970	47·64	0·049	−3·636	0·5388	0·8760
8	$\log k_{50} = f(\mathscr{F}, \mathscr{R})^a$	9	0·987	116·5	0·033	−4·092	0·5504	0·9336
9	$\log k_{40} = f(\mathscr{F}, \mathscr{R})^a$	9	0·957	32·78	0·040	−4·658	0·3891	0·5595
10	$\log k_{70} = f(\mathscr{F}, \mathscr{R})^b$	9	0·953	29·53	0·060	−3·240	0·8737	0·8363
11	$\log k_{60} = f(\mathscr{F}, \mathscr{R})^b$	9	0·970	47·20	0·050	−3·636	0·8954	0·8843
12	$\log k_{50} = f(\mathscr{F}, \mathscr{R})^b$	9	0·986	106·4	0·035	−4·094	0·9167	0·9402
13	$\log k_{40} = f(\mathscr{F}, \mathscr{R})^b$	9	0·958	33·56	0·039	−4·659	0·6491	0·5655
14	$\log k_{70} = f(F, R)^c$	9	0·969	45·91	0·049	−3·770	0·3902	0·2389
15	$\log k_{60} = f(F, R)^c$	9	0·986	101·8	0·034	−3·653	0·4000	0·2502
16	$\log k_{50} = f(F, R)^c$	9	0·985	98·73	0·036	−4·112	0·3932	0·2588
17	$\log k_{40} = f(F, R)^c$	9	0·930	19·18	0·050	−5·018	0·2948	0·1598
18	$\log k_{70} = f(F, R)^d$	14	0·969	84·93	0·047	−3·234	0·5273	0·8452
19	$\log k_{60} = f(F, R)^d$	14	0·963	69·25	0·048	−3·661	0·4796	0·7917
20	$\log k_{50} = f(F, R)^d$	14	0·965	73·56	0·049	−4·124	0·4934	0·8440
21	$\log k_{40} = f(F, R)^d$	14	0·971	91·83	0·034	−4·645	0·4233	0·6123
22	$\Delta H^{\neq} = f(\sigma)$	14	0·569	5·736	3·7	93·08	11·13	—
23	$\Delta S^{\neq} = f(\sigma)$	14	0·682	10·43	11·8	−36·77	47·52	—
24	$\Delta G^{\neq} = f(\sigma)$	14	0·948	107·2	0·40	105·7	−5·176	—

[a] The scale of constants taken from ref.[7]; [b] the scale of constants taken from ref.[8]; [c] the scale of constants taken from ref.[9]; [d] the scale of constants taken from ref.[10].

more precise the evaluation of inductive and mesomeric effects by introducing the dependence of both the effects on the position of substituent and application of multiple factors.

At the same time we also investigated the substituent effects on the values of activation quantities, i.e. the correlation of the calculated values of $\Delta H^{\neq}$, $\Delta S^{\neq}$, and $\Delta G^{\neq}$ on σ values (see Eqs (*22*)–(*24*), Table II). In accordance with ref.[14] the $\Delta H^{\neq}$ and $\Delta S^{\neq}$ values do not correlate with the σ values. The activation Gibbs energy, $\Delta G^{\neq}$, gives better correlation, the same being true of the rate constants.

Within the series investigated we made an attempt to find the isokinetic relation expressed by Eq. (*25*)

$$\mathrm{d}\Delta H = \beta \, \mathrm{d}\Delta S \qquad (25)$$

and graphically by the function $\log k = f(T^{-1})$. The constant β in Eq. (*25*) has the dimension of temperature and is called the isokinetic temperature, i.e. if the reactions could be realized at this temperature, they would proceed at identical rates, and above this temperature the reactivity order would be reversed. When adopting the coordinates $\log k$ and T^{-1} for a series of compounds, the isokinetic temperature is the point of intersection of the straight lines mentioned and it is found with difficulties. According to ref.[31], Eq. (*25*) is statistically incorrect, since the β value can be loaded with error, and the following Eq. (*26*) is recommended for estimation of isokinetic relation.

$$\log k = y_0 - H(T^{-1} - \beta^{-1})/2{\cdot}303R \qquad (26)$$

Also it is recommended to try to find the linear relation between te $\log k$ values at two different temperatures in order to reveal possible deviations of some points[31].

TABLE III

The regression coefficients of linear dependences between the individual $\log k$ values and between the $\Delta H^{\neq}$ and $\Delta S^{\neq}$ values

Equation	Function	*n*	*r*	*F*	*s*	a_0	a_1
27	$\log k_{70} = f(\log k_{60})$	14	0·977	256·5	0·040	0·6019	1·047
28	$\log k_{70} = f(\log k_{50})$	14	0·957	131·9	0·055	0·7971	0·9747
29	$\log k_{70} = f(\log k_{40})$	14	0·955	123·2	0·056	2·644	1·270
30	$\log k_{60} = f(\log k_{50})$	14	0·974	217·7	0·040	0·1607	0·9252
31	$\log k_{60} = f(\log k_{40})$	14	0·912	59·52	0·072	1·577	1·133
32	$\log k_{50} = f(\log k_{40})$	14	0·931	78·26	0·068	1·495	1·217
33	$\Delta H^{\neq} = f(\Delta S^{\neq})$	14	0·989	549·7	0·66	102·6	261·5

Figure 1 shows that the point of intersection of all the straight lines can be determined with difficulty. We found the linear relation between the individual log k values at various pairs of temperatures (see Table III, Eqs (*27*)–(*32*)) and the linear relation between the values $\Delta H^{\neq}$ and $\Delta S^{\neq}$ (Table III, Eq. (*33*)) which also is a condition of validity of the Hammett equation[14,31]. In Eqs (*27*)–(*32*) the a_1 coefficient is approximately equal to 1, hence according to ref.[32] the series studied can be classified as approximately isoenthalpic.

From the standpoint of local-anesthetic effects of phenylcarbamates an important property is their lipophilicity[1,33] expressed by the value of experimental distribution coefficient P' or by the estimated or published[8,10,33,34] substituent lipophilicity constants π. For the correlation equations used in studies of relations between biological activity and various physico-chemical properties within a compound series it is required that the individual parameters were not mutually intercorrelated[34].

In the present work we have also investigated the relation between the $\Delta G^{\neq}$ values and the lipophilicity expressed in the published[10] values π and π^- of the substituents depending on the position of the substituents in the aromatic ring. We have found that the $\Delta G^{\neq}$ values do not correlate with the π constants ($r = 0{\cdot}268$, $n = 14$, $F = 0{\cdot}926$).

In conclusion it must be noted that the substituents of the compounds studied were selected with respect to biological activity, and the selection is not wide enough to allow mutual evaluation of the correlations found.

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Translated by J. Panchartek.