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KINETICS OF PROPANESULFOCHLORIDE PHENOLYSIS IN THE PRESENCE OF DIMETHYLBENZYL AMINE. THE SOLVENT EFFECT*.

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Kinetics of propanesulfochloride interaction with phenol catalyzed by dimethylbenzyl amine in eleven protoinert solvents at 30°C has been studied. The reaction proceeds by two mechanisms, i.e. the sulfene mechanism (1) and that of the general base catalysis (2). When solvent ε is increasing, the contribution of (1) is increased while the portion of (2) falls down in the common reaction flow. To quantitatively estimate the effect of medium nature on the rate of competitive streams the four parameter Koppel-Palm equation was used. The most relevant solvation effects are: polarity for mechanism (1), and polarity, polarizability, and electrophility for mechanism (2). Nucleophility parameter may be actually ignored both in case of mechanism (2) and in case of (1). The obtained results have been interpreted in terms of the carbanion-like E2 transition state for (1) and S_N2 transition state for (2). Variation of the solvent nature permits direction of the process predominantly by pathway (1) or (2).

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* The XIV-th communication of the series "Alkanesulfonylation reactions"

Earlier we showed[1-4] that in alkanesulfonylation of phenols in the presence of trialkylamines two competitive mechanisms may be realized: the sulfene mechanism (1a) and that of the general base catalysis (1b)

$$\left.\begin{array}{l} RCH_2SO_2Cl \\ + \\ R'_3N \\ + \\ ArOH \end{array}\right\} \begin{array}{l} \xrightarrow{a} [RCH{=}SO_2] + ArOH + R'_3N{\cdot}HCl \\ \rightleftharpoons R\text{-}CH_2SO_2Cl + ArO\text{-}H\cdots NR'_3 \end{array} \Bigg\} \begin{array}{l} RCH_2SO_2OAr \\ + \\ R_3N{\cdot}HCl \end{array} \quad (1)$$

The extent of realization for each of the mechanisms depends on the structure of alkanesulfohalide[1], phenol[2], and tertiary amine[3] which affects the transition state structures and the ratio of the competitive flows in the end. It was interesting to study the effect of the solvent nature on the process in question.

The present paper presents results of investigation of the solvent effects on the rate and mechanism of propanesulfochloride interaction with phenol in the presence of dimethylbenzyl amine at 30°C. P- and m-xylene, benzene, tolyene, chloroform, chlorobenzene, ethyl acetate, chlorous methylene, cyclohexanon, nitrobenzene, acetonitrile, largely differing in their polarities, polarizabilities, electrophilities, and nucleophilities, were used as solvents.

Experimental

Propanesulfochloride obtained by method[5] and phenol were purified by repeated redistillation under vacuum, dimethylbenzyl amine was boiled over tosylchloride to remove primary and secondary amines, then dried over melted KOH, and distilled over a fresh sample of melted KOH and subsequently over metal sodium. The solvents used were purified according to methods[6,7].

Kinetic studies were made by the methods described elsewhere[3] at the following initial reactant concentrations: (a) propanesulfochloride 0.005 mole/l, (b) phenol 0-0.075 mole/l, (c) dimethylbenzyl amine 0.025 mole/l.

To control the process two methods were used: the

method of the potentiometric titration of chloride ions formed in the course of the reaction (PT) and that of the gas-liquid chromatography (GLC) (LHM-8MD N5 Model, flame ionization detector, chromosorb column 1m×3mm with 10% silicon SE-30, gas-carrier was helium) with the concentration of the end product, i.e. phenyl propane sulfonate determined by the internal standard.

In the case of acetonitrile measurements were only made by the PT method due to a poor internal standard solubility for measurements by the GLC method.

The reaction rate constants obtained under the pseudofirst order were calculated according to the formula

$$k_1 = 1/t \cdot \ln a/(a-x) \qquad (2)$$

The reaction rate constants were calculated either by dividing k_1 by m (with $m \gg a$) or (with $m \geq a$) using the formula

$$k_2 = 1/t \cdot 1/(m-a) \cdot \ln a(m-x)/m(a-x) \qquad (3)$$

In processing the experimental data the least square method[8] was used on the basis of the microcomputer "Electronika MK-54". Calculations by the multiparameter equations were carried out using DVK-2 computer.

Results and Discussion

At the joint realization of the general base catalysis (1b) and elimination-addition (sulfene)(1a) mechanisms the reaction rate can be described by the equation:

$$dx/dt = k_s(a-x)(m-x) + k_b(a-x)(b-x)(m-x) \qquad (4)$$

where k_s is the second order rate constant of the sulfene flow; k_b is the third order rate constant of the general base catalysis flow; x is the concentration of chloride ions (PT) or phenyl propane sulfonate (GLC) at the time t.

In the analysis of the reaction kinetics we observed a certain discrepancy of the results obtained by PT and GLC methods which was mentioned earlier[3]. Possible reasons for this we shall discuss below. In the estimation of the general base catalysis flow the data obtained by both methods coincide within the limits of the error. The sulfene

Table 1. The Influence of the Solvent Nature on the Kinetics of Phenol Propanesulfonylation Catalyzed by Dimethylbenzyl Amine, a 0.005, m 0.025 mole/l, 30°C

N	Solvent	ε [9]	k_s' [1] $\cdot 10^5$ l/mole·s	k_{obs} [1] $\cdot 10^5$ (l/mole·s)
				0.025
1	p-Xylene	2.27	2.14±0.07	4.7±0.1
2	Benzene	2.28	6.0±0.2	13.9±0.1
3	m-Xylene	2.37	1.77±0.04	4.5±0.1
4	Tolyene	3.38	3.3±0.1	7.1±0.2
5	Chloroform	4.81	80.2±0.9	84.0±0.8
6	Chloro-benzene	5.62	49±3	34.4±0.8
7	Ethyl acetate	6.02	55±2	35.2±0.4
8	Chlorous methylene	9.08	415±2	275±5
9	Cyclohexanone	18.3	574±8	135±9
10	Nitrobenzene	34.8	2100±200	1140±40
11	Acetonitrile [2]	37.6	10800±100	12100±300

Note. [1] k_s' values have been obtained using PT method for b=0. k_{obs} have been obtained using the GLC method, and k_s and k_b have been calculated from k_{obs}-b dependence, where k_s is a segment on the ordinate, and k_b is the tangent of the line slope angle.

The continuation of Table 1

for b (mole/l)			k_s [1]).10^5	k_b [1]).10^3
0.0375	0.0500	0.0750	l/mole·s	$l^2/mole^2$.S
-	9.2±0.1	13.3±0.1	0.5±0.2	1.72±0.05
-	26.0±0.2	34.6±0.2	4.0±0.2	4.1±0.4
-	8.5±0.1	12.6±0.1	0.43±0.06	1.62±0.01
10.6±0.2	13.4±0.4	20.7±0.1	0.30±0.04	2.70±0.09
89±1	100±2	115±2	67±3	6.4±0.5
43.2±0.4	50.0±0.4	66.0±0.4	19.1±0.8	6.3±0.2
-	45.2±0.4	59.2±0.8	23±2	4.8±0.5
-	338±2	372±10	230±20	19±3
159±4	177±2	225±11	90±3	17.8±0.6
1190±20	1220±40	-	1070±10	31±2
12500±400	-	14400±500	-	480±15

[2]) In the case of acetonitrile k_{obs}, k_s and k_b have been obtained using PT data.

flow was estimated by the PT data.

To estimate the nonspecific solvation effect on the rate of competitive flows (1a) and (1b) the Kirkwood equation was used.

$$\log k'_s = -(7.4\pm0.4)+(11.9\pm1.1)\cdot(\varepsilon-1)/(2\varepsilon+1); \quad R=0.96;\ S=0.37 \qquad (5)$$

$$\log k_b = -(4.1\pm0.5)+(5.7\pm1.3)\cdot(\varepsilon-1)/(2\varepsilon+1); \quad R=0.82;\ S=0.42 \qquad (6)$$

Elimination of the most diverging point (acetonitrile) appreciably improves the correlation.

$$\log k'_s = -(7.1\pm0.3)+(10.7\pm0.8)\cdot(\varepsilon-1)/(2\varepsilon+1); \quad R=0.98;\ S=0.25 \qquad (7)$$

$$\log k_b = -(3.6\pm0.2)+(4.1\pm0.6)\cdot(\varepsilon-1)/(2\varepsilon+1); \quad R=0.92;\ S=0.15 \qquad (8)$$

For the reaction proceeding by the sulfene mechanism a satisfactory correlation (R=0.98) between the process rate and the Kirkwood function is observed, the sensitivity of the latter to the variation of the varied parameter being 2.5 times higher than in the case of the general base catalysis flow.

Going back to the question of different estimations of the sulfene flow rate it should be noted that when the solvent ε is increasing the difference between k_s values obtained by GLC and PT - Δk_s ($\Delta k_s = k_s^{PT} - k_s^{GLC}$) methods is enhanced. The attempt to treat Δk_s dependence on medium polarity by the least square methods has led to equation (9) which is very similar to equation (7).

$$\log \Delta k_s = -(7.3\pm0.3) + (10.4\pm0.8)\cdot(\varepsilon-1)/(2\varepsilon+1); \quad R=0.98;\ S=0.23 \qquad (9)$$

The fact brings about the idea that the sulfene flow is involved in the observed differences. When the medium polarity is increased the solvation stability of the sulfene intermediate is apparently enhanced. The reaction stops by adding HNO_3 aqueous solution excess (1:5) besides neutralizing the base-catalyst results in essentially instant sulfene hydrolysis, and hence in the decreased phenylpro-

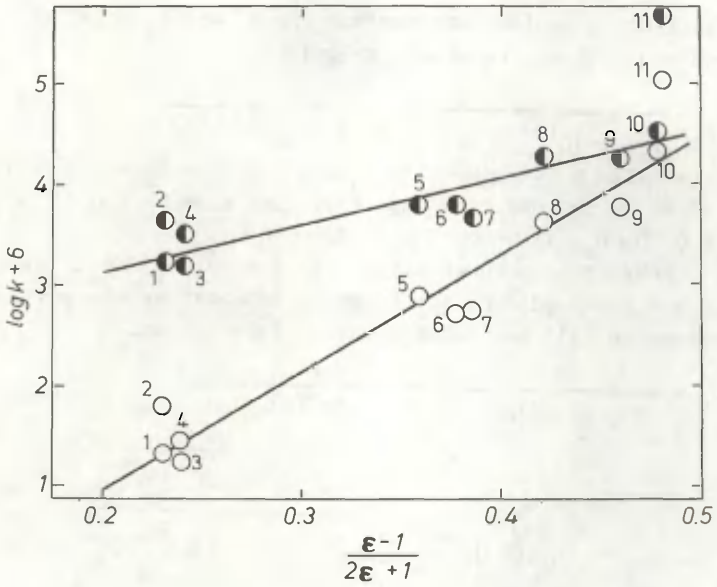

Fig.1. Dependence of the rate constant k'_s (◯) and k_b (◐) logarithms on the Kirkwood function. Solvent numeration corresponds to Table 1.

panesulfonate yield comparing to the chloride-ion yield formed in the first step (scheme 1a).

For the reaction proceeding by pathway (1b) the transition state is less polar and more bulky which makes correlation by the Kirkwood equation approximate only; this is apparently connected with the considerable contribution of non-specific solvation effects into transition state stabilization.

Expressions for contributions of the competing mechanisms in the general reaction flow are of form (10),(11).

$$D_s = \frac{k'_s}{k'_s + k_b \cdot b} = \frac{1}{1 + (k_b/k'_s) \cdot b} \qquad (10)$$

$$D_b = 1 - D_s \qquad (11)$$

Substituting in (10) expressions for k_s and k_b obtained from the Kirkwood equation, we get (12).

$$D_s = \frac{1}{1 + b \cdot 10^{(\Delta \log k_o + \Delta U \cdot (\varepsilon - 1)/(2\varepsilon + 1))}}, \qquad (12)$$

where $\Delta \log k_o = \log k_o^b - \log k_o^s$, $\Delta U = U_b - U_s = 4.1 - 10.7 = -6.6$. It follows from Eq. (12) that when $b = 0$, $D_s = 1$; $b \neq 0$, $0 < D_s < 1$; $b \to \infty$, $D_s \to 0$.

Substituting in equation (12) the values for $\Delta \log k_o$ and ΔU obtained from the Kirkwood dependences one gets expression (13) for model reaction in question.

$$D_s = \frac{1}{1 + b \cdot 10^{(3.5 - 6.6\ (\varepsilon - 1)/(2\varepsilon + 1))}} \qquad (13)$$

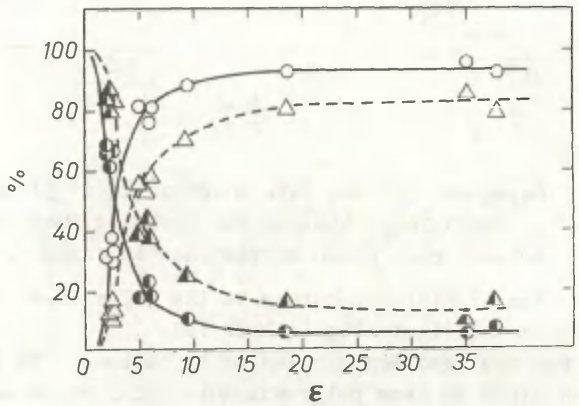

Fig.2. The influence of medium polarity (ε) on the realization extent (%) of the competing flows in the sulfene mechanism (○ △) and the general base catalysis mechanism (◐ ◭). b 0.025 (○ ◐), 0.075 (△ ◭) mole/l.

Fig. 2 shows that equations (11) and (13) describe well the dependence of contributions of the competing mechanisms on phenol concentration b and the solvent $(\varepsilon - 1)/(2\varepsilon + 1)$ value.

The obtained results indicate that when low-polar protoinert p- and m-xylene, benzene and toluene are used the process proceeds predominantly by the general base catalysis mechanism (1b). The growth of the solvent polarity results in an abrupt increase in the contribution of the elimination-addition mechanism (1a). When polar solvents (hexanon, nitrobenzene, acetonitrile) are used the reaction proceeds almost totally by the sulfene mechanism which is expressed in the weak influence of phenol concentration on the process rate.

In order to more fully take into account the influence of various solvation effects on the rate of the competing flows the four-parameter Koppel-Palm equation was used that separately considered the polarity, polarizability, electrophility and nucleophility effects of a solvent. Solvent charactaristics and logarithms for rate constants of the competing flows are given in Table 2.

Both in case of the sulfene flow (1a) and in case of the general base catalysis flow (1b) the Koppel-Palm equation describes the reaction rate dependence on the solvent nature.

$$\log k'_s = -(11.8\pm1.4) + (11.1\pm0.7)\frac{\varepsilon-1}{2\varepsilon+1} + (10.9\pm3.3)\frac{n^2-1}{n^2+1} + $$

$$+ (0.35\pm0.07)E + (0.002\pm0.001)B;\ R=0.994;\ S=0.18 \qquad (14)$$

$$\log k_b = -(8.3\pm2.0) + (4.5\pm0.9)\frac{\varepsilon-1}{2\varepsilon+1} + (10.7\pm4.9)\frac{n^2-1}{n^2+1} + $$

$$+ (0.38\pm0.11)E + (0.003\pm0.002)B;\ R=0.956;\ S=0.27 \qquad (15)$$

The results of a correlation analysis permit the following generalizations.

The influence of the solvent nature on the sulfene flow rate can be described by the Koppel-Palm equation with an excellent correlation (R=0.99). The contributions of separate solvent parameters into common dependence of the reaction rate (1a) on the solvent nature complies, according to equation (16), standardized scale, with the following sequence:

Table 2. Solvent Characteristics and Rate Constant Logarithms of the Competing Flows.

N	Solvent	$\frac{\varepsilon - 1}{2\varepsilon + 1}$ [9]	$\frac{n^2 - 1}{n^2 + 1}$ [9]	E [9]	B [9]	$-\log k'_s$	$-\log k_b$
1	p-Xylene	0.2292	0.3822	0	68	4.670	2.764
2	Benzene	0.2306	0.3852	2.1	48	4.222	2.387
3	m-Xylene	0.2390	0.3830	0	68	4.752	2.790
4	Tolyene	0.2395	0.3829	1.3	58	4.481	2.569
5	Chloroform	0.3587	0.3357	3.3	14	3.096	2.194
6	Chlorobenzene	0.3775	0.3968	0	38	3.310	2.201
7	Ethyl acetate	03850	0.3064	1.6	181	3.260	2.319
8	Chlorous methylene	0.4217	0.3398	2.7	23	2.382	1.721
9	Cyclohexanone	0.4601	0.3560	0.5	242	2.241	1.749
10	Nitribenzene	0.4788	0.4147	0	67	1.678	1.509
11	Acetonitrile	0.4803	0.2857	5.2	160	0.967	0.319

polarity $\gg$ electrophility $>$ polarizability $\gg$ nucleophility

$$\log k'_s = (0.90\pm0.05)\frac{\varepsilon-1}{2\varepsilon+1} + (0.34\pm0.10)\frac{n^2-1}{n^2+1} + (047\pm0.09)E +$$

$$+ (0.12\pm0.07)B;\ S_o = 0.14;\ R = 0.994 \qquad (16)$$

The influence of nucleophility is very small, which apparently indicates virtually complete absence of the catalytic solvent effect on the process in question.

The major role in the solvent influence on the rate of the reaction proceeding by the sulfene pathway (1a) is played by its polarity which is of practical use when it is necessary to choose a solvent for the process.

In the case of the general base catalysis flow, the Koppel-Palm equation is not quite adequate to describe the solvent effect on the rate, since a satisfactory correlation is only possible (R=0.96). However, the elimination of the most deviating point (acetonitrile*) results in a substantial correlation improvement (R=0.985). Comparison of contributions of separate solvent parameters (equation 17, standatdized scale) into common dependence of the reaction rate (1b) on the solvent nature gives the sequence:

polarity $\gg$ polarizability $\approx$ electrophility $\gg$ nucleophility

$$\log k_b = (0.95\pm0.08)\frac{\varepsilon-1}{2\varepsilon+1} + (0.57\pm0.14)\frac{n^2-1}{n^2+1} + (0.53\pm0.14)E$$

$$+ (0.2\pm0.1)B;\ R = 0.985;\ S_o = 0.23 \qquad (17)$$

The similar nature of the influence of solvent solution effects on the acid dissociation of phenols is observed in[11]. Proton transfer from phenol to the base (tertiary amine) in the transition state is known to play a decisive role in the general base catalysis mechanism[12]. Thus, the nature of the solvent influence indirectly confirms the realization of the general base catalysis mechanism (1b) in the reaction in question.

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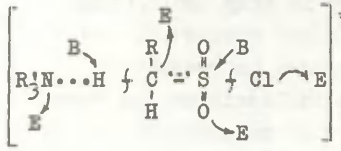
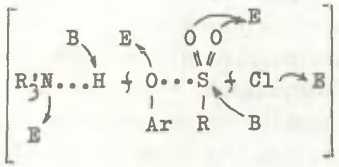
* The value of k_b in acetonitrile is obtained, in contrast to the rest of the solvents, by the PT results.

For the alkane sulfonylation reaction of phenols in the presence of trialkyl amines under investigation the following ways for specific solvation of the transition state (i.e. the carbanion-like E2 transition state A for the sulfene mechanism (1a) and S_N2 transition state B for the general base catalysis mechanism (1b)) at the expence of nucleophilic (B) and electrophilic (E) properties of the solvent may be represented (direction of the electron density shift is shown by arrows).



A



B

Correlation with the general parameters B and E does not afford any differentiation between the subtleties of the specific solvation mechanism but reflects the combined influence of each solvation effect on the redistribution of electron density in transition states.

It has been shown in this research that the solvent nature has an essential effect on the rate and mechanism of alkanesulfochloride interaction with phenol catalyzed by tertiary amines. A contribution of the solvent polarity is of special value. Its slightest increase (ε =1-7) changes completely the process mechanism from the general base catalysis to the sulfene mechanism. When the solvent polarity is increased, i.e. when its solvating properties are enhanced, an energy decrease in the transition state A is observed in greater extent than in the transition state B which results in variation of the dominating process mechanism from the general base catalysis for low polar media to the sulfene mechanism for high polar media. The influence of the specific solvation effects is less pronounced, especially for the elimination-addition mechanism (1a).

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RELATIONSHIP BETWEEN ACIDITIES OF CH-, NH- AND OH-ACIDS IN GAS PHASE AND IN DMSO

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The correspondence of acidities of series CH-, NH- and OH-acids has been found both in gas phase and in solvent in DMSO. It is shown that as for compound series with similar donor atoms, pK values most drastically change during transition from gas phase to solvent, in case rather strongly delocalized ions are used.

There are a number of papers given in literature (e.g. those by Bordwell[1]) dealing with the correlation of the acidities of CH-, NH- and OH-acids in gas phase and in DMSO. More general conclusions depending on the available experimental data about the acidity in both media can be found in[2-5]. The results obtained in those works are quite valueable, since the effects of structure upon the acidity of organic compounds in gas phase were correlated with those of solvation these compounds in DMSO, which allowed us to prognosticate the acidity variation of CH-, NH- and OH-acids in the DMSO solution. The pecularities of acidity variation depend on the compound type, consequently, the regularities can be noticed in a few related compound series[1,2,4,5] only. These effects have been found also when comparing the acidities in the gas phase and in aqueous solution[6].

In recent years, a lot of new data about the acidity of

organic compounds in gas phase and in solvents has been obtained. Therefore, it would be useful to analyze the data in order to get the quantitative correlation of the acidities of different series of CH-, NH- and OH-acids in gas phase and in DMSO. The acidity in solvent is quantitatively assessed by the pK values, the gas-phase acidity via changing the free energy of proton transfer in gas phase , $-\Delta G^{o}_{g}$.

Table 1 contains literature data concerning the acidities of different series of CH-, NH- and OH-acids, which have been classified both according to the reaction center nature and the ability to redistribute negative charge (cf.[4]). On the bases of those data were found the correlation dependences between the acidities of compound series in DMSO and in gas phase (Table 2), presented graphically in Figs. 1 and 2.

Table 1

Acidity of CH-, NH- and OH-Acids in DMSO (pK, absolute scale) and in Gas Fhase ($-\Delta G^{o}_{g}$, kcal/mol, absolute scale)

N	Compound	Acidity	
		pK	$-\Delta G^{o}_{g}$
1	2	3	4
	Series I. CH-acids forming carbanions with a delocalized charged		
1.	Toluene	42.0[7]	372.3[20]
2.	Diphenylmethane	32.2[8]	359.1[20]
3.	Fluorene	22.6[8]	345.6[21]
4.	Fluoradene	10.5[9]	327.5[4]
5.	Indene	20.1[8]	345.4[22]
6.	p-Nitrotoluene	22.5[10]	345.9[21]

Table 1 continued

1	2	3	4
	Series II. CH-acids, forming carbanions with a localized charge		
7.	Methane	56.0[11]	409.0[4]
8.	Cycloheptatriene	31.0[4]	367.9[20]
9.	Phenylacitylene	28.7[8]	362.6[20]
10.	Cyclopentadiene	18.0[8]	349.9[20]
11.	Benzene	~50	396.0[22]
12.	Naphtalene	~45	388.2[4]
13.	Acetylene	~31	367.2[20]
	Series III. CH-acids, forming carbanions of nitriles		
14.	Propionitrile	32.5[12]	366.1[20]
15.	Acetonitrile	31.3[8]	364.4[20]
16.	Phenylacetonitrile	21.7[8]	346.4[20]
17.	p-Nitrophenylacetonitrile	12.5[13]	325.4[4,23]
18.	Malononitrile	11.1[8]	330.7[4,23]
	Series IV. NH-acids, forming N-anions with a delocalized charge		
19.	m-Methylaniline	31.0[14]	360.3[20]
20.	Aniline	30.7[14]	359.8[20]
21.	p-Chloraniline	29.4[11]	355.2[20]
22.	m-Chloraniline	28.5[14]	353.8[20]
23.	m-Trifluormethylaniline	28.2[14]	351.8[20]
24.	p-Trifluormethalaniline	27.0[11]	348.3[20]
25.	p-Methylsulfonylaniline	25.6[14]	342.8[7]
	Series IVa .		
26.	p-Nitroaniline[a]	20.9[14]	338.8[4]
27.	2-Aminopyridine[b]	28.0[15]	355.1[24]

Table 1 continued

1	2	3	4
28.	4-Aminopyridine[b]	26.7[15]	350.9[24]
29.	4-Aminopyrimidine[b]	23.9[15]	346.1[24]
	Series V. NH-acids forming N-anions with a localized charge		
30.	Ammonia	41.0[16]	397.0[4]
31.	Pyrrole[b]	23.3[15]	353.0[20]
32.	Indole[b]	21.3[15]	343.0[22]
33.	Pyrazol[b]	20.4[15]	348.6[25]
34.	Imidazole[b]	18.9[15]	345.3[25]
35.	Indazole[b]	18.8[15]	342.7[25]
36.	Benztriazole[b]	12.6[15]	333.4[25]
	Series VI. OH-acids forming O-anions with a delocalized charge		
37.	p-Methylphenol	18.86[17]	344.5[23]
38.	m-Methylphenol	18.23[17]	343.8[23]
39.	Phenol	18.03[17]	343.4[21]
40.	p-Chlorophenol	16.74[17]	337.5[23]
41.	m-Chlorophenol	15.83[17]	336.3[23]
42.	m-Cyanphenol	14.76[17]	330.4[23]
43.	m-Nitrophenol	14.39[17]	329.0[23]
44.	p-Methylsulfonylphenol	13.6[5]	325.8[23]
45.	p-Nitrophenol	10.9[18]	322.5[23]
	Series VII. OH-acids, forming O-anions with a localized charge		
46.	Water	31.4[19]	384.0[4]
47.	Methanol	29.0[19]	372.6[20]

Table 1 continued

1	2	3	4
48.	2,2,2-Trifluorethanol	22.9[4]	356.8[20]
49.	tert-Perfluorbuthanol	10.9[4]	326.7[4]

Note. [a] the pK value, recalculated to the relative scale (+ 0.6 pK units) has been used for correlation. [b] pK values in relative scale, the difference between the relative and absolute scales is 0.6 pK units.

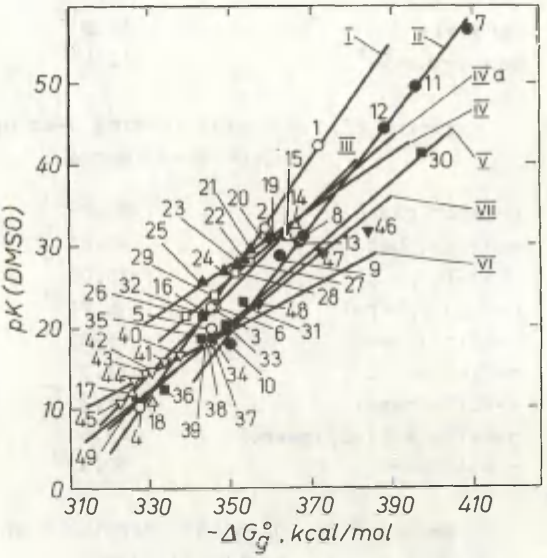

Fig. 1. Correlation between the acidities of CH-,NH- and OH-acid series in DMSO (pK) and in gas phase ($-\Delta G_g^\circ$). Numbers of compounds and series correspond to those of Table 1.

Table 2

Correlation Parameters of Eq. pK(DMSO) = a($-\Delta G_g^o$) - b for Compound Series I-IX (according to data of Table 1)

Series (N of compound)	a	b	r	s	n
I (1-4)	0.70	219.8	1.00	0.17	4
II (7-10)	0.63	200.1	0.997	2.02	4
III (14-17)	0.50	149.3	0.999	0.35	4
IV (19-25)	0.31	80.8	0.996	0.04	7
IVa (26-29)	0.41	118.4	0.993	0.19	4
V (30,31,33-36)	0.43	130.3	0.996	0.88	6
VI (37-44)	0.27	73.1	0.993	0.06	8
VII (47-49)	0.40	118.1	1.00	0.01	3
VIII (7,30,46)	0.98	346.2	0.989	6.79	3
IX (1,20,39)	0.83	266.1	0.999	0.58	3

Straight line I has with a maximum slope (in case of pK transfer to ΔG_g^o, the slope is equals to one) been directed through the points for strongly delocalized carban - ions, including the fluoradane anion poorly solvating DMSO[3,4] . For similar compound series the slope angles di - minish in the order carbonanions > N-anions > O-anions ;

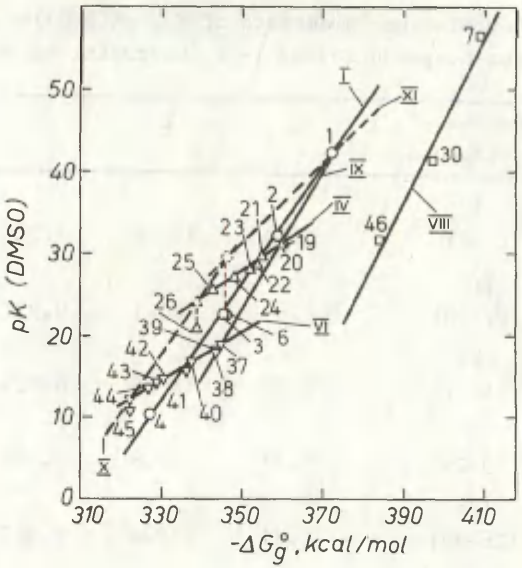

Fig. 2. Correlation between the acidities of series of CH-, NH- and OH-acids in DMSO (pK) and in gas phase (- ΔG_g^o). Compound numbers correspond to those of Table 1, numbers of series have been taken from Table 2. Straight lines (X, XI), composed in order to estimate the nitro group contribution to the p-nitrotouene pK are marked with dotted line.

solvation becomes more active with the growth of electro - negativity level of the atom of anionic center (Fig. 1 , Table 2, cf[2]).

Charge localization degree is a significant factor when determining the slopes of the lines for compound series with similar donor atoms. Thus, compounds 7-10,forming carbanions with a localized charge yield line II having a stronger slant than the delocalized carbanions of nitriles (line III). The same tendency is observed in NH- and OH-

acids. The slants of lines IVa (azines) and V (azoles)(more strongly expressed charge localization in N-anions) exceed those of line IV (anilines), while the slant of line VII (alcohols) (more strongly expressed charge localization in O-anions) exceeds that of line VI (phenols)(Fig.1, Table 2).

Consequently, in the case of the acids with similar anionic center atoms during transition from the gas phase to solvent in DMSO, the variation range of pK values grows narrower, the pK scale will be "compressed" after the charge localization degree in anion drops.

The slopes of lines II-VII are still smaller than that of the so-called "fixed" line I (Fig.1, Table 2). All points which are situated lower than line I refer to a better solvation of the corresponding anion. If the points are situated higher, the solvation of DMSO of a neutral compound predominates over the solvation of a similar anion (cf.[4,6]). Thus, in the case of the CH-acids (indene, p-nitrotoluene), forming carbanions with a delocalized charge, a down-directed deviation from line I can be noticed, since the solvation of the carbanions of those compounds is increasing (Fig. 1, Nos 5,6). By contrast with paper[1], malonitrile (N 18) deflects downwords from line III (nitriles), since the solvation of these compounds is mainly caused by its anion solvation (the point is deflected downwards even from line I). Analogously, owing to a substantial DMSO solvation contribution of hydroxide-anion[19], a remarkable downward deflection of the point marking water (N 46) from line VII (alcohols) can be observed. Nevertheless, similar CH- (CH_4, N 7) and NH-acids (NH_3, N 30) do not deflect from lines II and V, respectively, which were formed by the compounds with charge localization in anions (Fig. 1).

In the series of azoles V, indole (N 32) falling on line I undergoes rather unexpectedly, a deflection (compensation for the solvation of neutral compounds and anion). Triazole (N 36) is also situated quite close to line I (intersection of lines I and V, Fig. 1), although the downward deflection of benztriazole from lines I and V testifies that

the solvation of its anion becomes stronger, if compared with that of the anions of the compounds situated on those lines.

It would be interesting to mention that p-nitroaniline (N 26) and aminoazines (Nos 26-29) form a common line IVa; this became possible thanks to a substantial p-nitroaniline deflection from line IV, having been formed by the points for the other m- and p-substituted anilines. The deviation of p-nitroaniline results from the nitro group solvation in the corresponding anion, and consequently, also on the strengthening of its resonance effect[4,11]. Expectedly, aminoazines behave similarly, and that the solvation of aza-groups in aminoazines' anions leads to the strengthening of their electron-acceptor effect.

The deviation of p-nitrophenol from line VI for other m- and p-substituted phenols has the same reason, i. e. nitro group solvation, but the deflection is much smaller owing to a better charge localization on the oxygen atom of anionic center in phenoxide anions than in anilide an - ions[4,5,11]. Naturally, such a deflection of p-nitrotoluene should be maximal in the series of substituted toluenes.

As to the RX compound series, where R = H, Ph; X=CH_3, NH_2, OH, certain correlation relations can also be observed there (Fig. 2, Table 2, series VIII, IX) (cf. 2), the slopes of lines VIII and IX are rather close. Thus, proceeding from the found experimental values for p-nitrophenol and p-nit - roaniline, we can quantitatively estimate the contribution of nitro group solvation to the p-nitrotoluene acidity in DMSO. Line X passes through the p-nitrophenol and p-nitro-aniline points, taking into account the correction to the nitro group solvation (vertical intersection from point N 45 up to line VI and from point N 26 up to line IV) until its intersection with the vertical line at point N 6 in the case of p-nitrotoluene. The slope of the former line is quite similar with those of lines VIII and IX. Thus, the effect of nitro group solvation in p-nitrotoluene is ~ 7 pK units, in p-nitroaniline ~ 3 pK units, but in p-nitrophenol

$\sim$1.5 pK units. Line XI, connecting the two points (in case of toluene - N 1, and p-nitrotoluene; correction to solvation has been taken into account) characterizes the correlation between the acidities of m- and p-substituted toluenes in both media. Evidently, the variation of the line slope in order XI (toluenes) > IV (anilines) > VI (phenols) corresponds to that of electronegativity of the anionic center's atoms (Fig. 2).

All points higher than line I can be characterized with the prevalence of neutral compound solvation over that of the corresponding anion. The difference would be similar if there were no nitro group solvation, but in reality it is maximal in the case of p-nitrophenol (Fig. 2, N 45), smaller in the case of p-nitroaniline (Fig. 2, N 26), while in the case of p-nitrotoluene, neutral compound solvation is even a bit poorer than that of its anion (Fig. 2, N 6) and the point corresponding to p-nitrotoluene lies lower than line I.

The correlation relations between the acidities in the gas phase and in the DMSO solution found, can in the case of a number of aromatic and heteroaromatic CH-, NH- and OH-acids be used for the calculation of pK values, whose experimental finding is rather complicated. Thus, the equation for series II (localized carbanions, Table 2) was applied for the calculation of the pK for benzene, naphtalene and acetylene in DMSO (Table 1, Nos 11-13).

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NUCLEOPHILIC SUBSTITUTION AT TETRACOORDINATED SULFUR ATOM. III. REACTIVITY OF ANIONIC OXYGEN-CONTAINING NUCLEOPHILES - ARYLATE AND ALCOHOLATE IONS

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Kinetic behavior of arylate -and alcoholate anions has been studied in reactions with aryl esters of 4-toluene sulfonic acid in 5 % water-alcohol solution at 25° C and μ = 1.0 (KCl). The sensitivity to attacking nucleophile and leaving group natures can be described by means of the Brønsted equation, slopes being β_N=0.59 and β_X= -0.71. The reaction proceeds via a single transition state, and the transfer of the sulfonate group takes place by the concerted mechanism. The sensitivity of equilibrium process of aryl toluene sulfonates' formation to the nature of anionic oxygen-containing nucleophile has been studied on the bases of kinetic data (β_{eq}=1.30). A certain distortion of the Brønsted plot which is observed if nucleophile basicity $\geqslant$13, is caused by unfavorable solvation effects of the solvent. An equation based on the character of solvation

effects of water on the transition rate of sulfonate group into oxygen-containing anionic nucleophiles is proposed.

A number of by now well-known α-nucleophiles (hydroxamate, oxymate, hydroperoxide, and hypohalogenide anions) belong among anionic oxygen-containing compounds, but abnormally high reactivities of $HOO^{\ominus}$-, $ClO^{\ominus}$-, $BrO^{\ominus}$-ions were also found in the transition reactions of toluene sulfonate group[1]. The extent of these effects depends on the substrate nature, although this is not the only factor responsible for rate increase. For instance, the hydroperoxide ion which is one of the most unique α-nucleophiles, demonstrates increased reactivity both towards saturated and unsaturated substrates[2]. Hydroxamate and oxymate anions reveal their supernucleophilic properties towards the unsaturated electron-deficient carbon and phosphorus centers, while with alkyl halogenides, no remarkable reaction rate growth was observed. High rate values were recorded also for the compounds that hardly are α-nucleophiles. For instance, thioalcoholate anions react very rapidly with alkyl halogenides[3], arylacetates[4] and arylsulfonates[5] but the anionic forms of azoles show increased reactivity toward the aryl ethers of acetic acid[6], yet being less reactive than neutral nitrogen-containing compounds at their nucleophilic substitution near the sulfur atom[5]. Evidently, the causes of the abnormally high reactivity of α-nucleophiles are not similar, and from the point of view of our earlier task to search for and construct such supernucleophiles which could rapidly and irreversibly react with stable substrates[1,5], our interest is mainly focused on the detailed research into the reactivity of arylate and alcoholate ions in the transfer reactions of sulfonyl group. In these reagents, a negatively charged oxygen atom acts as a nucleophilic center. Since they cannot trace any abnormalities in kinetic behavior, the following circumstances must be established: a) the reaction-mechanism, b) the factors controlling the reaction rate, d) the contributions of resonance and solvation effects into the reactivities of these nucleophiles.

In order to perform the task set, we studied the nucleophility of the reactivity of arylate and alcoholate ions with the basicity ranging within pK_a 5-16. The character of the leaving group in aryl toluene sulfonates has been found and an attempt to quantitatively estimate the contribution of solvation effects into the experimentally recorded values of Brønsted parameters has been made.

Experimental

4-Nitrophenyl-4'-toluene sulfonate (NPTS) reaction with alcoholate- and arylate-ions. The dependence of the observed constants of NPTS alcoholysis (k_{obs}, s^{-1}) on the medium acidity and on the total concentration of alcohol (Fig.1 a) is rather typical of the processes where the main buffer component - the alcoholate-ion acts as the reactive form. The rate of the reaction is expressed as follows:

$$k_{obs}=k_{OH^\ominus}\, a_{OH^\ominus} + k_2(ROH)_0 \qquad (1)$$

If $(ROH)_0=0$, the interception (Fig. 1a) coincides in the range of experimental error with $k_{OH^\ominus}\, a_{OH^\ominus}$, determined in some independent experiments expresses the contribution of alkaline hydrolysis while the slope characterizes the apparent second order rate constant at the given pH value, based on the concentrations' sum of alcohol (k_2', $M^{-1}\, s^{-1}$). For the NPTS alcoholysis, the second order rate constant ($k_2'=k_{RO^\ominus}$, $M^{-1}\cdot s^{-1}$) was derived from equation

$$k_2'=k_2\alpha=k_2\frac{k_a}{2K_a+a_{H^\oplus}} \qquad (2)$$

where α denotes the contribution of the alcoholate-ion in the case of a fixed pH value (see Fig. 1б), K_a is the acidic ionization constant. The calculated k_2 values are summud up in Table 1.

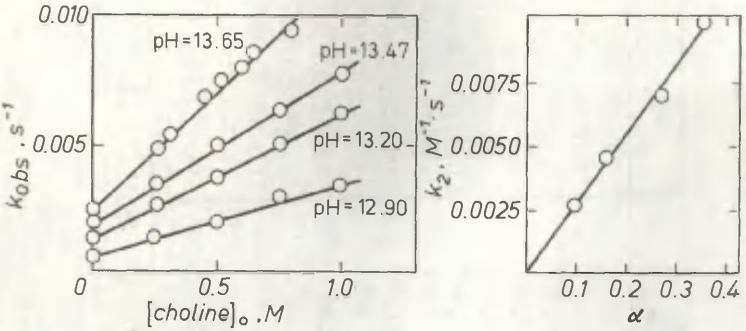


Fig.1. NPTS interaction with choline in 5 % ethanol at 25°C μ =1.0 (KCl).

a) Dependence of the observed rate constants k_{oba}, s^{-1} on the total of choline concentrations.

b) Processing of kinetic results in correspondence with expression (2).

Unlike alcoholysis, the anamorphisms for the reactions of phenolate-ions with NPTS have rather complex character : in the case of phenol concentration increase initially, the k_{obs} values rise, afterwards drop, passing through the maximum (Fig.2). Such a tendency is probably connected with the accumulation of the complex of ether and phenol (or phenolate-ion) whose formation is caused by hydrophobic interactions.

As to the reactions of pyridines and other hydrophobic molecules with esters of carboxylic acids, the association described above leads also to the nonlinear kinetic dependences[9].

Regardless of the existence of well-grounded approaches to the description of bell-shaped relationship[10], we did not succeed in carrying out a detailed kinetic analysis of the NPTS analysis, since this is rather complicated to establish both the stoichiometry of the complexes as well as the nature of associating components. Particularly,

Table 1

Experimental Conditions, Basicities of Alcoholate- and Arylate-Ions (pK_a) and their Reactivities (k_2, $M^{-1}s^{-1}$) Relative to NPTS in 5% Aqueous Ethanol at 25°C, μ = 1.0 (KCl)

N°	Nucleophile	pH	Nucleophile concentration, M	Total number of tests	pK_a	k_2
1.	$HOCH_2CH_2O^{\ominus}$	13.10-13.20	0.5-4.0	8	15.1[7]	0.040±0.004
2.	$HOCH_2CHOHCH_2O^{\ominus}$	13.20-13.65	0.8-1.8	6	14.1[7]	0.017±0.002
3.	$(CH_3)_3N^{\oplus}CH_2CH_2O^{\ominus}$	12.90-13.65	0.2-1.0	20	13.9[7]	0.027±0.001
4.	$CH{\equiv}C\text{-}CH_2O^{\ominus}$	12.60-13.38	0.0125-2.0	20	13.55[7]	0.035±0.001
5.	$CHF_2CF_2CH_2O^{\ominus}$	12.45-12.74	0.12-1.4	16	12.74[7]	0.0058±0.0001
6.	$CF_3CH_2O^{\ominus}$	12.00-13.00	0.2-1.0	10	12.37[7]	0.0036±0.0002
7.	$4\text{-}CH_3OC_6H_4O^{\ominus}$	12.45	0.075-0.3	7	10.21[8]	$(4.9\pm0.4)\cdot10^{-4}$
8.	$C_6H_5O^{\ominus}$	10.00-10.62	0.2-1.0	20	9.98[8]	$(9.9\pm0.5)\cdot10^{-5}$
9.	$4\text{-}ClC_6H_4O^{\ominus}$	10.41	0.1-0.3	7	9.38[8]	$(8.2\pm0.8)\cdot10^{-5}$
10.	$4\text{-}BrC_6H_4O^{\ominus}$	10.52	0.05-0.2	9	9.36[8]	$(5.8\pm0.5)\cdot10^{-5}$
11.	$3\text{-}ClC_6H_4O^{\ominus}$	9.90	0.2-0.4	8	9.02[8]	$(5.0\pm0.5)\cdot10^{-5}$
12.	$4\text{-}CH_3OOOC_6H_4O^{\ominus}$	10.00	0.2-0.5	8	8.05[8]	$(1.3\pm0.2)\cdot10^{-5}$
13.	$2,3,5,6\text{-}C_6F_4HO^{\ominus}$	6.90-7.20[a]	0.05-0.2	8	5.61±0.05[b]	$(4.7\pm0.9)\cdot10^{-7}$
14.	$C_6F_5O^{\ominus}$	6.90-7.20[a]	0.05-0.2	8	5.50±0.04[b]	$(4.0\pm0.9)\cdot10^{-7}$
15.	$HO^{\ominus}$	-	-	-	-	0.008[1]

Notes. a) Medium acidity was maintained by means of phosphate buffer $[KH_2PO_4+K_2HPO_4]_o$=0,01M

b) pK_a were determined by means of potentiometric titration at μ=1.0 (KCl), 25°C in 5 % aqueous ethanol.

either phenol or the phenolate-ion participate in complex-formation. Moreover, the reactivities of the complexes with varying compositions can substantially differ from each other and their reactivities are a great deal poorer than that of the non-associated substrate. This can be proved by the NPTS interaction with hydrated 4-pyridine aldehyde. The formation of non-reactive associates even leads to the inhibation of alkaline hydrolysis (Fig.3).

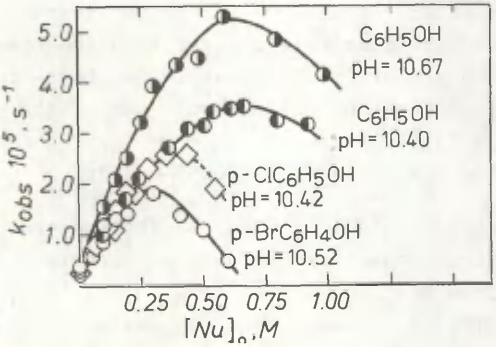


Fig. 2. Dependence of observed rate constants for NPTS reactions with arylate-ions on total concentration of phenols is 5 % ethanol, 25°C, μ = 1,0 (KCl).

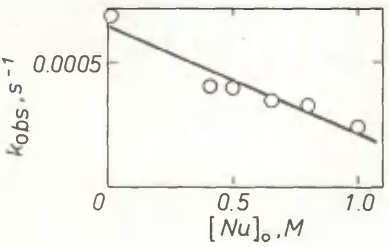


Fig. 3. Effect of 4-pyridine aldehyde additions (pH=12.92) on alkaline hydrolysis rate of NPTS in 5 % ethanol, 25°C, μ = 1.0 (KCl).

Nevertheless, it would always be possible for the phenols studied in the present paper to choose such a nucleophile concentration range where the k_{obs} values increase proportially to the increase of $(ArOH)_o$, i.e. complex formation can be practically neglected. In this case, when using expressions (1) and (2) it is possible to find the second order rate constants characterizing the nucleophilic reactivity of the phenolate-ion (see Table 1).

Both alcoholysis and phenolysis of NPTS including the nucleophilic attack of the $RO^{\ominus}$ ion to the tetracoordinated sulfur atom of the substrate proceed with the break of the -S-OAr bond only (see Experimental). The plots for phenolate- and alcoholate-anions fall onto one of the Brønsted relationships (3).

$$\log k_2=(-9.64\pm0.39)+(0.59\pm0.03)pK_a \qquad (3)$$

Nevertheless, starting with the choline anion, the points for highly basic alcoholate ions undergo negative deviations from Brønsted relationships (3), increasing parallel to the pK_a rise of alcohol. Maximum deviation is observed for the OH^--ion, equalling $\Delta=-1.66$.

Similar behavior of phenolate-, alcoholate- and OH^--ions was observed in the reaction with 4-nitrophenyl acetate (NPA). In such a case, the Brønsted relationship is distorted starting from the choline point[4] as this is with NPTS.

Table 2

Experimental Conditions, Leaving Group Basicities (pK_a) and Reactivity of $OH^{\ominus}$- and $CHF_2CF_2CH_2O^{\ominus}$-ions (k_2, M^{-1}, s^{-1}) to Aryl Esters of 4-Toluene Sulfo acid in 30% Aqueous Ethanol at 25°C, μ=1.0 (KCl)

	Substrate	pK_a[a]	λ, nm[b]	Nu	n[c]	pH	k_2
1	2	3	4	5	6	7	8
1.	2,6-dinitrophenyl-4-toluene sulfonate	3.56±0.04 (3.71)	430	$OH^{\ominus}$ $RO^{\ominus}$	6 4	11.76-12.66 11.02	2.87±0.03 2.64±0.04
2.	2,4-dinitrophenyl-4-toluene sulfonate	3.88±0.02 (4.11)	370	$OH^{\ominus}$ $OH^{\ominus}$ $RO^{\ominus}$	7 7 4	11.76-12.82 11.77-12.88 11.82	0.71±0.03 1.61±0.09[d] 0.83±0.08
3.	2,5-dinitrophenyl-4-toluene sulfonate	5.26±0.06 (5.22)	440	$OH^{\ominus}$ $RO^{\ominus}$	5 5	12.39-13.11 11.80	0.38±0.01 0.45±0.04
4.	2,4,6-trichlorophenyl-4-toluene sulfonate	6.67±0.04 (5.99)	313	$HO^{\ominus}$	5	12.93-13.42	0.008±0.0003
5.	4-nitrophenyl-4'-toluene-sulfonate	7.51±0.03 (7.15)	400	$OH^{\ominus}$ $OH^{\ominus}$ $HO^{\ominus}$	5 16 5	12.48-13.27 12.74-13.58 12.88-13.32	0.0025±0.0001 0.008±0.0003[d] 0.0028±0.0003
6.	2,4-dibromophenyl-4-toluene sulfonate	8.56±0.02 (7.74)	315	$OH^{\ominus}$	6	12.52-13.41	0.0012±0.0002
7.	4-phenylazophenyl-4'-toluene sulfonate	8.66±0.03	417	$OH^{\ominus}$ $PO^{\ominus}$	5 4	12.72-13.46 12.50-13.00	$(5.5\pm0.1)\cdot10^{-4}$ $(6.0\pm0.6)\cdot10^{-4}$
8.	3-chlorophenyl-4-toluene sulfonate	9.67±0.04 (9.02)	294	$OH^{\ominus}$	5	12.72-13.46	$(1.6\pm0.1)\cdot10^{-4}$

Notes. a) Ionization constants of substituted phenols were determined spectrophotometrically in 30 % aqueous ethanol; in parentheses are given the pK_a values in water[8,12].

b) λ^{max}, nm for substituted phenols.

c) Total number of experiments.

d) k_2 values for alkaline hydrolysis of aryl sulfonates in 5 % aqueous ethanol.

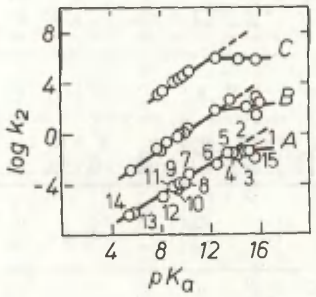


Fig. 4. Brønsted relationships for reactions of arylate and alcoholate anions with NPTS (A) in 5 % ethanol and NPA (B) and with 3-nitrophenyl methane sulfinate (NPMS) (C) in water. Numbers of points on relationship A correspond to those given in Table 1. Relationships (B) and (C) have been composed according to the data from papers [4,11].

Interaction of Aryl Esters of 4-Toluene Sulfo Acids with 2,2',3,3'-Tetrafluoropropylate- and Hydroxyl-Anions.

The effect of leaving group's nature on the rate of nucleophile attack of the tetracoordinated atom of sulfur aryltoluene sulfonates by hydroxyl- and 2,2',3,3'-tetra - fluoropropylate ions was studied in a 30 % aqueous ethanol.* The use of a 5 %-aqueous ethanol instead of a 5% -solution yields us an increase in the leaving group (cf. the pK_a values of substituted phenols in water and in a 30 % ethanol, Table 2), and attacking nucleophile basicities, which can, certainly, affect the reactivity of the $OH^{\ominus}$- and $HCF_2CF_2CH_2O^{\ominus}$- ions. Nevertheless, both those effects compensate for each other in transition state, and the k_2 values but insigni - ficantly change during the reaction transition from a 5% to 30 % aqueous ethanol (see Table 2). The rate of aryl - toluene sulfonates' interaction with $OH^{\ominus}$- and $HCF_2CF_2CH_2O^{\ominus}$- anions in the case of the leaving group basicity change by 5-6 pK_a units, respectively, can be described by the equa - tions of Brønsted (4) and (5). In the case of any nucleo - phile, onto individual relationships (4) and (5) lie the points for the arylsulfonates whose leaving groups in ortho position contain crowded substituents.

$$\log k_2 = (2,82\pm0.31)-(0.69\pm0.06)pK_a \qquad (4)$$

$$\log k_2 = (2.96\pm0.66)-(0.71\pm0.12)pK_a \qquad (5)$$

The absence of steric effects of ortho-substituents evidences that the rate determining transition state of the

---

* The series of experiments was conducted in a 30% to aque- ous ethanol, since the aryl esters of 4-toluene sulfo acid have rather poor solubility in a 5 % solution.

reaction has got a bipyramidal structure in the peaks of which are situated the leaving and attacking groups, thus acting like transition states with the participation of amines and thioalcoholate anions[5].

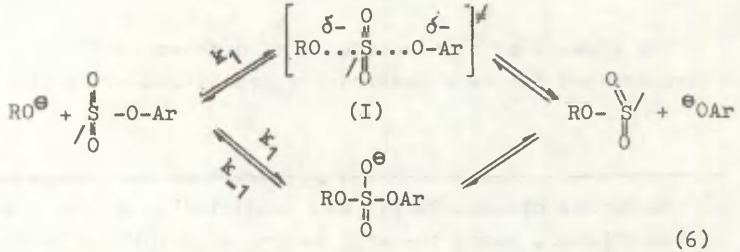
One should also take into consideration that the sensitivity of the reaction to the leaving group nature will undergo a slight change (by ≈10%), if the pK_a values of substituted phenols determined in water are used for compiling Brønsted relationships. This proves the validity of comparison of the experimental results obtained in 5 % and 30 % water-alcohol mixtures.

Discussion

Mechanism of Reactions of Arylate- and Alcoholate-Anions with Aryl Esters of 4-Toluene Sulfoacid.

The transition of 4-toluene sulfonate group from arylsulfonate to the alcoholate and phenolate anions can proceed according to the coordinated mechanism (I) or in keeping with the stage mechanism, containing the formation of the penta-coordinated medium product of addition (II) having a trigonal bipyramidal structure with the attacking Nu and leaving X groups in axial positions.

The organic sulfur compounds - sulfuranes having bipyramidal structure have been found by the time being and they can be safely identified[13].



(6)

It is rather difficult to make choice between those alter - native mechanisms of sulfonyl group transfer, although the

information permitting to prefer either one or another reaction mechanism can be obtained by means of the analysis of the extrathermodynamic correlations which obey either the Brønsted or Hammett[14] equations.

The studied reaction is a permanent equilibrium process where the exchanging Nu and X groups (arylate- and alcoholate ions) are of similar nature. Therefore, if the reaction mechanism is a stage one, then for the nucleophiles with pK_a (Nu) > pK_a(X), the process rate will be controlled by the attack of the anionic oxygen-containing nucleophile upon the tetracoordinated sulfur atom of the substrate(step k_1, in scheme (6)). For the arylate anions whose pK_a (Nu)< pK_a(X), the intermediate (II) decomposition into reaction products (step k_2 in scheme (6)) should be considered as the rate-determining step. The corresponding transition states have varied charge distributions, but the transition states for the nucleophiles with pK_a (Nu)<pK_a (X) appearing later,demand a somewhat higher sensitivity of reaction rate to the basicity of the attacking arylate-ion. Consequently, the variation of nucleophile nature brings about a change in the rate determining step thus also leading to the break of the Brønsted relationship. The breaking point is similar to that of a nucleophile. Its basicity value is in keeping with that of the pK_a of the leaving group 4-nitrophenolate ion ($k_{-1} \approx k_2$ in Scheme (6)).

Nevertheless, for the NPTS reaction with arylate ions the Brønsted relationship holds, and onto the straight line fall the points of arylate-anions whose basicity is either higher or lower than that of the 4-nitrophenolate ions.Analogous kinetic behavior of arylatetrifluoroethylate-, and acetate ions ($pK_a \approx 4\text{-}13$) was observed also in the reactions of 4-nitrophenyl-4'-nitrobenzene sulfonate (NPNS)[15]. Since there is no kinetic evidence for the change of rate limiting step of those structurally similar substrates (similar situation is observed for the interaction of substituted sultones with arylate-ions[16]), it permits us to decide between two alternative reaction routes - the concerted route and the stage one - in favor of the coordinated transfer

mechanism of toluene sulfonate group. I.e. the reaction studied proceeds via only one transition state (I).Certainly, the results obtained also refer to the probability of the formation of the penta-coordinated intermediate whose lifetime approximates to the time of activation act ($t \approx 10^{-13}$s). But as in this case, the differences between the structures of the two transition states and intermediate (II) are negligible, the problem concerning finding the change of the reaction mechanism appears to be of semantic nature.

In keeping with the principle of microscopic-reversibilities the coordinated mechanism of the arylsulfonate group transfer onto arylate anions demands that the direct reaction and the back reaction of a permanent equilibrium process (6) should proceed via general transition state. Therefore, the β_N and β_X values enable us according to Eq. (7) to quantitatively assess the sensitivity level of the equilibrium process of aryl toluene sulfonate formation (β_{eq}) to the arylate ion basicity.

$$\beta_{eq} = \beta_N - \beta_X = 1.30 \pm 0.15 \qquad (7)$$

On the basis of values β_N, β_X and β_{eq} we can find the values of the effective charges at the reacting reagent centers, in transition state, in reaction products, as well as the Lefler-Grunwald parameters ($\alpha = \beta/\beta_{eq} = \partial \log k / \partial \log K_{eq}$) for the forming ($\alpha_N$) and breaking ($\alpha_X$) bonds. The results are given in Table 3. Similar characteristics for a series of related substitution processes taking place in the vicinity of the sulfonilic center are summed up there. An example of substitution by the carbonyl atom of carbon obeying the stage mechanism is also given.

The information obtained using the Brønsted sensitivity parameters (β_N,β_X) is per se too limited to estimate the bond formation and bond breaking levels in the transition state. Fortunately,the changes of effective charges, i.e. the Lefler-Grünwald parameters, connected with the change variation of the effective charge in the calibrated equi - librium help to overcome this complexity. We should also like to mention that the transition states for the correlated

Table 3

The Leffler-Grunwald Parameters and Effective Charges for Reactions of Sulfonate and Acetyl Groups Transfer onto Arylate Anions* [4,14-16]

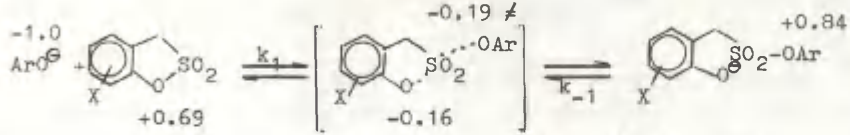
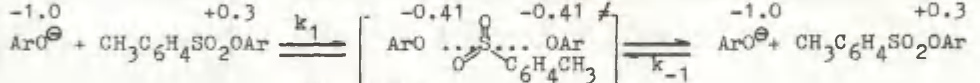
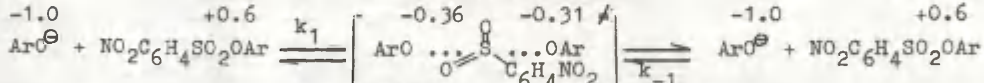
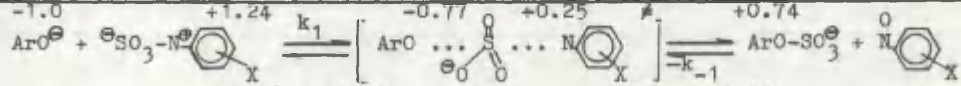
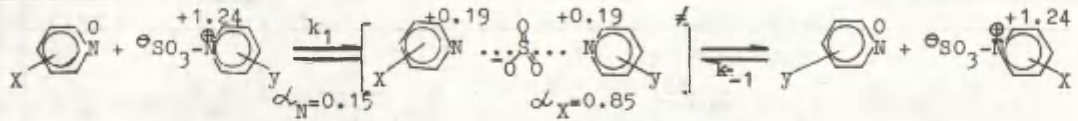
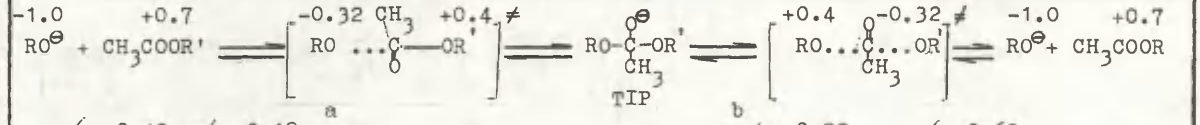
	Coordinated mechanism of reaction
1.	
2.	
3.	
4.	

Table 3 continued

5.	
	Stage mechanism of reaction
6.	

Notes.* Determination errors of β_X and β_N which form the basis for α_X and α_N do not exceed 10 %.

a) Rate determining attack of $RO^{\ominus}$-anion.

b) Rate determining decomposition of TIP.

reactions, including those studied in the present paper(see Table 3, Nos 1-3) have rather high symmetry levels, while their structures do not remarkably differ in the substituents' nature in the sulfonate group undergoing transition. In the case of the transition of toluene sulfonate,4-nitrobenzene sulfonate and alkylsulfonate (the interaction of sultones with the arylate-ion) groups, the formation degree and bond breaking level coincide in the corresponding transition states of reactions within the range of experiment error ($\alpha_N \approx \alpha_X \approx 0,5$). At the same time, for series 4,5 (Table 3), α_X exceeds α_N, although the transition states are symmetrical again. The essential differences between those two groups lie in the fact that transition states 4-5 (Table 3) are looser than 1-3 for the transfer of the sulfonyl group from the uncharged substrate. In the latter case the basicity of the attacking nucleophile might be considered the major attacking power, while at the formation of transition states 4-5, both direct reverse election donation from the negatively charged oxygen atom of sulfonyl center either onto the splitting-off pyridine or arylate ion takes place.

The analysis of the Leffler-Grunwald parameters for the process studied and for similar transfer reactions of sulfonate groups studied in literature[14-16] on the one hand and for the formation of acidic acid esters[4], on the other hand, whose mechanisms are strictly identified (see Table 3) should be of interest from the point of view of finding the differences in the mechanism of the aryl sulfonate group transfer. In the case of the transfer of acetyl group from aryl acetates onto the $RO^{\ominus}$-anions, the formation level of the bond (α_N) reflects the level of bond breaking (α_X) in the transition state of the reaction, not depending on which of the reaction steps, either the nucleophile attack or the decomposition of the tetrahedral intermediate product (TIP) acts as the rate determining one. This statement is also valid for the transfer of acetyl group onto the $RS^{\ominus}$-anions[4]. Yet, it has already been mentioned that in the case of the transfer of sulfonyl group from aryl-4-toluene sulfonate and aryl-4-nitrobenzene sulfonate to the $RO^{\ominus}$ and $ArO^{\ominus}$anions, the

bond formation and breaking levels in the corresponding transition states practically coincide(see Table 3),resembling that of the coordinated mechanism of sultones' reaction with arylate ions[16]. When dealing with the coordinated mechanism of the sulfonate group transfer to the $ArO^{\ominus}$anions (the interaction of N-sulfonyl pyridinium cations with arylate ions[14]), we must notice that in the rate determining transition state, the bond formation with the attacking arylate ion is expressed very weakly, and the bond with the leaving substituted pyridine and arylate anion undergoes a substantial break in the opposite direction.

In those reactions, the break of the bond with a leaving group anticipates the bond formation with the attacking arylate anion (see Table 3), which can hardly be expected at the formation of penta-coordinated intermediate products of addition. Thus, the analysis of the Leffler-Grunwald parameters also gives evidence of the coordinated symmetric mechanism of sulfonate group transfer in the reaction studied.

Role of Resonance and Solvation Effects - Curvilinear Brønsted Correlations.

The reactivity of arylate- and alcoholate ions to NPTS cannot be described in the framework of the single Brønsted equation (3), but in the case of the transfer to the highly basic alcoholate anions, $pK_a \approx 13$, the reaction rate sensitivity to the nucleophile basicity weakens, approaching value $\beta_N \approx 0.1$ (Fig. 4). Analogous kinetic behavior of arylate and alcoholate ions was observed in the nucleophilic substitution reactions with 3-nitrophenyl methane sulfinate (NPMS)[11], NPA[4], acetoxymethoxypepidine-perchlorate (AMPP), etc.[17]

In paper[18], an attempt to give a general explanation to the nonlinear correlation dependences of Brønsted was made. It is assumed that the value expressing a typical sensitivity to the basicity of arylate and alcoho-

late anions equals β_N 0.1-0.3, while the points for less basic arylate anions are liable to remarkable negative deviations connected with resonance interactions in the nucleophile in the initial state. The latter demand structural reorganization of the reagent leading to the charge localization at the nucleophile center before the arylate anion attack onto the substrate's electrophilic center. Thus, for arylate and alcoholate anions is always realized the early transition state, although their behavior is experimentally described by means of various Brønsted dependences. It is also possible that in the present situation resonance interactions may bring about rather high sensitivities of arylate ions. At the same time, high values of β_N 0.5-0.8 detected in the reactions of 2,4-dinitrophenyl acetate (2,4-DNPA) NPA, AMPP with fluorinated alcohols, aldehydes, and ketones [17] whose pK_a values are either close to or smaller than those of arylate anions do not permit us to confine ourselves to the suggestions given in [18] only. The curvilinear Brønsted relationships were also traced in the elimination reactions where different oxygen-containing anionic compounds act as the general basic catalysts of proton transfer. In those processes, the role of resonance effects is even more negligible.

There is not any sufficient explanation to the behavior of oxygen-containing anionic nucleophiles in NPTS yet, if we proceed from the assumption that the violation of the Brønsted relationships reflect certain structural changes in the transition state and its shift toward the reagent - like ones when the basicity of the attacking alcoholate anion becomes stronger. First, similar curvilinear Brønsted relationships (Fig. 4) were found in the reactions of arylate and alcoholate ions with NPA (β_N drops from 0.68 to 0.17[4]) and NPMS (β_N drops from 0.75 to 0[11]). These substrates react with the anions of oxygen-containing nucleophiles 10^6 -10^8 times faster than NPTS (Fig. 4). The sensitivity to the NPA and NPMS arylate anions' attack is β_N=0.68[4] and β_N=0.75[11], thus being quite close to β_N=0.59 NPTS (cf. β_N for NPNS[15], β_N=0.68). In addition to that, for NPTS, NPA and NPMS, the

break at correlation dependences A, B, and C (Fig. 4)at the transfer from arylate to highly basic alcoholate ions takes place if the nucleophile basicity close to $pK_a \approx 13$, and its position does not especially depend on the substrate's nature and reactivity. Secondly, for the nucleophilic attack upon aryltoluene sulfonates by $HO^{\ominus}$- and $HCF_2CF_2CH_2O^{\ominus}$-anions and upon 4-nitrobenzene sulfonates[15] by the $PhO^{\ominus}$-ion, β_X have quite close values (-0.71 and -0.91, respectively).Coinciding, though much smaller absolute values, when $\beta_X \approx -0.3$, could be observed in the case of a rate-determining,TPP formation in the reactions of arylate-, alcoholate- and hydroxyl-ion with aryl acetates[4]. Since the sensitivity to the leaving group nature does not change within each substrate class, being rather independent of the nucleophile-type (either arylate-, alcoholate- or hydroxyl-anions) participating in the reaction, it must be stated that in their transition states, the effective charges on leaving groups are determined according to the β_X values both in the case of arylsulfonate and acetyl group transfers. The same is valid for the attacking nucleophile, but a change in the effective charge in the transition state at the nucleophile center in arylate and alcoholate anions should be characterized by the β_N whose value is in the region of 0.6-0.8, and not by $\beta_N \approx 0.1$-0.3, as it was claimed by the authors of [18]. Thus, in those exchange processes, the distributions of effective charges at the reacting centers are of a similar type both for highly basic and weakly basic oxygen-containing anionic nucleophiles. Finally, - the nonlinear correlations of the Brønsted type were also observed in the case of the interaction of anionic oxygen-containing nucleophiles with AMPP, 2,4-DNPA, NPA[17], and 1-acetyl-4-methyl-pyridine-cation[19], as well as in the elimination and ionization of the CH acids, where arylate anions act as general basic catalysts of proton transfer[20], it is typical of these processes proceeding according to various mecha - nisms that the Brønsted slopes change from $\beta_N = 0.7$ to $\beta_N \approx 0.2$ -0.3 when transferring from the weakly basic alcoholate anions to the highly basic ones.

The present kinetic data (see Fig. 4) show that the violation of Brønsted relationships for the exchange processes with NPTS NPA and NPMS participation cannot stem from the structural change in the transition state with variation of the nature of oxygen-containing anionic nucleophile. Most probably, the transition state structure for weakly basic and highly basic nucleophiles remains unchanged, and the sharp deviations observed at the correlation relationship"structure reactivity"should reflect the differences between the characters of solvation states of arylate and alcoholate anions in water, i.e. here we deal with the kinetically expressed solvation effects of the solvent.

In aqueous solutions, oxygen-containing anionic nucleophiles mostly form hydrogen-bonded 1:3[21] complexes. In such complexes, lone electron pairs of the anionic atom of oxygen participating in the formation of hydrogen bonds with water molecules are blocked by the solvent and therefore, the nucleophile attack onto the substrate should be preceded by the step of anionic nucleophile desolvation. In the course of the latter process, at least one of the three molecules of solvation water will be isolated (step K_d in Scheme (8))*.

$$RO^{\ominus}_{s} \xrightleftharpoons{K_d} RO^{\ominus}_{d} \xrightarrow{k_2^d(s)} \text{products} \qquad (8)$$

Evidently, the aryl sulfonate group (acetylaryl acetates, etc.[17]) transfer to the nucleophile is a complicated process including the restructuring of the anionic solvate shell already in the initial state, since the transition state is subjected to the equilibrium solvation; the time necessary for the reorganization of solvent molecules is much longer than the activation time[22].

The differences in the free desolvation energies of alcoholate and arylate ions are rather negligible, in the

* In Scheme (8) $RO^{\ominus}_{s}$ and $RO^{\ominus}_{d}$ denote the solvated and desolvated forms of anionic nucleophile, respectively, k_2^d - the reactivity of the desolved form, S-substrate.

gas phase reaching - (9-17) kcal/mol[23]. But, regardless of the fact that the transfer of anionic forms into the prototropic solvent will level these differences, they can be observed experimentally. Since in the transfer from D_2O to H_2O, practically no differences in the solvation effects were found for carboxylate and arylate anions ($\Delta pK_a^{D_2O}$ $pK_a^{H_2O} \approx 0$), while for the alcoholate ions they are quite significant ($\Delta pK_a \approx 0.4\text{-}0.5$)[24], which also confirms the above-mentioned statement. The results of the study of the character of the effect of ortho-tert-buthyl groups on the pK_a values of arylate anions lead us to the same conclusion: the influence of those two groups weakens with the decrease of the basicity of substituted phenols, becoming almost equal to zero for ArOH whose $pK_a \leqslant 7$[25]. The latter indicates that the loss of one of the ligands - water molecule - from the solvate shell of the arylate anion does not bring about any changes in the free energies of hydrogen-bonded complexes with contents 1:3 and 1:2.

The existence of the nonlinear Brønsted relationships for the toluene sulfonate group (as for relationships B,C for NPMS and NPA) transfer given in Fig. 4 cannot be explained with the unfavorable solvation effects for alcoholate ions ($K_d < I$) and with their absence for arylate anions ($K_d \geqslant I$). Nucleophile basicity directed the reaction, but solvation effects should equally affect both the rate of process (9), and the pK_a value of the attacking nucleophile (10). Equations (9) and (10) illustrate the fact that in the transition state of the reaction studied and in the standard process of ionization, the solvation effects are compensated in the whole variation range of pK_a of the oxygen-containing anionic reagent.

$$\log k_2 = \log k_2^d + \log K_d \qquad (9)$$

$$pK_a = pK_a^d + \log K_d \qquad (10)$$

Uncompensated solvation effects can appear in the case of ion hydroxyl only, whose $pK_a \approx 15.74$ is based on the constant value of ionic product of water and on the concentration of water $n \approx 55,5$ M of the later, assuming that water is in the

monomeric state.

The violations of Brønsted relationships A-C (Fig. 4) are caused by the varied mechanism of conveying electron effects in anions onto the nucleophilic center and the corresponding changes in the pK_a and log K_d values. In the arylate ions, resonance effects are probably responsible for the extremely low log K_d sensitivity to basicity (11), i.e., value $|\beta^d| \to 0$, while the basicities of solvated and desolvated forms are rather close ($pK_a \approx pK_a^d$).

$$\log K_d = \beta^d pK_a^d + C_1 \qquad (11)$$

But, for the alcoholate ions whose $pK_a \geqslant 13$, there seems to be no resonance stabilization of anionic forms, and $|\beta^d| \to 0$. Simultaneous solving of equations (9-11) gives us the Brønsted relationship combining the experimentally determined log k_2 and pK_a values and taking into account the solvation effects which per se are in keeping with nonlinear relationship (11).

$$\log k_2 = \left(\frac{\beta + \beta^d}{1 + \beta^d}\right) pK_a + C' \qquad (12)$$

In Eq. (12) $C' = C + (1-\beta^d)/(1+\beta^d)C_1$, where C=-9.64 (see Eq (3)).

The obtained correlation equation (12) adequately describes the kinetic behavior of nucleophiles in the reactions of permanent exchange, where the attacking and leaving groups are of similar nature. For the nucleophiles whose $|\beta^d| \to 0$, the correlation will be transformed to the Brønsted equation for arylate ions (see Fig. 4). At relatively high $|\beta^d|$ values when solvation brings about a sharp drop in the concentration of the active form of anion nucleophile ($[RO^\ominus]_d = K_d[RO^\ominus]_o$) the Brønsted relationships will be violated, but the experimentally determined sensitivity equals:

$$\beta^{exp.} = \beta + \beta^d / 1 + \beta^d \qquad (13)$$

Since the $\beta^{exp.}$ values for the reactions of highly basic alcoholate anions with NPTS, NPMS and NPA fall into interval 0.1-0.3, relationship (13) permits us to quantitatively estimate parameter β^d. The values of $\beta^d = -(0.5-0.7)$ are remarkably higher than those for tertiary amines ($\beta^d = -(0.2 - 0.4)$)[26].

The important feature of Eq. (12) stands in the fact that it enables one to assess the meaning of solvation effects for transition states with various structures. As to the early transition state ($\beta \approx \beta^d$/ in Eq. (12)), solvation effects play significant role. The best examples are the Brønsted dependences for the reactions of substituted quinuclidines with 2,4-dinitrophenyl phosphates, 4- nitrophenyl phosphate, as well as with phosphorylated pyridine and 4-morpholinopyridine, in the case of which the β^{exp} values have the negative sign, but the reaction rate decreases with the increase in the nucleophile basicity. Evidently, low positive values β^{exp} 0.1 also reflect unfavorable solvent effects[26]. For late transition states ($\beta \gg \beta^d$|), the role of solvation effects becomes much less significant, since the structure of the transition state resembles that of unionized alcohol, solvation effects are balanced and they only slightly affect the rate of the process and pK_a values. The latter phenomenon takes place in the reactions of phenyl acetates with alcoholate and arylate ions, if the TPP decomposition acts as the rate determining step. For those nucleophile classes rate constants yield the common Brønsted relationship with $\beta_N = 1.5$[4].

There are also some interpretation difficulties of data about the reactivity of the anions of propargyl alcohol, choline, trifluoroethanol, tetrafluoropropanol to NPTS(Nos 3-6, Fig. 4), whose plots lie onto the Brønsted relationship for arylate anions. Similar anomalous phenomena have also been traced in other exchange processes for instance, in the reactions with NPA[4], NPMS[11], phenylacetate[4], etc.It is quite possible that for the fluorinated alcohols, containing charged substituents and unsaturated groupings,the p-π, π, and σ-resonance interactions and field effects are responsible for the weakening of the solvation of nucleophilic center and for a drop in the β^d value. For those nucleophiles, one and the same effective charge at the reacting centers in transition state demands also that the solvation of the attacking and leaving $RO^{\ominus}$ ion will be of similar types. In the case of the exchange processes where

the attacking and leaving groups are of varied nature, in the transition state of the reaction, the solvation effects at the reacting centers are not balanced, and the Brønsted relationships may become destorted either earlier or later than it is observed for permanent exchange processes. This can be exemplified by the action of the $RO^{\ominus}$- and $ArO^{\ominus}$-ions in the reaction, with 4-nitrophenyl acetate. Under the conditions of the rate determining attack of arylate and alcoholate anions, their behavior is subjected to the individual Brønsted relationships, with the breaking point at $pK_a \approx 10$[4]. Quantitative estimation of those effects is certainly a very complicated task.

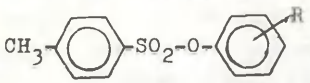
Experimental

The oxygen-containing nucleophiles (alcohols, phenols) of commercial origin were purified according to the standard methods.

The aryl esters of 4-toluene sulfo acid were prepared by acylating the corresponding phenols with toluene sulfochloride in the presence of triethylamine[5]; the melting points and solvents for recrystallization are given in Table 4.

Table 4

Melting Points and Solvents for Recrystallization of Aryl Esters of 4-Toluene Sulfoacids



R	Melting point, °C	Solvent for recrystallization
1. 2,4-dinitro-	123(122-123[12])	absolute ethanol
2. 2,6-dinitro-	135-136(134-135[12])	"
3. 2,5-dinitro-	116(115-117[12])	"
4. 2,4,6-trichloro-		hexane

Table 4 continued

R	Melting point, °C	Solvent for recrystallization
5. 4-nitro-	98(97-97,5[12])	absolute ethanol
6. 2,4-dibromo-	120(120[27])	toluene-hexane
7. 4-phenylazo-	161-162	absolute ethanol
8. 3-chloro-	42-44	toluene-hexane

Inorganic "extra pure" or "chemically pure" reactives were used without additional purification.

The ionization constants of substituted phenols were determined spectrophotometrically in 30 % ethanol at 25°C, ionic strength μ = 1.0 (supported by introduction of 1M KCl).

The alcoholysis, phenolysis, and alkaline hydrolysis of aryl esters of 4-toluene sulfo acids were controlled by means of the UV-spectrophotometry, according to the accu - mulation of the corresponding arylate ions at the wave - lengths given in Table 2. The methods of kinetic measurements used for finding pseudofirst order rate constants (k_{obs}, s^{-1}), have been discussed in detail in papers[1,5]. In slow reactions (e.g. the interaction of pentafluor - and 2,3,5,6-tetrafluor phenols with NPTS), these methods underwent slight modifications: the reaction was taken to a certain level of substrate transformation (~10-15%), after which kinetic solvents were alkalized (with 5M of NaOH solution) up to pH~11; and the optical density of the isolated 4-nitrophenolate ion, i.e. the D_t value, was obtained. The value of D_∞ was found after the complete alkaline hydrolysis of NPTS, the k_{obs} value was calculated as shown in[1,5]the control test proved that the contribution of the spontaneous NPTS hydrolysis and of the hydrolysis catalyzed by the phosphate buffer into the observed pseudofirst order rate constants did not exceed 1-2%. The kinetic measurement took place at ionic strength (μ=1.0) (1M KCl). Usually, 5 % aqueous ethanol was used as a solvent.

Reaction products were analyzed by contrasting the UV-spectra of reaction products to those of model solvents,

made up of probable reaction products, forming in the case of the -S(=O)-O-bond break of aryl esters of 4-toluene sulfo acid. In all cases, takes place only the nucleophile attack onto the tetracoordinated sulfur atom of the substrate.

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MECHANISM OF HYDROLYSIS OF MALTOSE AND β-CYCLODEXTRIN IN AQUEOUS SOLUTION OF ACETIC ACID

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Rate measurements of the acetic acid-catalyzed hydrolysis of maltose and β-cyclodextrin in water and D_2O at 120°C were carried out. Kinetic data and solvent isotope effect are in accord with the specific acid catalysis mechanism.

β-Cyclodextrin (β-CD) is an oligosacharide, containing seven residues of glucose connected into a cycle by α-(1→4) glycosidic bonds[1]. The ability of cyclodextrins to form inclusion complexes with many organic or inorganic compounds[2] is the reason of high interest in these compounds.

Linear maltooligosaccharides, containing 3-7 residues of glucose became important in the recent years, because of their uses in enzymology and clinical analysis. The partial hydrolysis of cyclic maltooligosaccharides (α- and β-CD) is the most convenient way for the preparation of them. Separation of individual maltooligosaccharides is easier in this case than from the products of acidic hydrolysis of amylose[3]. Full-understanding of the mechanism and kinetics of hydrolysis of cyclodextrins and linear oligosaccharides is essential in order to achieve high yields of the desirable linear maltooligosaccharides.

Acidic hydrolysis of glycosidic bond had been investigated fairly well[4]. But very insufficient data have been reported on the hydrolysis of β-CD. The only authors on this subject are J.Szejtli and co-workers who investigated the hydrolysis of β-CD in hydrochloric acid[5,6]. A specific hydrogen ion catalysis established for some synthetic α-glycosides was adopted for this reaction, as well as for acid hydrolysis of other oligosaccharides.

It is interesting to examine the possibility of general acid catalysis, when oligosaccharides are hydrolyzed in the presence of organic acids. In this paper we report the kinetic data for the hydrolysis of β-CD catalyzed by acetic acid in water and in D_2O at 120°C. The hydrolysis of maltose, as a model compound containing isolated α-(1→4) glycosidic bond was investigated under the same conditions.

Experimental

Starting materials. Monohydrate of maltose (puriss. p. a.) and β-CD (purum) from "Fluka" (Switz.) was used without purification. Acetic acid p.a. "Reachim" (USSR) was used. The concentration of solution of acetic acid was checked titrimetrically. Solutions of oligosaccharides for kinetic investigations were prepared gravimetrically. It was estimated from elemental analysis that 1 mole of β-CD contained 10 moles of crystalline water. This result was used for calculations of concentration of β-CD.

Deuterium oxide (99.95% D) and tetradeuterium acetic acid (99.5% D) from "Fluka" were used for determination of solvent isotope effect.

Deuterium - β-CD containing 7.5 mole D_2O per mole of β-CD was prepared by twofold evaporation in vaccuo of β-CD solution in D_2O. Deuterium maltose was prepared in the same way. Glucose, maltose (puriss. p.a.) from "Fluka" and maltohexaose (research grade) from "Sigma" (USA) were used to check the Somogyi - Nelson method for determination of reducing sugars.

Kinetic Measurements. Fussed glass ampoules with solution of oligosaccharide were dipped in glycerol-contained thermostate UT-2 (GDR) at 120°±0.2°C. Ampoules were taken out from time to time and cooled in water and determination of concentration of the products was carried out.

The concentration of glucose - a product of hydrolysis of maltose - was determinated with enzymic analyser PLAG-1 (USSR) containing the membrane with immobilized glucosooxydase[7]. The concentration of reducing sugars from the reaction of hydrolysis of β-CD was determinated according to Somogyi - Nelson[8]. The optical density of coloured complex was measured at 740 nm on a spectrophotometer "Specord M-40" (GDR) (3 determinations were performed for every sample of reaction mixture). From 3 to 6 parallel experiments were carried out for every rate constant determination. It was shown by using standard solutions of glucose, maltose and maltohexaose that the sensitivity of the Somogyi - Nelson method was the same to the reducing groups of all these saccharides.

Results and discussion

Rate constants of hydrolysis of maltose and β-CD are presented in the table. In the case of maltose observed rate constants have been calculated from equation of pseudo-first order kinetics by the least square method. Hydrolytic ring opening of β-CD gives linear oligosaccharide maltoheptaose, which is hydrolyzed further at a higher rate than - CD itself. Therefore, the reaction does not follow first order kinetics. The pseudo-first order rate constant of the ring opening was obtained from the initial rate of hydrolysis by the treatment of kinetic curve by cubic splain method[9]. β-CD contains 7 glycosidic bonds. The pseudo-first order rate constant for hydrolysis of a simple bond given in the table equals:

$$k_1 = v_o/7\left[\beta\text{-CD}\right]_o \qquad (1)$$

Table

Rate Constants of Hydrolysis of Maltose and β-Cyclodextrin in Aqueous Solution of Acetic Acid at 120°C

Solvent	Concentration of acetic acid, $mol \cdot l^{-1}$	Concentration of hydrogen ions, $x10^4$, $mol \cdot l^{-1}$	Hydrolysis of maltose		Hydrolysis of β-CD	
			First order rate constant $k_1 \cdot 10^5$, sec^{-1}	Second order rate constant $k_2 \cdot 10^3$, $l \cdot mol^{-1} \cdot sec^{-1}$	First order rate constant $k_1 \cdot 10^5$, sec^{-1}	Second order rate constant $k_2 \cdot 10^3$, $l \cdot mol^{-1} \cdot sec^{-1}$
H_2O	0.01	2.84[a]	0.41 ± 0.06[b]	14.4 ± 2.1	-	-
H_2O	0.1	9.08[a]	1.11 ± 0.04	12.2 ± 0.4	0.191 ± 0.012	2.10 ± 0.14
H_2O	1.0	28.8[a]	3.42 ± 0.24	11.9 ± 2.4	0.456 ± 0.082	1.58 ± 0.28
D_2O	0.11[c]	5.3[d]	1.35 ± 0.18	23.0 ± 2.5	0.200 ± 0.018	3.74 ± 0.34

a - calculated according to equation $pK_a = 1170.48/T - 3.1694 + 0.013399 \cdot T$ from[10, 12]

b - standard deviation of 4-6 parallel experiments

c - concentration of CD_3COOD

d - calculated for ions D^+ according to equation $pK_a = 1278.92/T - 3.0490 + 0.013702 \cdot T$, from[11]

where v_o - initial rate of hydrolysis obtained from kinetics curve; $[\beta\text{-CD}]_o$ - initial concentration of β-CD.

The second order rate constant according to specific acid catalysis mechanism:

$$k_2 = k_1/[H^+] \qquad (2)$$

The values of pK_a for acetic acid and deuteroacetic acid at 120°C were necessary for the calculation of second order rate constant. We did not find that data in literature and calculated the pK_a values by extrapolation of empirical equations $pK_a = f(T)$ [10-12]. The equation for acetic acid was checked up to 90°C [12].

When passing from experiment 1 to 3 (see Table) the concentration of undissociated acetic acid in reaction mixture increases more than 100 fold. Because the rate constant k_2 does not increase, but rather slightly decreases, the contribution of general acid catalysis to the process of hydrolysis is insignificant. This conclusion was confirmed by the reverse kinetic solvent isotope effect ($k_{D^+}/k_{H^+} = 1.8\text{-}1.9$), characteristic of specific acid catalysis [13]. Thus, the reaction of hydrolysis of maltose and β-CD proceeded according to specific acid catalysis mechanism in aqueous solution of acetic acid.

Hydrolysis of single glycosidic bond in β-CD proceeded 6-7 times slower than in maltose (see Table). It may be explained by the action of several factors. Because of big volume of hydrated hydrogen ions their local concentration may be lower in the cavity of β-CD than in the solution. The analysis carried out on space-filling "Tartu models" showed that the conformation of glycosidic bond in the molecule of β-CD is different from the main conformation of maltose [14]. Glycosidic oxygen of β-CD is less "open" to the attack of catalyst than in maltose.

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EFFECT OF REAGENT STRUCTURE ON FORMATION RATE OF ARYL VINYL KETONES IN REACTIONS OF ß-HALOGEN PROPIOPHENONES WITH AMINES

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Dependence of formation rate of aryl vinyl ketones on their structures with amine series in reactions of ß-cloro- and ß-iodo-propiophenones substituted in nucleus is studied. It is shown that the introduction of electron-donating substituents into ß-halogen propiophenones brings about a decrease in the C-X bond order in carbanionic transition state which is characteristic of E2 processes. Sensitivities to substituent effect in substrate's benzene ring and to leaving group nature are similar.

It has been shown [1-3] when studying the mechanism of interaction of ß-halogen propiophenones with amines that the first step of this interaction comprises the formation of aryl vinyl ketones (Eq. (1)) which then in the reactions with the primary and secondary amines form addition products - ß-amino propiophenones (Eq. (2))

$$ArCOCH_2CH_2X + NR^1R^2R^3 \longrightarrow ArCOCH = CH_2 + R^1R^2R^3\overset{+}{N}H \cdot X^- \quad (1)$$

$$ArCOCH = CH_2 + NHR^1R^2 \longrightarrow ArCOCH_2CH_2NR^1R^2 \quad (2)$$

It bas also been established in[1-3] that the formation of aryl vinyl ketones proceeds according to the E2 mechanism via the anion-like transition state. For the purposes of the detailed studies of the mechanisms of those reactions we have continued our research into the effect of reagent structure on the formation rate of aryl vinyl ketones. Namely, substituent effects on their interaction rate with different amines in ß-halogen propiophenones was studied.

For the nucleophiles studied, the rate of aryl venyl ketones' formation was determined conductometrically according to the accumulation of the hydrogen halide salts of amines. The rate can in all cases (Table 1) be described by means of a second order reaction (the first one for any reaction).

Representatives of various classes (primary, secondary, tertiary) of amines (isobutyl amine, piperidine, triethyl amine) and also 4-N,N-dimethylaminopyridine were used as nucleophiles. The former have already been studied when examining the effect of nucleophile structure onto the rate of interaction with ß-halogen propiophenones[1-3]. The measurements were carried out at a large amine excess. It follows from the obtained data (Table 1) that in all cases the reactivity of the studied amines varies in the reactions with substituted ß-halogen propiophenones in the following order: piperidine > triethyl amine > isobutyl amine > N,N-dimethylaminopyridine. The obtained reactivity series is analogous to that observed for the interaction of amines with unsubstituted ß-halogen propiophenones[2] and is mainly conditioned by nucleophile basicity. The introduction of electron-acceptor substituents into the meta- and para-positions of ß-chloro- and ß-iodo-propiophenones accelerates the reaction while that of electron-donor substituents retards the reactions with participation of all these amines.

The quantitative estimation of substituent effect on the process rate in the benzene ring of ß-chloro- and ß-io-

Table 1

Rate Constants $k \cdot 10^2$ ($l \cdot mol^{-1} \cdot s^{-1}$) of Aryl Vinyl Ketones' Formation in Reactions of ß-Halogen-Propiophenones ($RC_6H_4COCH_2CH_2X$) with Amines in Acetonitrile, 298 K

$RC_6H_4COCH_2CH_2X$		Amine			
R	X	Isobutylamine	Piperidine	Triethyl amine	N,N-dimethylamino-pyridine
4-OCH_3	Cl	0.365±0.008	7.79±0.31	1.93±0.01	0.215±0.009
4-CH_3	Cl	0.790±0.010	15.2 ±0.9	4.0 ±0.3	0.380±0.002
H	Cl	1.90 ±0.04[2]	30.3 ±0.8[2]	7.42±0.09[2]	0.776±0.039
4-Cl	Cl	3.77 ±0.09	75.1 ±2.5	19.1 ±0.2	2.22 ±0.13
3-NO_2	Cl	33.7 ±0.8	730 ±30	126 ±7	22.0 ±0.9
4-OCH_3	Br	3.99 ±0.09[2]	103 ±2[2]	24.9 ±0.7[2]	2.41 ±0.28
4-CH_3	Br	7.43 ±0.02[2]	140 ±1[2]	46.50±0.6[2]	4.29 ±0.29
H	Br	12.9 ±0.2[2]	231 ±5[2]	74.4 ±0.8[2]	7.59 ±0.46
4-Cl	Br	35.4 ±0.8[2]	692 ±2[2]	233 ±7[2]	19.8 ±0.9
3-NO_2	Br	248 ±10[2]	2870 ±70[2]	1280 ±30[2]	130 ±8
4-OCH_3	I	10.6 ±0.6	238 ±9	93.1 ±3.2	8.80 ±0.33
4-CH_3	I	13.0 ±0.7	264 ±8	141 ±8	13.6 ±0.7
H	I	31.2 ±0.3[2]	673 ±6[2]	214 ±2[2]	24.6 ±0.9
4-Cl	I	74.2 ±0.8	1556 ±58	565 ±15	60.0 ±3.0
3-NO_2	I	418 ±9	6220 ±290	2224 ±31	328 ±15

Table 2

Parameters of Eq. (3) for Reactions of ß-Halogen Propiophenones ($RC_6H_4COCH_2CH_2X$) with Amines, Acetonitrile, 298 K

Amine	X = Cl				X = Br			
	$-\log k_o$	ρ^o	s	r	$-\log k_o$	ρ^o	s	r
Isobutyl amine	1.90±0.09	2.04±0.25	0.18	0.979	0.95±0.05[2]	1.92±0.15[2]	0.11[2]	0.991[2]
Piperidine	0.62±0.06	2.09±0.18	0.13	0.989	-0.35±0.03[2]	1.63±0.08[2]	0.06[2]	0.995[2]
Triethyl amine	1.22±0.07	1.91±0.19	0.14	0.986	0.16±0.05[2]	1.85±0.15[2]	0.11[2]	0.990[2]
N,N-dimethyl-aminopyridine	2.19±0.05	2.17±0.15	0.11	0.993	1.19±0.05	1.86±0.14	0.10	0.991

Amine	X = I			
	$-\log k_o$	ρ^o	s	r
Isobutyl amine	0.61±0.04	1.79±0.11	0.08	0.994
Piperidine	-0.71±0.04	1.61±0.13	0.09	0.990
Triethyl amine	-0.31±0.04	1.51±0.10	0.07	0.993
N,N-Dimethyl-aminopyridine	0.67±0.04	1.71±0.11	0.08	0.994

do-propiophenones by means of the Hammett-Taft equation (3) shows

$$\log k = \log k_o + \rho^o \delta^o \qquad (3)$$

that the reactions studied have rather high ρ^o values (see Table 2). The comparison of the ρ^o values evidences that if the substrate's activity rises (transition from chlorine derivatives to the iodine ones), parameter ρ^o decreases for all amines studied. Analogous phenomenon confirms the conclusion[2,3] that the C-H bond break level decreases in the transition state in the substrate with the "best" leaving group.

It was found during the research into the effect of the leaving group nature on the rates of those processes depending on the substituent character in the substrate's benzene ring that the γ values, which quantitatively characterize this property according to Eq. (4)[4] becomes less intense

$$\log k = \log k_o + \gamma\tau \qquad (4)$$

in the case the substrate's activity grows (Table 3). This may be connected with the increase in the C-X bond order in the transition state at the introduction of electron-acceptor substituents into the ß-halogen propiophenone molecule[5].

In order to compare the contributions of substituent effects in the substrate's benzene ring and those of its leaving group nature, the data of Table 1 were processed according to Eq. (5) in natural and normalized[6] scales (see Table 4). Obtained parameters ρ^o and γ are in the natural scale (Table 4) equal to the mean values, found using one-parameter equations (3) and (4), respectively.

$$\log k = \log k_o + \rho^o \delta^o + \gamma\tau \qquad (5)$$

The comparison of the ρ^o and γ values in the normalized scale[6] shows that the sensitivity to the substituent effect in the benzene ring of the substrate (ρ^o) and to the

Table 3

Parameters of Eq. (4) for Reactions of β-Halogen Propiophenones ($RC_6H_4COCH_2CH_2X$) with Amines in Acetonitrile, 298 K

R	Isobutyl amine				Piperidine			
	-log k_o	ρ	s	r	-log k_o	ρ	s	r
4-OCH_3	4.99±0.01	0.75±0.01	0.003	1.00	3.72±0.16	0.77±0.03	0.05	0.999
4-CH_3	4.25±0.27	0.64±0.06	0.08	0.995	3.00±0.21	0.65±0.04	0.06	0.997
H^2	3.83±0.09	0.62±0.02	0.03	0.999	2.85±0.20	0.68±0.04	0.06	0.998
4-Cl	3.68±0.12	0.67±0.03	0.04	0.999	2.42±0.07	0.68±0.02	0.02	0.9997
3-NO_2	2.40±0.22	0.57±0.05	0.07	0.996	0.74±0.17	0.47±0.04	0.06	0.996

R	Triethyl amine				N,N-dimethylamine pyridine			
	-log k_o	ρ	s	r	-log k_o	ρ	s	r
4-OCH_3	4.62±0.22	0.85±0.05	0.07	0.998	5.46±0.26	0.81±0.06	0.08	0.998
4-CH_3	4.09±0.09	0.79±0.02	0.03	0.9997	5.11±0.15	0.79±0.03	0.05	0.999
H^2	3.67±0.10	0.74±0.02	0.03	0.9995	4.70±0.20	0.76±0.04	0.06	0.998
4-Cl	3.29±0.10	0.76±0.02	0.03	0.9996	4.12±0.18	0.72±0.04	0.06	0.999
3-NO_2	2.11±0.30	0.66±0.06	0.09	0.994	2.69±0.17	0.59±0.04	0.05	0.998

Table 4

Correlation Parameters* of Reaction Rate Constants of Substituted β-Halogen Propiophenones with Amines According to Eq. (5)

Amine	log k_o		ρ^o		γ		S		R**
	nat.	norm.	nat.	norm.	nat.	norm.	nat.	norm.	
Isobutyl amine	-4.09±0.17	-4.96±0.21	1.91±0.09	0.75±0.04	0.65±0.04	0.65±0.04	0.12	0.14	0.992
Piperidine	-2.87±0.17	-3.52±0.22	1.78±0.09	0.73±0.04	0.65±0.04	0.67±0.04	0.12	0.15	0.991
Triethyl amine	-3.79±0.17	-4.46±0.19	1.76±0.09	0.67±0.03	0.76±0.04	0.73±0.03	0.11	0.13	0.993
N,N-dimethyl-aminopyridine	-4.67±0.17	-5.36±0.19	1.92±0.09	0.71±0.03	0.74±0.04	0.69±0.03	0.12	0.13	0.993

*Values "norm." - in the normalized scale[6]; "nat." - in the natural scale

** R - the multiple correlation coefficient

Table 5

Characterization of Derivatives of ß-Halogen Propiophenones of $RC_6H_4COCH_2CH_2X$

	R	X	Melting point, °C	% found			Brutto-formula	% caloulated		
				C	H	X		C	H	X
1	4-OCH_3	Cl	63-63.5	60.24	5.63	17.61	$C_{10}H_{11}ClO_2$	60.46	5.58	17.85
2	4-CH_3	Cl	80-81.5 (79-81[7])				$C_{10}H_{11}ClO$			
3	H	Cl	48-49 (48.5-49[8])				C_9H_9ClO			
4.	4-Cl	Cl	51-52 (51-52[7])				$C_9H_8Cl_2C$			
5	3-NO_2	Cl[*]	44-46	67.39	3.80	16.47	$C_9H_8ClNO_3$	67.53	3.77	16.60
6	4-OCH_3	Br	71-71.5 (71-71.5[2])				$C_{10}H_{11}BrO_2$			
7	4-CH_3	Br	91.5-92 (84.5-85.5[7])				$C_{10}H_{11}BrO$			
8	H	Br	58.5-59.5 (56[7], 61[9])				C_9H_9BrO			
9	4-Cl	Br	54.5-55.5 (53.5-54.5[7])				C_9H_8ClBrO			
10	3-NO_2	Br	54.5-55.5 (54.5-55.5[2])				$C_9H_8BrNO_3$			
11	4-OCH_3	I	63.5-64.5	41.27	3.59	43.65	$C_{10}H_{11}IO_2$	41.40	3.82	43.74
12	4-CH_3	I	80.5-81.5	43.67	4.10	46.01	$C_{10}H_{11}IO$	43.82	4.04	46.30
13	H	I	63-64 (61.5-63[10])				C_9H_9IO			
14	4-Cl	I	63-64	36.56	2.80	54.85	C_9H_8ClIO	36.70	2.74	55.13
15	3-NO_2	I[**]	32-33	35.27	2.50	41.41	$C_9H_8INO_3$	35.43	2.64	41.60

[*] % found: N 6.70; % calculated: 6.55 [**] % found: N 4.60; % calculated: 4.59

leaving group nature in it (γ) almost coincide. The fact should be considered when determining the changes in the transition state position on the reaction coordinate if the reagents' structures are changed.

Thus, the obtained results concerning the studies of the formation rate of aryl vinyl ketones in the reactions of ß-halogen propiophenones substituted in the nucleus with the amine series confirm the earlier made conclusion[2,3] that in the transition state C-H bond break degree decreases for the substrate with the "best" leaving group. It was found that the introduction of electron-donor substituents into the substrate leads to the reduced C-X bond order. The sensitivity to the substituent effect in the substrate's benzene ring and to its leaving group nature are similar.

Experimental

Acetonitrile and the amine used were purified according to the known methods. Substituted ß-halogen propiophenones (Table 5, Nos 3, 6-10, 13) were obtained as described in [2]. 4-methoxy-ß-chloro-propiophenone (Table 5, No 1) was obtained from ß-chloro-propionyl chloride and anizole in the presence of $AlCl_3$. 3-Nitro-ß-chloro-propiohenone was obtained by nitrating ß-chloro-propiophenone with a 100 %-nitric acid at 0° C (keeping it for 5 min.). Substituted ß-iodo-propiophenones (Table 5, Nos 11-15) were obtained according to the Finkelstein reaction from the corresponding substituted ß-chloro-propiophenones and anhydrous sodium iodide in acetone. Their structures have been established with the PMR spectra.

Kinetic measurements and mathematical treatment of the obtained data were carried out as described in[1].

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KINETICS OF INTERACTION OF NUCLEUS-SUBSTITUTED CHLORO-1,3,5-TRIAZINES WITH ARYLAMINES IN ACETONITRILE

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Kinetics of reactions of nucleus-substituted chloro-1,3,5-triazines with 3-nitro-4-methyl aniline in acetonitrile at 25°C obeys the second-order kinetics. For rate constants the Hammett relationship is valid, $\rho = 10.5 \pm 1.8$, showing that the s-triazine ring's ability to transfer substituent effects is rather well expressed here. The step-wise addition-elimination mechanism with tetrahedral intermediate formation in rate limiting stage is suggested.

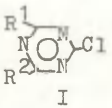
The derivatives of 1,3,5-triazine are being widely used in organic synthesis[1,2]. Bi- and trifunctional 1,3,5-triazine substituents have arisen great interest as monomers for obtaining novel classes of polymeric materials[3]. As a rule, initial monomers are obtained by means of successive halogen exchange in cyameric chloride in the reactions of nucleophilic substitution.

The processes of nucleophilic aromatic substitution have been rather intensely studied, which cannot be said

about the kinetics and mechanism of similar substitution reactions of halogen or other active groups in heteroaromatic systems, including the s-triazine one. We can mention only a few studies dealing with the kinetics of cyameric chloride kinetics[4-7].

In our previous paper[8] we suggested relying upon the kinetic regularities and the analysis of the ρ-Hammett parameters according to nucleophile structure the existence of stage addition-elimination mechanism with formation of tetrahedral intermediate product for the interaction of cyanuric chloride with arylamines in acetonitrile.

In order to confirm the applicability of the mechanism, in the present paper we have studied the kinetics and effects of substituents in substrate on the reaction rate of chloro-1,3,5-triazines substituted in nucleus, falling under type I with 3-nitro-4-methyl aniline in acetonitrile at 25°C.

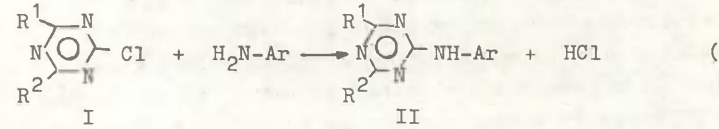


I

$R^1 = Cl$, $R^2 = OC_6H_5$, a; $R^1 = Cl$, $R^2 = OCH_3$, b;
$R^1 = R^2 = OC_6H_5$, c; $R^1 = Cl$, $R^2 = N(C_6H_5)_2$, d.

All kinetic measurements were conducted under pseudo-monomolecular conditions at large excesses of substrate I, as compared with aryl amine. Up to conversion level>90% only one chlorine atom is substituted in dihalogen-1,3,5-triazines Ia,b,c.

The comparison of the UV-spectra of reaction mixtures and of the previously synthesized products of reactions II a-d shows that the processes studied proceed quantitatively and irreversibly according to scheme (1):



I II (1)

The reaction rate was monitored spectrophotometrically according to the loss of colored amine at λ=400 nm. If the reagent ratio is (I)>($ArNH_2$)~10^{-5} mol·l^{-1}, observed pseudo-

first order rate constants $k^{I}_{obs}(s^{-1})$ tend in most cases to vary after achieving a 25-30 % conversion level of reagents. This change can result from a partial binding of the initial amine into hydrochloride, from the autocatalytic effect revealed either by the latter compound or by product II; from the results of the catalysis with by-compounds forming in quantities close to that of amide II owing to the insignificant substrate catalysis or to the HCl interaction with a solvent. In order to weaken the influence of those factors, low aryl amine concentrations, $< 5 \cdot 10^{-5}$ mol·l^{-1}, was used. In some cases k^{I}_{obs} were found, its conversion degree being $< 30\%$. Under such conditions the errors of finding observed rate constants did not exceed 5%. In the studied variation range of substrate's concentration functions "k^{I}_{obs}-[I]" appear to be linear, initiating from the origin, which corresponds to the kinetics of bimolecular interaction. Second order rate constants $k^{II}(l \cdot mol^{-1} \cdot s^{-1})$ calculated from those dependences are given in Table 1 as well as the data for cyameric chloride reaction with this amine in acetonitrile[8].

Table 1

Second Order Rate Constants k^{II} of Reactions of Chloro-1,3,5-triazines (I) Substituted in Nucleus with 3-nitro-4-methyl Aniline in Acetonitrile at 25°C

Substrate I	Variation range of substrate's concentration, $[I]10^2$ mol·l^{-1}	$k^{II} \cdot 10^3$, $l \cdot mol^{-1} \cdot s^{-1}$
$R^1 = R^2 = Cl$	0.28 + 2.22	779±46[8]
a, $R^1 = Cl$, $R^2 = OC_6H_5$	0.50 + 2.00	15.3±0.3
b, $R^1 = Cl$, $R^2 = OCH_3$	1.33 + 2.67	4.3±0.2
c, $R^1 = R^2 = OC_6H_5$	5.00 + 65.0	0.134±0.006
d, R^1=Cl, R^2=$N(C_6H_5)_2$	10.0 + 25.0	0.040±0.003

The data about the reaction rate sensitivity to the substrate's structure have been widely used in literature for the identification of the mechanisms of aromatic nucleophilic substitution[9]. But, we are not aware of any papers where this approach has been used for establishing

the substitution mechanism in heteroaromatic s-triazine systems.

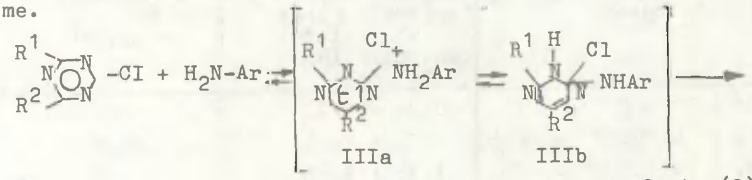
The effects of substituents R^1 and R^2 in I on the rate of the aminolysis studied can be described by means of the Hammett equation using the sums of σ_{R^1} and σ_{R^2} for meta - substituents in benzene nucleus:

$$\log k^{II} = -(8.5 \pm 1.0) + (10.5 \pm 1.8)\Sigma\sigma_{R^1,R^2} \qquad (2)$$

$$S = 0.53;\ r = 0.95;\ N = 5.$$

Before processing k^{II} from Table 1 according to the Hammett equation, the values were corrected, dividing them by 3 in the case of cyameric chloride aminolysis, and by 2 in the case of the reactions of substrates 1a,b,c depending on the number of reaction centers (chlorine atoms) in an electrophilic reagent. The fact that relationship"$\log k^{II} - \Sigma\sigma_{R^1,R^2}$" is valid tells us about the additivity effects of substituents R^1 and R^2 in s-triazine nucleus.

In Table 2 value ρ for the process studied is compared to the analogous sensitivity parameters for the aminolysis of substituted aryl chlorides. The data show that the sensitivity of s-triazine system is about twice higher than that of benzene system. Since for aromatic nucleophilic substitution the observed ρ values are linked with[4-8] stepwise substitution mechanism, the ρ value for the aminolysis of substituted chloro-1,3,5-triazines is even in a closer agreement with such a mechanism which is given in the scheme.

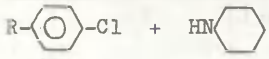
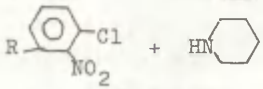
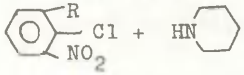
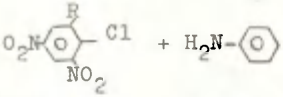
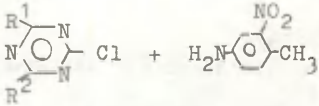


There is a ground to expect that the probability of realization of the mechanism is higher in the case of s-triazine system in comparison with the benzene one, because the forming tetrahedral intermediate IIIa may be additionally stabilized on the expense of isomerization into neutral form III b.

The reasons for such a high ρ value of substitution in chloro-1,3,5-triazine system, whose absolute value is actually being rather close to the benzene system sensitivity in the reactions of electrophilic aromatic substitution should be given a special treatment.

Table 2

ρ-Hammett values for Aminolysis of Aryl Chlorides and Substituted Chloro-1,3,5-Triazines in Aprotic Media

Reaction series	Reaction Conditions	ρ	Refe - rences
	Benzene, 45°C	5.24	10
	Benzene, 100°C	4,80	11
	Benzene, 75°C	4.21	12
	Acetonitrile, 50°C	4.70	13
	Acetonitrile, 25°C	10.5±1.8	This work

We can assume that in the framework of a common scheme of substitution mechanism in the aromatic and heteroaromatic substrates (scheme (3)) the higher ρ value in the second case can be connected with the transition state which is much closer to tetrahedral intermediate III than in the first case.

There is another explanation for the difference between the absolute values of ρ for similar processes of aromatic and heteroaromatic substitution: extremely high tendency of the s-triazine ring to transfer electron effects in comparison with that of benzene ring. In such a case,

for a correct contrasting of ρ values, another ρ scale for s-triazine derivatives should be introduced. Unfortunately, literature data concerning the research into the transfer of electron effects in this system are rather poor[4]. There are also references there that the ability of heteroaromatic and aromatic systems to transfer electron effects practically coincide[14]. Therefore, this problem should be studied yet.

Experimental

2-Chloro-4,6-diphenyloxy-1,3,5-triazine[4], 2,4-dichloro-6-methyloxy-1,3,5-triazine[15], 2,4-dichloro-6-phenyloxy-1,3,5-triazine[16], 2,4-dichloro-6-N-diphenylamino-1,3,5-triazine[17] were obtained and purified according to known methods. The purification techniques of 3-nitro-4-methyl-aniline, acetonitrile and the methods of kinetic measurements were described in[8],

UV-spectra were registered on a "Specord M 40".

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E_T-PARAMETERS OF SOME SURFACTANTS AND THEIR SOLUTIONS

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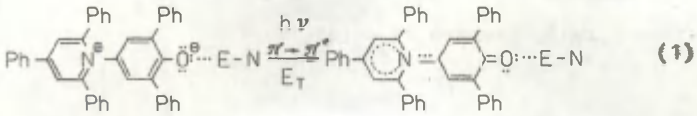
E_T-values of gross polarity of some nonionic individual surfactants as well as the aqueous solutions of the two of them, Triton X-100 and Tween 80, were determined. It was also found that already very small additions of those surfactants to water led to a very sharp and substantial decrease of the gross polarity of the latter. A new approximate measure of the solubilization power $\Delta = E_T - E_T^\circ$, where E_T and E_T° values pefer, respectively, to solvation complexes of N-phenolpyridinium betaine with water and surfactant molecules in aqueous solution has been suggested.

Earlier[1] the influence of the concentration of an interfaoial catalyst, Bu_4NBr, on the Dimroth-Reichardt's E_T-parameters of the aqueous solutions of this salt was studied (see scheme (1), where E-N refers to the solvent molecule, E - is its electrophilio and N - the nucleophilic solvation centers).



(1)

I

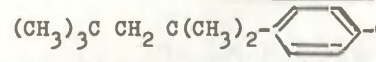
$\mu_g \approx 14.6$ D $\quad \mu_g \gg \mu_e \quad \mu_e \approx 6$ D

Meanwhile, it was shown that the increase of the concentration of that quaternary salt in its aqueous solution up to 3M (or up to 30 molal solution) results in a very substantial decrease of the E_T-parameter of the latter,whioh is close to the values much more characteristic of the melted salt (e.g., $C_6H_5COON(n\text{-}C_6H_{11})_4$, etc.) or of the dipolar aprotic solvent DMSO than water[2].

In its turn in Ref. 3 the influence of the very low concentrations (as a rule, the molar concentration of the surfactant $M_S \leq 0.1$) of various nonionogenic (e.g., Triton X-100, Brij 35), anionic (SDS, SDeS, STS, SHS), and cationic surfactants on the E_T values of their dilute aqueous solutions was studied. It was shown that the presence of even relatively small amounts of those surfactants in water initiates a very substantional and sharp drop of the E_T - value of water due to the assumed[3] solubilization of betaine dye (I) by the micelle-formation processes between the latter and nonionic or ionogenic detergents.

In the present work the E_T-parameters of some widely used nonionic surfactants, such as poly-oxy-1,2-ethanediyl esters of longohain saturated or non-saturated fatty acids (Tweens) and ether of alkylsubstituted phenols (e.g. Triton X-100) (see scheme (2) and (3)):

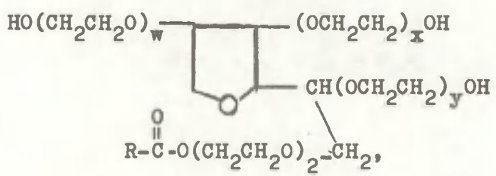
Triton X-100



$$(CH_3)_3C\ CH_2\ C(CH_3)_2-C_6H_4-O(CH_2CH_2O)_X\ H, \qquad (2)$$

where $5 \leq x \leq 15$, average MW = 647,

Tweens



where w + x + z + y = 20;

$R = CH_3(CH_2)_7CH{=}CH(CH_2)_7$-	Tween 80
$R = C_{17}H_{35}$	Tween 60
$R = C_{15}H_{31}$	Tween 40
$R = C_{11}H_{23}$	Tween 20

were studied.

In the oase of Triton X-100 and Tween 80 also the dependence of the E_T-parameters of the aqueous solutions of those surfactants on the wide variation of the ration of the components of those binary mixtures was also studied.

For the comparison with the results of the above-mentioned experiments the E_T-values for some aqueous solu - tions of methyl-oellosolve (MCS), anhydrous $C_6H_5OCH_2CH_2OH$, and aqueous solutions of anionic surfactant SDS (sodium dodecyl sulfate) were also measured.

The first steps for the study of the influence of nonionic surfactant (Triton X-100) additions on E_T-parameters of its solutions in dipolar aprotic solvent DMSO, in apolar 0.216) were also taken.

Experimental

Surfactants Triton X-100 (average molecular weight - 647, d_4^{25} = 1.0595, n_D^{25} = 1.4890), Tween 80 (molecular weight 1309), Tween 60, Tween 40, Tween 20 and SDS were made by

Terak (Berlin) and Aldrich.

Benzene (chemically pure) and DMSO (chemically pure) were purified as described in[4]. Water-rich aqueous solutions of Tween 80 have slightly acidic reactions ($5 \leq pH \leq 7$). Therefore the determination of the E_T-values in those solvents was possible only in the presence of small amounts of alkali (KOH or NaOH).

Solvatochromic shifts of long-wavelength absorption maximum of 2,6-diphenyl-4-(2,4,6-triphenyl-1-pyridino)phenoxide (Aldrich) were measured spectrophotometrically (Hitachi EPS-3T) at 25°C (as a rule) in the thermostated cells relative to the blank solutions identical in composition to each sample except the solute-dye (I).

The accuracy of the assignment of the wavelengths of the absorption maximum was in the range $\pm$ 1-2 nm.

The results of the determination of E_T-values are summarized in Table 1.

Table 1

Solvatochromic Shifts of the Maximum of the Long-Wavelength Absorption Band of Pyridinium-N-Phenoxide Dye (I) in Some Individual Surfactants and in their Binary Mixtures with Water and Organic Solvents[a]

System	M_S	N_S	E_T(kcal/mol)	
			25°	50°
1 2	3	4	5	6
1. Water-Triton X-100	0	0	63.1[2]	-
	0.004		53.0[3]	52.1[3]
	0.01		52.9[3]	-
	0.018	0.03	53.4	-
	0.024	0.04	52.5	-
	0.032	0.059	52.9	-
	0.049	0.091	52.6	-
	0.06	0.16	52.4	-
	0.15	0.30	52.6	-
	0.20	0.40	52.2	-

Table 1 continue

1	2	3	4	5	6
		0.23	0.50	52.5	-
		0.31	0.68	-	51.6
		0.41	1.0	52.4	51.7
		0.53	1.3	-	51.5
		0.55	1.4	52.0	51.4
		0.87	3.3	51.5	51.0
		1.34	13.3	49.9	-
		1.47	25.9	-	49.1
		1.57	68.4	47.6	47.4
		1.63	100	46.7	45.2
2.	Water-Tween 80	0	0	63.1[2]	
		0.011	0.02	52.8	
		0.017	0.03	52.3	
		0.077	0.20	52.7	
		0.105	0.22	52.9	
		0.178	0.41	52.0	
		0.360	1.17	51.9	
		0.68	10.4	49.2	
		0.79	37.4	-	47.8
		0.81	100	48.7	47.0
3.	Tween 60		100	-	48.3
4.	Tween 40		100	-	47.9
5.	Tween 20		100	-	47.7
6.	H_2O-SDS	0	0	63.1	
		0.01		57.5[3]	-
		0.05		57.6[3]	56.8[3]
		0.072		58.3	-
		0.13		58.4	-
		0.14		58.4	-
		0.44		58.6	-
		1.24		57.5	-
7.	CH_3OH-H_2O-(N_{CH_3OH}-0.216) Triton X-100	0.13	0.30	53.8	
8.	DMSO - Triton X-100	0	0	45.7[4]	

Table 1 continue

1	2	3	4	5	6
		0.17	1.35	45.8	
9.	C_6H_6 - Triton X-100	0	0	35.2[5]	
		0.038	0.35	37.0	
		0.067	0.60	37.5	
		0.074	0.70	37.8	
		0.16	1.6	43.2	
		0.37	4.1	42.5	
10.	$C_6H_5OCH_2CH_2OH$	0	0	53.4	
11.	H_2O - $CH_3OCH_2CH_2OH$	0	0	63.1[2]	
		2.39	5.0	60.7	
		2.66	5.7	60.5	
		4.85	12.4	58.4	
		5.42	14.6	57.8	
		9.27	38.1	55.2	
		11.46	68.5	54.0	
		12.7	100	52.5	

a - M_S - molar concentration of surfactant or alcohol in binary mixtures surfactant-water, alcohol-water, surfactant-benzene or surfactant-DMSO; N_S - molar fraction (in %) of surfactant or alcohol in the above-mentioned binary systems.

Discussion

As one can see from Scheme (2) Triton X-100 is the ether of 4-(2',2'-dimethyl-3',3'-dimethylbutyl) phenol and polyethylenglycol $HO(CH_2CH_2O)_xH$ (where $10 \leq x \leq 15$). Therefore, one can expect that it should behave relative to N-phenolpyridinium betaine as hydroxylic electrophilic solvent which resembles monoethers of mono-, di- or triethylenglycole the solvating power of which is modified by the presence of lipophilic alkylsubstituted benzene ring and "etheral" oxygen atom. According to that hypothesis one can predict that the E_T-value for Triton X-100 should fit into the limita

determined by the E_T-values for 2-methoxyethanol (52.5 kcal /mol) and phenetole or anisole (E_T is[2], respectively, 36.4 and 37.2 kcal/mol). On assumption of the statistically equal contribution of the "hydroxylic" and "aromatic" components into the gross solvent effect one can predict for the Triton X-100 the E_T-value which equals E_T = (52.5+36.4)/2 = = 44.4 kcal/mol.

On the other hand, the E_T-value of Triton X-100 could be even more correctly predicted on the basis of the assumption that its gross solvent effect adds up from the "hydrocarbon" (which models the contribution of $(CH_3)_3CCH_2C(CH_3)_2$-group into the solvent effects) and "hydroxylic" contributions taken both with the same statistical weight. The former could be estimated using the E_T-value for the "proper" hydrocarbon solvent-heptane or octane (E_T=31.1 kcal/mol[2]), whereas the latter might be represented by the E_T-value for the phenylcellosolve (see Table 1, E_T=53.4 kcal/mol).

One can see that such an estimate of E_T=(53.4+31.1)/2= = 47.3 kcal/mol surprisingly well coincides with the experimentally determined value (46.7 kcal/mol) for this surfactant-solvent.

From the viewpoint of solvent-solute interactions which can influence the energies of π- π^* transitions of N-phenolpyridinium betaine (scheme (1)) surfactants from the Tween-family (scheme (3)) display the characteristic features of the alcohol $R_1CH_2(OC_2H_4)_mOH$ (which includes the $(OCH_2OH_2)_m$-fragment), THF and ester, $RCOOR_2$ (see scheme(3)).

By analogy with the procedure for Triton X-100 one can use for the initial, very rough estimation of the gross-polarity value for the Tween-family the assumption that it adds up from separate contributions from "hydroxylic", tetrahydrofurane and ester components, which could be represented respectively by E_T-parameters of methylcellosolve (52.5 kcal/mol), THF (37.4 kcal/mol[2]) and ethyl acetate (38.1 kcal /mol[2]). Tween contains in its molecule 3 roughly equal "hydroxylic" fragments. Therefore, one can assume that the statistical weight of these fragments into the energetics of solvent-solute interactions should be 3 times higher than for

the contributions from two other types of structural units.

Starting from these assumptions one estimates the E_T for Tween family as $E_T = (3x52.5 + 37.4 + 38.1)/5 = 46.6$ kcal/mol which is only somewhat lower(by less than 2 kcal/mol) than the corresponding experimental values from Table 1.

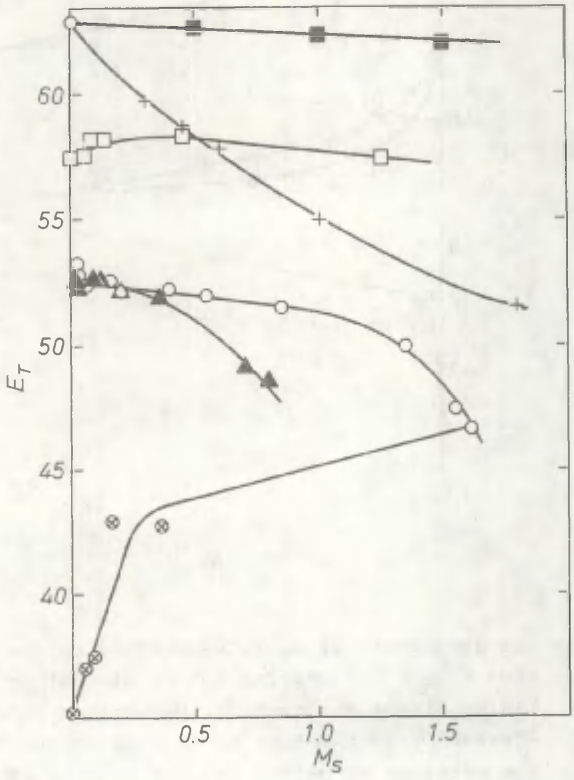


Fig. 1. The dependence of E_T-values (25°C) on molar concentration M_S of surfactant or alcohol in the following binary systems. 1. H_2O-Triton X-100 (○); 2. H_2O - Tween 80 (△); 3. H_2O-SDS (□); 4. H_2O-Bu_4NBr (+); 5. H_2O-MCS (■); 6. benzene - Triton X-100 (⊗).

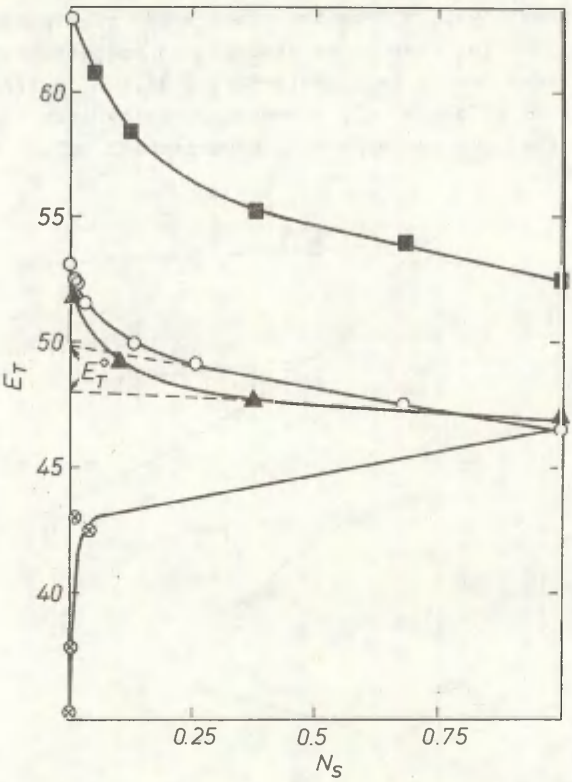


Fig. 2. The dependence of E_T values (25°C) on the mole fraction ((N_S) of ' surfactant or alcohol in the following binary mixtures: 1. H_2O-Triton X-100; 2. H_2O -Tween 80; 3. H_2O-MCS; 4. benzene-Triton X-100. For the notation of points see Fig. 1. The dashed line shows the extrapolation of the linear areas of the relationships between E_T and N_S values to the in - finite dilution in the aqueous solution (see the text).

The comparison of the experimental E_T-values within the Tween family shows a rather slight decrease of that quantity with the decrease of the length of the saturated hydrocarbon chain in the ester fragment of the surfactant(see Scheme (3) and Table 1; the transfer from $R=C_{17}H_{35}$ to $R = C_{11}H_{23}$ decreases the E_T-value only by 0.6 kcal/mol). At the same time, the transfer from the surfactant which contains the saturated hydrocarbon radical R (i.e. Tween 60, Tween 40, and Tween 20) to the surfactant which includes unsaturated radical R (i.e. to Tween 80, see scheme (3)), leads to a rather modest (see Table 1 N° 2-5) increase of the gross polarity of the individual representatives of this family of surfactants.

The dependences of E_T-parameters on the compesition of binary mixtures of Triton X-100 and Tween 80 with water are shown in Figs. 1 and 2. For the comparison these plots include also the dependences of E_T-values on the variation of the ratio of the components in the case of aqueous methylcellosolve as well as for the aqueous Bu_4NBr[1], aqueous SDS and mixtures of benzene with surfactant Triton X-100.

The joint analysis of the present results and literature data[3] shows that in the case of aqueous solutions of Triton X-100, starting already from the surfactant concentrations comparable with critical micellar concentration (cmc)*, the E_T-value of water (63.1 kcal/mol[1]) drops very sharply (more than by 10 kcal/mol) to the range of 52.5-53.0 kcal/mol.(see Table 1 and Figs. 1 and 2).

One can see that practically starting with Triton X-100 concentrations $5x10^{-4}$M the further decrease of the E_T-parameter towards the value characteristic of the pure individual surfactant is much slower.

A similar pattern of the change of the E_T-value is characteristic also of the mixtures of another surfactant, Tween 80, with water (Fig. 1 and 2, Table 1). As before, here the most significant decrease in the E_T-value occurs

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* According to Ref. 7 cmc value for Triton X-100 equals $3x10^{-4}$ M.

also at the surfactant concentrations which are lower than 0.01 M. A further relatively modest decrease in the E_T-parameter of this system is analogous to that for the previous system of aqueous Triton X-100 and resembles also some other examples from Ref. 3.

On the other hand, one can see (Figs. 1,2) that similar transition from pure water into 0.1 M aqueous solutions of Bu_4NBr or methylcellosolve decrease the E_T-parameter of water only by the amount (less than 1 kcal/mol) which is sometimes comparable with the experimental uncertainty for the determination of that quantity.

It is assumed[3] that the anomalously sharp drop of the gross polarity in the very dilute aqueous solutions of surfactants is connected with the solubilization of N-phenolpyridinium betaine dye by the micelle-formation process. It seems possible [4,8] that in this case the latter process reduces to the transfer of the betaine dye (I) specifically solvated by the electrophilic molecules of water in the aqueous medium ($ArO^-...nH_2O$) into a new solvation complex between betaine and specifically (hydrogen bond, hydrophobic interactions, etc.) solvating molecules of nonionic surfactant S (Triton X-100, Tween 80 etc.)*:

$$\underset{\text{II}}{ArO^-...nH_2O} + mS \overset{K}{\rightleftharpoons} \underset{\text{III}}{(ArO^-...kS)(n-l)H_2O} + (m-k)S + lH_2O \qquad (4)$$

Due to the increase in the concentration of the surfactant and after reaching the values comparable with the cmc the solvation equilibrium (4) shifts towards the formation of solvation complex-micelle (III).

Mioropolarity within the micelle depends mainly on the solvation characteristics (dielectric permittivity, electrophilicity, hydrophobicity, etc.) of the surfactant which, in their turn, are in the aqueous solution somewhat modi-

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* Formal aspects of the influence of nonspecific and specific solvent-solute interactions on several chemical and physical processes (solvolysis, spectral transitions, etc) in various binary solvent systems were studied in Ref. 4,9.

fied by the presence of the specifically as well as nonspecifically solvating water molecules, and their clusters. Therefore, it seems reasonable to assume that the most significant change of the E_T-parameter due to the change of the surfactant concentration (N_S or M_S) in water corresponds to the micelle-formation process which will be completed at surfactant concentrations ($M_S \approx 10^{-4} \div 10^{-2}$) comparable to or somewhat larger than the critical micellar concentration.

In coordinates E_T vs. N_S (or M_S) (see Fig. 1 and 2)the processes of shifting and establishing the micelle- formation equilibrium (4) should be reflected[4,8,9] by a sharp drop of E_T-value as response to very small additions of a surfactant to water. A further decrease in the E_T-parameter is already much slower due to the decrease in the nonspecific[9] solvation power of the medium (the effect of the decrease in the dielectric permittivity of the solvent seems to dominate over the contribution from the increase of the polarizability of the medium) during the transfer from water-rich aqueous solutions of the surfactant towards the mixtures where the latter component dominates.

Alongside with the change of the intensity of the influence of nonspecific solvent-solute interactions on the properties of solvation complexes (III), the intensity of the hydrogen bonding or other specific interactions within that solvation complex can also change*.

After the point where all the solute species (e.g. N-phenolpyridinium betaine) exist in the form of the solvation complexes - micelles (III) and on conditions of the lack of any further shifts of solvation equilibrium (4) and

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* Certainly, further successive substitutions of water molecules in the solvation shells of betaine dye for the surfactant molecules are not ruled out.This statement means that in the solvation complexes(III) the stepwise change of the coordination numbers (n-l) and k can take place which, in its turn, is equivalent to the further shift of the position of the solvation equilibrium (4).

the invariability of its stoichiometry, the observed dependence of the E_T-value on the concentration (molar fraction) of one of the components should be described by the linear function of the composition of the binary mixture[4,8,9]. According to its physical meaning such a relationship should reflect the influence of the solvent-solute interactions on the $\pi \rightarrow \pi^*$ transition energies in the solvation complexes(III) of the betaine dye.

The extrapolation of that linear region of the curve it towards the zero concentration (N_S) of the surfactant (i.e., into the pure water) should give the E_T-value (see Fig. 2) which corresponds to the long-wavelength $\pi \rightarrow \pi^*$ transfer (scheme (1)) in solvation complexes (III) of the surfactant with the N-phenolpyridinium betaine dye at the infinite dilution in water.

As a rule, different surfactants have variable comp - lex-formation abilities. Therefore, it is natural that in case of various surfactants (for a fixed solute)the above-mentioned complexes-micelles should be characterized by different E_T°-values. The equilibrium constant K which corresponds to the complex-formation equilibrium (4) should be considered as a natural measure of the intensity of the interactions between the solute and surfactant at given conditions. From a practical viewpoint it seems more simple to suggest as a measure of the micelle-formation (solubilization) ability of a given surfactant the difference

$$\Delta = E_T - E_T^\circ, \qquad (5)$$

in the spectral $\pi \rightarrow \pi^*$ transition energies of the N-phenolpyridinium dye determined, respectively, in pure water(E_T) and by the above-described extrapolation procedure (E_T°).

Alongside with the aqueous solutions, the similar micelle-formation effect of surfactant Triton X-100 on the E_T values is, probably, present also for aqueous methanol (at $N_{CH_3OH} = 0.216$, see Table 1, N° 7).

Significant changes of the E_T-parameter are also induced by the additions of Triton X-100 to benzene. One can see that in this case the surfactant acts as a sufficiently

polar electrophilic component which leads to a significant though not extraordinary changes in E_T-values (compare with the results of our earlier work[5]).

DMSO and Triton X-100 have very similar gross polarity values (see Table 1). Therefore it is not a surprise that in this case the additions of Triton X-100 does not cause practically any solvent effect on the E_T-value of the betaine dye. However, it should be mentioned that the influence of the DMSO additions to water[4] and benzene[5] is much less intense than the influence of the Triton X-100 additions on the E_T-parameters of these two solvents.

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KINETIC STUDY OF ALKALINE HYDROLYSIS OF SUBSTITUTED PHENYL TOSYLATES

XVI. RESULTS OF KINETIC MEASUREMENTS OF o-SUBSTITUTED TOSYLATES IN CONCENTRATED AQUEOUS $n\text{-}Bu_4NBr$ SOLUTIONS

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The kinetics of alkaline hydrolysis of o-substituted phenyl tosylates $CH_3C_6H_4SO_2OC_6H_4\text{-}X$(X=2-$NO_2$, 2-Cl, 2-F, 2-$OCH_3$, 2-$N(CH_3)_2$, 2-$CH_3$) was measured in 2.25 M tetra-n-butylammonium solution at 30,50,60,75 and 85°C as well as in 1 M of $n\text{-}Bu_4NBr$ solution at 50 and 75°C.

In addition to that, the data for some m- and p-substituted phenyl tosylates were given.

It was found earlier by Steigman and Sussman[1,2] that the ortho effect detected in the case of acidic dissociation of substituted benzoic acids in water disappeared when going to 7.75 molal tetrabutylammonium bromide solution. According to Steigman and Sussman[1,2], such a phenomenon is caused by the water molecules which are probably more remarkably involved in the stabilization of meta- and para-substituted benzoic acids than in the case of ortho-substituted benzoic acids, since in the case of the latter the carbonyl and hydroxyl groups are not on the same plane with the

benzene ring. In concentrated aqueous tetrabutylammonium bromide solutions the water molecules are strictly organized and the difference in the solvation of ortho-substituted benzoic acids and meta- and para-substituted benzoic acids disappears.

It was of interest to find out whether the analogous situation might occur in the case of the alkaline hydrolysis of phenyl tosylates. It should be remembered that in the case of water solution there was detected a considerable difference in the log k values for ortho-substituted and para-substituted derivatives, i.e. the ortho-effect[3-5] was revealed.

In the previous paper[6] the values of rate constants k ($M^{-1} \cdot s^{-1}$) for the alkaline hydrolysis of phenyl tosylates with substituents in meta- and para-position in 2.25 molar tetrabutylammonium bromide solution at 40, 50, 75 and 85°C and in 1 molar n-Bu_4NBr solution at 75° C were published.

In the present paper the analogous data for seven ortho-substituted and some meta - and para-substituted phenyl tosylates are given (Table 1).

The preparation and characteristics of the phenyl tosylates studied, the purification of the alkaline (n-Bu_4NOH) and n-Bu_4NBr salt, as well as the methods of kinetic measurements have been reported earlier.[4-7].

The kinetics of the alkaline hydrolysis of phenyl tosylates were measured using spectrophotometers SF-4 and SF-4A on the wavelengths given in Table 1.

The second order rate constants were calculated by dividing pseudofirst order rate constants k_1 by the alkali concentration. The measurements at each salt concentration were repeated several times and the arithmetic means of the corresponding second order rate constants k_2 were calculated.

In order to avoid the specific salt effect of alkali n-Bu_4NOH, the concentration of alkali used varies only in a narrow interval (0.0617-0.0077).

The rate constants k ($M^{-1} \cdot s^{-1}$) for the alkaline hy-

Table 1

Rate constants k ($M^{-1} \cdot sec^{-1}$) for Alkaline Hydrolysis of Substituted Phenyl Tosylates $CH_3C_6H_4SO_2OC_6H_4$-X in the Presence of $n\text{-}Bu_4NBr$ Additions

X	Temperature, °C		k ($M^{-1} \cdot sec^{-1}$)	n		
1	2	3	4	5	6	7
2-NO_2	30.0	2.25	$(1.78 \pm 0.29) \cdot 10^{-2}$	4	0.0770	420
	50.0	2.25	$(1.71 \pm 0.06) \cdot 10^{-1}$	4	0.0658	
		1.00	$(3.54 \pm 0.06) \cdot 10^{-2}$	6	0.0617	
	75.0	2.25	$(8.89 \pm 0.27) \cdot 10^{-1}$	5	0.0658	
		1.00	$(2.48 \pm 0.08) \cdot 10^{-1}$	4	0.0770	
	85.0	2.25	1.21 ± 0.02	6	0.0617	
2-F	30.0	2.25	$(6.18 \pm 0.09) \cdot 10^{-4}$	3	0.0770	289
	50.0	2.25	$(6.09 \pm 0.17) \cdot 10^{-3}$	4	0.0658	
		1.00	$(2.07 \pm 0.03) \cdot 10^{-3}$	4	0.0770	
	75.0	2.25	$(3.09 \pm 0.24) \cdot 10^{-2}$	4	0.0617	
		1.00	$(1.33 \pm 0.05) \cdot 10^{-2}$	5	0.0770	
	85.0	2.25	$(8.76 \pm 0.20) \cdot 10^{-2}$	6	0.0617	
2-Cl	30.0	2.25	$(7.68 \pm 0.71) \cdot 10^{-4}$	3	0.0770	300
	50.0	2.25	$(8.14 \pm 0.38) \cdot 10^{-3}$	4	0.0658	
		1.00	$(2.14 \pm 0.03) \cdot 10^{-3}$	4	0.0617	

Table 1 continue

1	2	3	4	5	6	7
	75,0	2.25	$(3.38 \pm 0.37) \cdot 10^{-2}$	5	0.0658	
		1.00	$(1,30 \pm 0,06) \cdot 10^{-2}$	5	0.0770	
	85.0	2,25	$(1.18 \pm 0,02) \cdot 10^{-1}$	6	0,0617	
2-OCH_3	50.0	2,25	$(1.14 \pm 0,14) \cdot 10^{-4}$	4	0.0658	298
	60.0	2.25	$(2.88 \pm 0.34) \cdot 10^{-4}$	3	0,0770	
	75,0	2.25	$(1.14 \pm 0.16) \cdot 10^{-3}$	5	0.0658	
		1.00	$(4,43 \pm 0,52) \cdot 10^{-4}$	5	0.0770	
	85,0	2.25	$(3,89 \pm 0,46) \cdot 10^{-3}$	9	0.0770	
2-CH_3	50,0	2.25	$(2,21 \pm 0,05) \cdot 10^{-4}$	4	0.0658	294
	60,0	2.25	$(3.68 \pm 0,64) \cdot 10^{-4}$	3	0,0770	
	75.0	2.25	$(1.40 \pm 0.23) \cdot 10^{-3}$	4	0.0658	
		1.00	$(5.64 \pm 0.31) \cdot 10^{-4}$	4	0.0770	
	85,0	2.25	$(6.19 \pm 0.04) \cdot 10^{-3}$	6	0.0617	
2-$N(CH_3)_2$	50.0	2.25	$(3.82 \pm 0.15) \cdot 10^{-4}$	3	0.0770	320
	60.0	2.25	$(1,33 \pm 0.13) \cdot 10^{-3}$	3	0.0770	
	75.0	2.25	$(4.03 \pm 0.29) \cdot 10^{-3}$	4	0.0770	
		1.00	$(2.85 \pm 0,17) \cdot 10^{-3}$		0.0770	
	85,0	2,25	$(1,13 \pm 0.15) \cdot 10^{-3}$	3	0.0770	
2-NH_2	75,0	2.25	$(3.55 \pm 0.10) \cdot 10^{-3}$	3	0.0770	310

Table 1 continue

1	2	3	4	5	6	7
4-Cl	75.0	2.25	$(2.37 \pm 0.11) \cdot 10^{-2}$	3	0.0770	304
		1.00	$(8.33 \pm 0.33) \cdot 10^{-3}$	3	0.0770	
$4\text{-}NO_2$	30.0	2.25	$(1.47 \pm 0.21) \cdot 10^{-2}$	3	0.0770	410
$3\text{-}NO_2$	30.0	2.25	$(3.06 \pm 0.10) \cdot 10^{-3}$	3	0.0770	430
$4\text{-}OCH_3$	85.0	2.25	$(2.78 \pm 0.18) \cdot 10^{-3}$	3	0.0770	315
$4\text{-}OH_3$	85.0	2.25	$(3.05 \pm 0.10) \cdot 10^{-3}$	3	0.0770	300
$4\text{-}NH_2$	85.0	2.25	$(7.84 \pm 0.69) \cdot 10^{-4}$	3	0.0770	305

* Number of parallel measurements at the salt concentration considered.

rolysis of phenyl tosylates measured in the presence of $n\text{-}Bu_4NBr$ salt additions, are given in Table 1.

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KINETIC STUDY OF ALKALINE HYDROLYSIS OF SUBSTITUTED PHENYL TOSYLATES XVII. DISCUSSION OF RESULTS OF KINETIC MEASUREMENTS OF o-SUBSTITUTED TOSYLATES IN CONCENTRATED AQUEOUS n-Bu_4NBr SOLUTIONS

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The results of kinetic measurements of the alkaline hydrolysis of o-substituted tosylates $CH_3C_6H_4SO_2OC_6H_4$-X in 2.25 and 1 molar tetrabutylammonium bromide solutions, published in the previous paper have been discussed.

The σ_o^o constants for o-substituents in the case of 2.25 and 1 molar tetrabutylammonium bromide solutions, as well as the corresponding values of the Arrhenius equation parameters log A and E have been determined.

It has been found that the ortho effect, i. e. the difference $\log k^{o-x} - \log k^{p-x}$ (k^{o-x} and k^{p-x} - rate constants for o- and p-substituted derivatives) considerably decreases during transition from water to 2.25 and 1 M n-Bu_4NBr solutions.

Using the program of multiple regression analysis, were treated the log k values for o-substituted derivatives together with the data for m- and p-substituted phenyl tosylates in the case of 2.25 and 1M

$n\text{-}Bu_4NBr$ solutions as well as in water at various temperatures.

As a measure of the ortho effect in the case of the reaction studied, scale σ_I was proposed.

In 2.25 M $n\text{-}Bu_4NBr$ solution the reaction series studied obeys one and the same isokinetic relationship both in the case of o-substituted as well as m- and p-substituents, which was not observed when using water solution without salt additions.

In the present paper, the results of kinetic measurements of the alkaline hydrolysis of ortho-substituted phenyl tosylates $CH_3C_6H_4SO_2OC_6H_4\text{-}X$ (X=2-NO_2, 2-Cl, 2-F, 2-OCH_3, 2-$N(CH_3)_2$, 2-CH_3) in 2.25 M tetrabutylammonium bromide solution at 30, 50, 60, 75 and 85° C as well as in 1 M $n\text{-}Bu_4NBr$ solution at 50 and 75° C, published in previous paper[1], have been discussed.

It should be reminded that in recent years, concentrated tetrabutylammonium bromide solutions as mediums for realization of various processes with participation of organic compounds, has aroused interest both from theoretical as well as practical aspects. On the one hand, it was suggested that at transition from water to concentrated Bu_4NBr solutions there takes place a transition to some less electrophilic media, which is proved by the increase in the values of the constants of sensitivity towards substituent effects (ρ) [2-5] and the decrease in the corresponding E_T parameters[4,6]. It should be mentioned that during the transition from water to the solution of inorganic salts like NaCl, $NaClO_4$, et al., the increase in the E_T parameters and the decrease in the constants of sensitivity towards the substituent effect are observed[2-5]. On the other hand, the concentrated $n\text{-}Bu_4NBr$ solutions reveal the appearance of the salting-in effect in organic compounds. A considerable decrease in the rates of the alkaline hydrolysis of phenyl benzoates[4] and phenyl tosylates[1] (especially in the case of the unsubstituted derivatives and compounds with the electron-donor substituents) gives some indication of it. These conclusions

are rather significant for the synthesis of organic compounds, especially for that of esters by the phase-transfer catalysis method which has become rather widespread in recent years. It is known that the quaternary ammonium salts and hydroxides can be rather successfully used as phase - transfer catalysts[7].

The variation of the log k values for the alkaline hydrolysis of phenyl tosylates when passing from water to 1 and 2.25 molar tetrabutylammonium bromide solution is presented in Fig. 1. During transition from water to 1 M tetrabutylammonium bromide solution, negative salt effect was discovered in the case of all ortho-substituted as well as meta- and para-substituted derivatives.

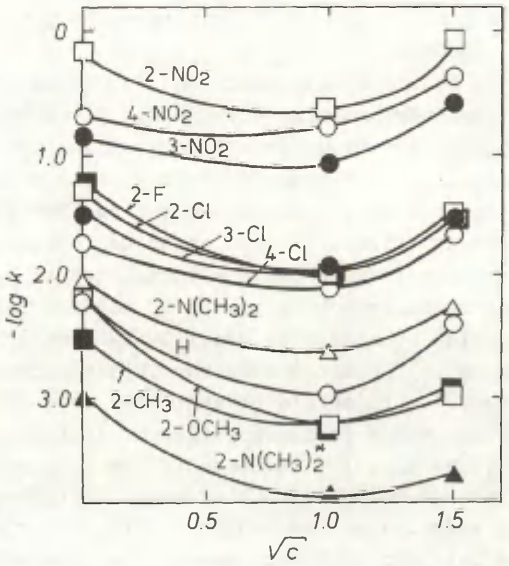

Fig. 1. Relationship between log k^X and $\sqrt{c}$ at 75° C. (C - concentration of n-Bu_4NBr in water). 2-$N(CH_3)_2^*$ denotes the relationship for 2-$N(CH_3)_2$ where log $k^* = \log k^X + \rho^\circ\sigma_R^\circ$.

But in the case of ortho-substituents, the latter effect is stronger than in the case of the corresponding para- and meta-substituents. If for meta- and para-substituents the value of the negative salt effect grows with the increase in the σ values for the corresponding phenyls, the values of salt effects for ortho-substituted derivatives do not depend so much on the substituent nature. The corresponding changes in the rate constants are similar to those for unsubstituted derivatives (Table 1).

The analogous situation can be noticed in the case of the pK_a values for the acidic dissociation of benzoic acids when passing from water to 7.75 molal tetrabutylammonium bromide solution. The values of salt effects $\Delta pK_s^x = pK_s^x - pK_{H_2O}^x$ (index s denotes the salt solution and x - substituents) for ortho-substituted benzoic acids relatively weakly depend on the substituent (see Table 1), thus resembling the alkaline hydrolysis of phenyl tosylates.

From the data for the alkaline hydrolysis of phenyl tosylates in 2.25 and 1 M $n\text{-}Bu_4NBr$ solution at 75° C, were calculated the values of σ^o_{ortho} for ortho-substituted phenyls, using the following equation:

$$\sigma^o_{ortho} = \frac{\log k^x_{ortho} - \log k^H_o}{\rho^o_{m,p}} \qquad (1)$$

k^H_o is the rate constant for the unsubstituted derivative (x = H).

It follows from the σ^o_{ortho} values in Table 2 that the ortho-effect, observed in the case of water medium considerably decreases after transition to concentrated $n\text{-}Bu_4NBr$ solutions. A similar situation was observed in the case of the acidic dissociation of benzoic acids[8]. The $N(CH_3)_2^-$ and NH_2-substituents should be considered exceptional. Here the σ^o_{ortho} values calculated from the log k values for the alkaline hydrolysis of phenyl tosylates in 2.25 M and 1M $n\text{-}Bu_4NBr$

Table 1

Values of $\Delta \log k_s^X = \log k_s^X - \log k_{H_2O}^X$ for the Alkaline Hydrolysis of Phenyl Tosylates at 75° C and $\Delta pK_s^X = pK_s^X - pK_{H_2O}^X$ for the Acidic Dissociation of Benzoic Acids at 25° C[8]

X	$\Delta \log k_s$				ΔpK_s (7.75 m Bu_4NBr)	
	1 M Bu_4NBr		2.25 M Bu_4NBr		ortho	para
	ortho	para	ortho	para		
H	-0.744	-0.744	-0.320	-0.320	2.10	2.10
NO_2	-0.585	-0.031	0.109	0.319	2.62	1.14
Cl	-0.608	-0.517	-0.194	0.073	2.66	1.62
F	-0.678	-0.697*	-0.312	-0.254	2.54	1.57
Br	-	-	-	-	2.63	1.51
CH_3	-0.753	-0.932*	-0.357	-0.367**	2.51	2.17
OCH_3	-1.171	-0.961	-0.730	-0.375**	2.51	2.22
Ph	-	-	-	-	2.91	1.94
$N(CH_3)_2$	-0.548	-1.465*	-0.394	-0.777*	-	-

* - calculated when $\rho^o = 2.66$ and $\log k_o^H = 2.900$

** - calculated when $\rho^o = 2.50$ and $\log k_o^H = 2.417$

Table 2

Values of σ^{o}_{ortho} Calculated from log k for the Alkaline Hydrolysis of Phenyl Tosylates at 75°C

Substituent	2.25 M Bu_4NBr	1 M Bu_4NBr	H_2O
NO_2	0.946	0.811	1.15
F	0.362	0.403	0.531
CI	0.377	0.381	0.482
CH_3	-0.176	-0,132	-0,247
OCH_3	-0.211	-0.132	-0.078
NH_2	-0.014	-	0.066
$N(CH_3)_2$	0.008	0.132	0.052

solutions, considerably exceed the corresponding σ^{o} values for para-substituents as it was found in the case of water solution.

The log k values for ortho-substituted phenyl tosylates in 2.25 M and 1 M n-Bu_4NBr solution as well as in water, including the data for meta- and para-substituted derivatives, were treated according to equation:

$$\log k^{x}_{m,p(ortho)} = \log k^{H}_{o} + \rho^{o}_{m,p(ortho)}\sigma^{o} + \rho_{I(ortho)}\sigma_{I} \quad (2)$$

where $\sigma^{o}_{para} = \sigma^{o}_{ortho}$ were used.

The data treatment including additional term $\rho^{o}_{R(ortho)}\sigma^{o}_{R}$ in Eq. (2) was carried out as well. However, in the case of all steps of data processing term $\rho^{o}_{R(ortho)}\sigma^{o}_{R}$ was excluded as insignificant.

For comparison, the log k values were treated according to the following equations also:

$$\log k^{x}_{m,p} = \log k^{H}_{o} + \rho^{o}_{m,p}\sigma^{o} \quad (3)$$

$$\log k^{x}_{(ortho)} = \log k^{H}_{o} + \rho_{I(ortho)}\sigma_{I} + \rho^{o}_{R(ortho)}\sigma^{o}_{R} \quad (4)$$

The treatment of the log k values according to Eq. (4) also embraced the log k value for unsubstituted derivative. The results of this statistical data processing are given in Table 3.

The data treatment was carried out on a "Nord-100" computer using the program of multiple regression analysis, composed by V. Palm [9,10]. When calculating, the "recommended" values of σ^{o} from Tables[11] and the σ_{I} and σ_{R}^{o} constants, given in the paper by V. Palm[12] were used.

The log k values for 2.25 M n-Bu_4NBr solution at 87,75 and 50° C and 1 M n-Bu_4NBr solution at 75° C[1,5] as well as the log k for water solution without additions of salt at 85, 75, 50 and 15° [13-16] were also subjected to the statistical data treatment according to Eqs. (2)-(4).

It was assumed in the data treatment that in the case of 2-$N(CH_3)_2$- and 2-NH_2- substituents the resonance term is absent and during the all-embracing data treatment in the case of those substituents the correction for $\rho_{m,p,}^{o}\sigma_{R}^{o}$ was included.

It follows from the results of the statistical data treatment, given in Table 3 that Eq. (3) satisfactorily describes the whole data set of the alkaline hydrolysis of phenyl tosylates both in concentrated tetrabutylammonium bromide solutions and in water.

As to salt solutions, the deviations from relationship (3) tend to be somewhat larger than those in the case of water solution without additions.

Thus, in the case of the reaction studied by us, for ortho-substituents the additional inductive influence, represented by the $\rho_{I(ortho)}\sigma_{I}$ term, can be observed. At the same time, the term of polar resonance is the same for both ortho-substituents and para-substituents (except 2-NH_2- and 2-$N(CH_3)_2$-substituents) in the case of 2.25 M and 1 M n-Bu_4NBr solutions, as well as in the case of the pure water solution without salt additions (see Table 3). Consequently, as to the reaction studied, the term $\rho_{I(ortho)}\sigma_{I}$ in Eq. (2) could be considered as the measure of the ortho ef-

Table 3

Results of Statistical Data Treatment of log k Values Aoocording to the Following Equations:

$$\log k^{x}_{m,p} = \log k^{H}_{0} + \rho^{o}_{m,p}\sigma^{o} \quad (1)$$

$$\log k^{x}_{m,p(ortho)} = \log k^{H}_{0} + \rho^{o}_{m,p(ortho)}\sigma^{o} + \rho_{I(ortho)}\sigma_{I} \quad (2)$$

$$\log k^{x}_{(ortho)} = \log k^{H}_{0} + \rho_{I(ortho)}\sigma_{I} + \rho^{o}_{R(ortho)}\sigma^{o}_{R} \quad (3)$$

Data treatment aocording to Eqs. (1),(2) and (3) included also the data from ref.[1,5,13-16]

Tempera-ture, °C	Eq.	Parameters	H_2O	2.25M Bu_4NBr	1M Bu_4NBr
1	2	3	4	5	6
75	(1)	Iog k^{H}_{0}	-2.086±0.034	-2.417±0.060	-2.900±0.060
		$\rho^{o}_{m,p}$	1.67 ±0.08	2.50 ±0.12	2.66 ±0.12
		r	0.993	0.996	0.996
		s	0.088	0.076	0.075
		s_o	0.119	0.092	0.086
		n/n_o	8/8	5/5	5/5
	(2)	Iog k^{H}_{o}	-2.128±0.029	-2.525±0.042	-2.878±0.050
			-2.155±0.020***	-2.486±0.055*	-2.870±0.062*
			-2.110±0.031*		
		$\rho^{o}_{m,p(ortho)}$	1.75 ±0.06	2.71 ±0.08	2.58 ±0.09
			1.80 -0.04***	2.63 ±0.10*	2.62 ±0.07*

Table 3 continued

1	2	3	4	5	6
			1.70 ±0.06*		
		$\rho_{I(ortho)}$	0.898±0.113	0.55 ±0.14	0.53 ±0.15
			0.918±0.074**		
			0.917±0.108*	0.55 ±0.14*	0.53 ±0.16*
		r	0.994	0.996	0.994
			0.998**		
			0.994*	0.993*	0.992*
		s	0.090	0.109	0.118
			0.059**		
			0.086*	0.112*	0.125*
		s_o	0.108	0.090	0.107
			0.071**		
			0.109*	0.113*	0.129*
		n/n_o	15/15	12/12	11/11
			14/15**		
			13/15*	10/10*	10/10*
	(3)	$\log k_0^H$	-2.207±0.055	-2.521±0.096	-2.977±0.116
			-2.200±0.053	-2.508±0.122	-2.969±0.129*
		$\rho_{I(ortho)}$	2.82 ±0.13	3.32 ±0.23	3.27 ±0.27
			2.78 ± 0.12*	3.25 ±0.27*	3.22 ±0.29*

Table 3 continued

1	2	3	4	5	6
		$\rho^{o}_{R(ortho)}$	1.68 ±0.13	2.73 ±0.24	2.28 ±0.29
			1.53 ±0.15	2.53 ±0.35	2.11 ±0.37*
		r	0.996	0.993	0.988
			0.996*	0.989*	0.984*
		s	0.086	1.153	0.177
			0.076	0.175*	0.187
		s_o	0.092	0.123	0.154
			0.088*	0.159*	0.178*
		n/n_o	8/8	8/8	7/7
			6/6*	6/6	6/6
50	(1)	$\log k^{H}_{0}$	-2.917±0.013	-3.381±0.109	
		$\rho^{o}_{m,n}$	1.84 ±0.04	3.01 ±0.19	
		r	0.998	0.994	
		s	0.046	0.122	
		s_o	0.065	0.110	
		n/n_o	13/13	4/4	
	(2)	$\log k^{H}_{0}$	-2.933±0.015	-3.424±0.100	
			-2.923±0.015*	-3.322±0.093*	
		$\rho^{o}_{m,n(ortho)}$	1.88 ±0.04	3.11 ±0.17	
			1.84 ±0.04	2.90 ±0.17*	
		$\rho_{I(ortho)}$	0.98± 0.07	0.59 ± 0.29	

Table 3 continued

1	2	3	4	5	6
			1.00 ±0.07	0.58 ±0.23*	
		r	0.998	0.987	
			0.998*	0.988	
		s	0.059	0.223	
			0.053*	0.178*	
		s_o	0.072	0.159	
			0.066*	0.153*	
		n/n_o	20/20	10/10	
			18/18*	9/9*	
	(3)	log k_O^H	-2.980±0.059	-3.423±0.212	
			-2.968±0.064	-3.395±0.180*	
		$\rho_{I(ortho)}$	2.99 ±0.14	3.75 ±0.50	
			2.94 ±0.15*	3.59 ±0.41*	
		$\rho^o_{R(ortho)}$	1.86 ±0.14	3.06 ±0.54	
			1.70 ±0.19*	2.53 ±0.52*	
		r	0.996	0.973	
			0.995*	0.976*	
		s	0.092	0.325	
			0.093*	0.260*	

Table 3 continued

1	2	3	4	5	6
		s_o	0.092	0.230	
			0.100[*]	0.218[*]	
		n/n_o	8/8	7/7	
			6/6[*]	6/6[*]	
85	(1)	$\log k_0^H$	-1.760 ± 0.025	-2.071 ± 0.031	
		$\rho^o_{m,p}$	1.54 ± 0.05	2.73 ± 0.07	
		r	0.996	0.998	
		s	0.055	0.084	
		s_o	0.083	0.066	
		n/n_o	7/7	7/7	
	(2)	$\log k_0^H$	-1.842 ± 0.030	-2.040 ± 0.058	
			-1.807 ± 0.026[*]		
		$\rho_{m,p(ortho)}$	1.73 ± 0.06	2.58 ± 0.10	
			1.63 ± 0.05[*]		
		$\rho_{I(ortho)}$	0.75 ± 0.12	0.44 ± 0.21	
			0.78 ± 0.09[*]		
		r	0.993	0.990	
			0.996[*]		
		s	0.094	0.129	
			0.071[*]		

Table 3 continued

1	2	3	4	5	6
		s_o	0.118	0.117	
			0.098*		
		n/n_o	15/15	13/13	
			13/13*		
	(3)	$\log k_0^H$	-1.847 ± 0.056	-1.993 ± 0.165	
			-1.846 ± 0.074*	-1.972 ± 0.014*	
		$\rho_{I(ortho)}$	2.58 ± 0.13	2.94 ± 0.38	
			2.57 ± 0.017*	2.82 ± 0.32*	
		$\rho^o_{R(ortho)}$	1.87 ± 0.14	2.41 ± 0.41	
			1.83 ± 0.21*	2.00 ± 0.41*	
		r	0.996	0.987	
			0.993*	0.976*	
		s	0.089	0.251	
			0.112*	0.203*	
		s_o	0.097	0.226	
			0.118*	0.216*	
		n/n_o	8/8	7/7	
			6/6*	6/6	
15	(1)	$\log k_0^H$	-4.329 ± 0.114		
		$\rho^o_{m,p}$	2.11 ± 0.20		

Table 3 continued

1	2	3	4	5	6
	r	r	0.986		
		s	0.123		
		s_o	0.166		
		n/n_o	4/4		
	(2)	$\log k_0^H$	-4.361 ± 0.049		
			$-4.339 \pm 0.096^{*}$		
		$\rho^o_{m,p(ortho)}$	2.16 ± 0.08		
			$2.12 \pm 0.016^{*}$		
		$\rho^o_{I(ortho)}$	1.50 ± 0.14		
			$1.49 \pm 0.17^{*}$		
		r	0.996		
			0.989^{*}		
		s	0.102		
			0.123		
		s_o	0.885		
			0.153		
		n/n_o	9/9		
			$7/7^{*}$		
	(3)	$\log k_0^H$	-4.696 ± 0.199		
		$\rho_{I(ortho)}$	4.23 ± 0.44		

Table 3 continued

1	2	3	4	5	6
		$\sigma^{o}_{R(ortho)}$	1.67 ± 0.38		
		r	0.997		
		s	0.118		
		s_o	0.079		
		n/n_o	5/5		

x - The log k values for 2-NH_2- and 2-$N(CH_3)_2$-substituted derivatives were excluded before data treatment.

xx - The log k value for 4-$N(CH_3)_2$-derivative was excluded as a significantly deviating point.

s_o - Normalized standard deviation s

fect (i.e., log k^{X}_{ortho} - log k^{X}_{para}) and the ortho effect depends linearly on σ_I as it is presented in Fig. 2.

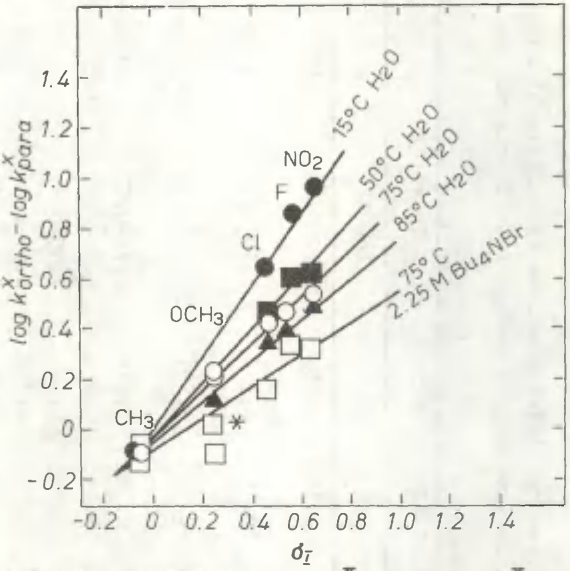

Fig. 2. Relationship between log k^{X}_{ortho} - log k^{X}_{para} and σ_I. * - value of log k for 2-OCH_3- phenyl tosylate in 2.25 M Bu_4NBr at 75°C determined from the dependence of log k on 1/T.

One can see that (Table 3) the ortho effect decreases after transition from water to concentrated n-Bu_4NBr solutions and to higher temperatures as well. The ortho effect increases when passing to lower temperatures both in the case of salt solutions and water without any salt additions.

Activation parameters E and log A for 2.25 M n-Bu_4NBr solution, calculated from the relationship between log k and 1/T (Fig. 3) are given in Table 4. For comparison the analogous values for water are also shown there. The relationship between activation energies E and log k at 75° C for both 2.25 M n-Bu_4NBr solution and water are represented in Fig.4. If the water without salt additions was used as a medium, the points for meta- and para-substituents form one straight

Table 4

Values of log A and Activation Energies (kcal/mol) for Alkaline Hydrolysis of Substituted Phenyl Tosylates $CH_3C_6H_4SO_2OC_6H_4$-X in Presence of n-Bu_4NBr Additions and in Water [13, 17, 18]

X	In presence of n-Bu_4NBr (2.25 M)					In water	
	C salt	log A	E	s	r	log A	E
2-NO_2	2.25	10.35±1.14	16.65±1.73	0.178	0.989	7,10±0.42	11.63±0.61
	1.00	9.0	15.4				
2-F	2.25	10.31±0.83	18.68±1.26	0.109	0.996	7.10±0.06	13.33±0.10
	1.00	9.2	17.6				
2-Cl	2.25	10.35±1.19	18.61±1.79	0.155	0.991	7.78±0.38	14.46±0.39
	1.00	8.3	16.04				
2-OCH_3	2.25	10.73±1.23	21.65±1.91	0.152	0.975	7.74±0.07	15.87±0.11
2-CH_3	2.25	10.88±2.13	21.66±3.32	0.169	0.965	8.42±0.07	17.31±0.11
2-$N(CH_3)_2$	2.25	11.16±0.85	21.49±1.31	0.109	0.996	7.35±0.12	15.00±0.18
4-NO_2	2.25	10.16±0.55	16.64±0.82	0.098	0.996	8.57±0.16	14.75±0.24
3-NO_2	2.25	9.91±1.04	16.61±1.54	0.095	0.997	8.20±0.17	14.42±0.25
3-Cl	2.25	10.28±1.09	18.40±1.66	0.179	0.985	8.56±0.18	16.02±0.28
H	2.25	11.55±1.10	22.15±1.7	0.152	0.988	8.47±0.21	16.85±0.31
		11.29±1.41*	21.76±2.18*	0.199	0.981		

* - when calculating the log A and E values, the data for C_{OH} = 0.0329[5] were also included

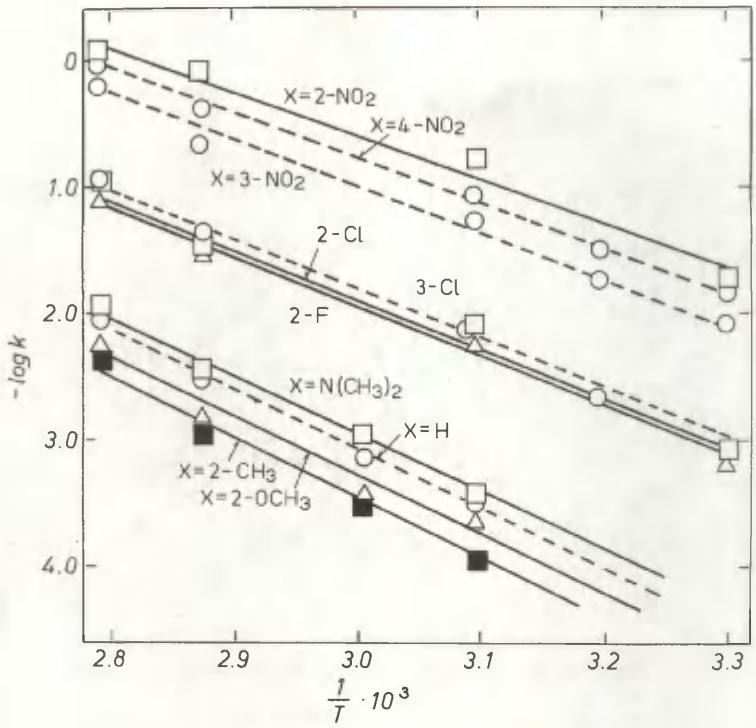

Fig. 3. Relationship between log k and 1/T.

line and the points for ortho-substituents fall onto the other, different line.

$$E_{m,p} = 13.24(\pm 0.26) - 1.7(\pm 0.14) \log k$$

$$r = 0.975;\ s_o = 0.220;\ s = 0.257;\ n/n_o = 9/9$$

$$E_{(ortho)} = 11.11(\pm 0.51) - 2.24(\pm 0.29) \log k$$

$$r = 0.960;\ s_o = 0.283;\ s = 0.559;\ n/n_o = 6/6$$

In the case of the 2.25 M Bu_4NBr solution the points for ortho-, meta- and para-substituents fall practically onto one and the same straight line:

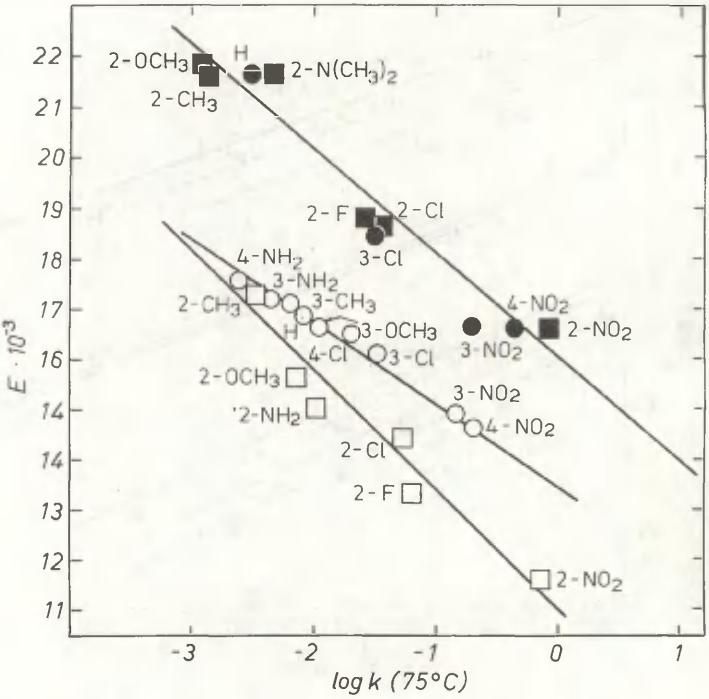

Fig. 4. Relationship between E values and log k at 75° C for water and 2.25 M n-Bu_4NBr solution.

$$E_{m,p(ortho)} = 15.80 - 2.10(\pm 0.19) \log k$$

$r = 0.963$; $s_o = 0.269$; $s = 0.600$; $n/n_o = 10/10$

For ortho-substituted phenyl tosylates without the 2-$N(CH_3)_2$- derivative the relationship

$$E_{(ortho)} = 16.26(\pm 0.48) - 1.88(\pm 0.22) \log k$$

$r = 0.965$; $s_o = 0.260$; $s = 0.554$; $n/n_o = 5/5$

is observed.

In the case of the isoentropic reaction series, the

theoretical value of the slope for the relationship between E and log k at 75° C is equal to 1.59 (in kcal).

Thus, it could but roughly be considered that the reaction series studied turns into an isoentropic one only, when passing to 2.25 M Bu_4NBr solution in the case of ortho-substituents as well. If water without any salt additions was used as a medium, the isoentropic relationship was observed in the case of meta- and para-substituents[15]. When passing from water to 2.25 M n-Bu_4NBr solution the activation energy for ortho-substituted derivatives increases usually more than in the case of the corresponding para-substituents. At the same time, the medium effect on the activation energy $\Delta E^c = E_{Bu_4NBr} - E_{H_2O}$ for all ortho-substituted derivatives does not[4] practically differ from the analogous values for the unsubstituted ones (Fig. 5). The same is valid for the

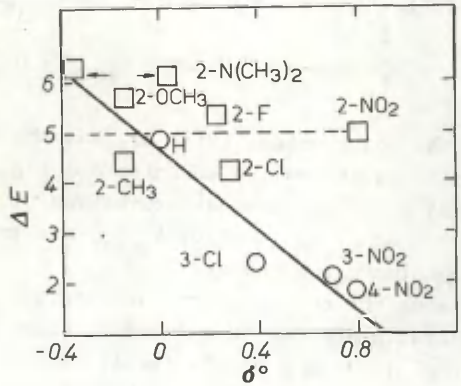

Fig. 5. Dependence of $\Delta E = E_{Bu_4NBr} - E_{H_2O}$ on σ°. For ortho-substituents $\sigma^\circ_{para} = \sigma^\circ_{ortho}$ was used.

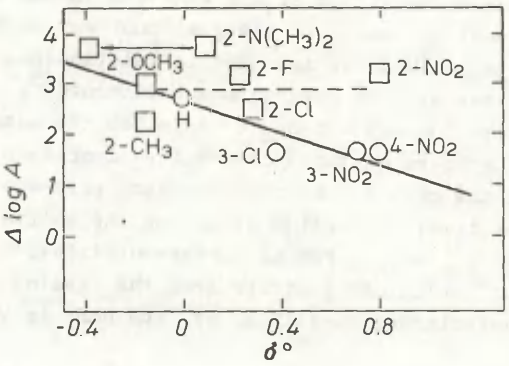

Fig. 6. Dependence of $\Delta\log A = \log A_{Bu_4NBr} - \log A_{H_2O}$ on σ^o.
For ortho-substituents $\sigma^o_{para} = \sigma^o_{ortho}$ was used.

changes in the log A values (Fig. 6). But the difference in medium effects on activation energies and log A in the case of ortho- and para-substituted derivatives (i.e., $\Delta E^c_{ortho} - \Delta E^c_{para}$ and $\Delta\log A^c_{ortho} - \Delta\log A^c_{para}$) are proportional to the σ_I constants (see Figs. 7, 8).

Discussing the nature of the ortho effect observed, it is at the first glance quite natural to consider the detected additional term as a purely inductive one, which from the ortho-position is considerably higher than from the para-position situated at a greater distance. However, it is hardly correct to consider such additional influence electrostatical, since this effect grows with the increase in the dielectric permittivity of the medium and, on the contrary, disappears in the case of nonpolar solvents[17] ((for H_2O ε = 81,9 at 15° C, ε = 70.0 at 50.0° C and for 1 M, Bu_4NBr solution at 25° C ε = 50,6 [18]).

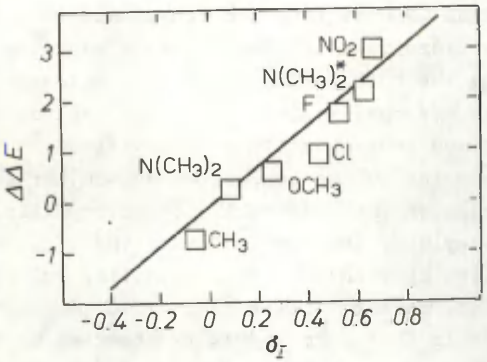

Fig. 7. Dependence of $\Delta\Delta E = \Delta E_{ortho} - \Delta E_{para}$ on σ_I.
* For ortho-$N(CH_3)_2$-substituent value $\sigma_I - \sigma_R^o$ was used.

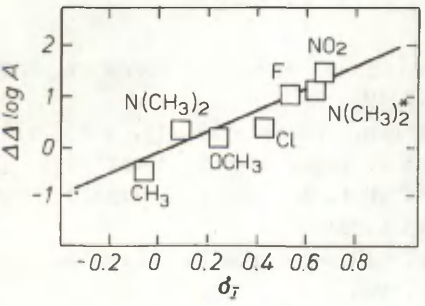

Fig. 8. Dependence of $\Delta\Delta \log A = \Delta \log A_{ortho} - \Delta \log A_{para}$ on σ_I.
* For ortho-$N(CH_3)_2$-substituents value $\sigma_I - \sigma_R^o$ was used.

It can be assumed from the above-said that in the case of alkaline hydrolysis of phenyl tosylates among the reasons causing the ortho-effect, can be mentioned the difference in the hydrophilic (electrophilic) solvation of ortho-substituted and para-substituted derivatives.

When passing to the concentrated n-Bu_4NBr salt solution, the role of the hydrophilic (electrophilic) solvation of phenyl tosylates decreases[5,6], and then follows the transition to the hydrophobic (or lipophilic) solvation of phenyl tosylates, causing the salting-in of phenyl tosylates. The decrease in the ortho-effect is observed as a result of the diminishing role of the hydrophilic (electrophilic) solvation of phenyl tosylates.

The fact that the values of activation parameters E and log A which change during the transition from water to 2.25 M n-Bu_4NBr solution in the case of ortho-substituted derivatives exceed those in the case of para-substituted ones also speaks in favor of different roles of the solvation of ortho- and para-substituted phenyl tosylates during the alkaline hydrolysis.

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BIOMIMETIC MODELLING OF SPATIAL STRUCTURE OF ACETYLCHOLINESTERASE ACTIVE SITE WITH CYCLODEXTRINS.

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The application of ß-cyclodextrin in modelling of spatial structure of active site of acetylcholinesterase has been proved on the basis of results of comparative analysis of specificities of both studied systems toward substituted phenylacetates. Proceeding from spatial structure of biomimetic model molecule a spatial model of acetylcholinesterase active site, describing the shape and dimensions of cation-binding site and localization and orientation of catalytic nucleophile in the active site has been created.

During the prolonged and extensive studies of acetylcholinesterase (AChE, EC 3.1.1.7) reactions a great number of active site models, dealing with chemical and spatial structure of the active site region have been designed.

The chemical structure of catalytic groups has been proposed on the basis of affinity modification studies and through the interpretation of the dependences of AChE-catalyzed reactions on pH and ionic strength. The fundamental results of these studies were the identification of serine hydroxyl in the role of a catalytic nucleophile [1-3] and the detection of catalytically important acidic and basic

groups [4-13]. The contribution of electrostatic interaction to the binding of cationic ligands with AChE has been taken by many authors as proof of the presence of anionic group(s) at the binding site of AChE [5,13,14] but so far no conclusive solution has been found to this problem [15,16].

The geometry of the AChE active site and the location of the catalytic groups within the active site have been modelled by using the principle of the complementarity of the active site structure to the structure of the specific substrates and inhibitors [4,5,7,9,10-17]. According to geometric complementarity the spatial structure of the AChE active site has been depicted as an area suitable for the accommodation of the acetylcholine molecule in the extended conformation [13,15] (see Fig.1 and Fig.2).

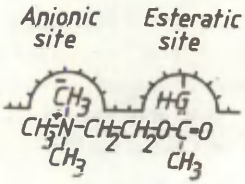


Fig. 1. The model of AChE active site according to Wilson [13].

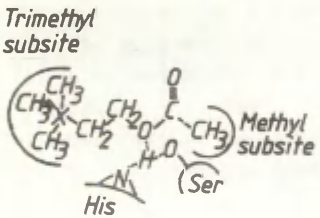


Fig.2. The model of AChE active site according to Hasan et al.[15].

To explain the QSAR of organophosphorus compounds one additional area has been included in the AChE active site model proposed by Järv et al. [16] (Fig 3.).

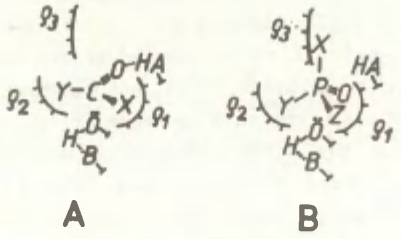


Fig. 3. The model of AChE active site according to Järv [16].

In the present paper the AChE active site structure has been studied by using the methodology of biomimetic chemistry requiring the modelling of active sites of biological macromolecules with cavity-containing organic model molecules [18]. For modelling the AChE active site we have selected cyclodextrin molecules. The common characteristic used in the comparison of the properties of AChE and cyclodextrins is the specificity of both systems toward substituted phenylacetates. The comparison of the specificity of AChE (our data) and different cyclodextrins (data from literature) toward common substrates has revealed a surprisingly strong similarity between the specificity of AChE and of β-cyclodextrin. As the reasons for the specificity of cyclodextrins toward substituted phenylacetates lie in the spatial features of the cyclodextrine molecules [18], the similarity in specificities of two systems studied points to the similar spatial structure of the β-cyclodextrin and AChE active sites. Using this line of reasoning, a spatial model for the AChE active site is proposed on the basis of the spatial structure of β-cyclodextrin molecule.

MATERIALS AND METHODS

AChE from cobra *Naja naja oxiana* venom, purified by affinity chromatography [19], was generously donated by Dr. Raivo Raba, Institute of Chemical Physics and Biophysics, Tallinn. The molar concentration of the enzyme active sites in the solution was calculated from the initial rate of the

enzymatic hydrolysis of acetylthiocholine (1 mM at 25° C, 0.15 M phosphate buffer, pH 7.5) making use of the molecular activity of AChE $a_m = 1.10\ 10^4\ s^{-1}$.

Acetylcholine iodide and acetylthiocholine iodide from Reakhim, (USSR), were used after their recrystallization from absolute ethanol. 3-methylphenol, 4-methylphenol, 3-nitrophenol, 4-nitrophenol, from Reakhim, 3-chlorophenol, 4-chlorophenol, 3-*tert*-butylphenol and 4-*tert*-butylphenol from Aldrich were used after recrystallization or redistillation under reduced pressure. Phenylacetates with neutral substituents were prepared according to the standard method by reacting an appropriate phenol with acetic anhydride [20]. The purity of the products was checked by means of gas cromatography. Iodides of 3- and 4-trimethyl-ammoniophenols were prepared by the methylation of 3- and 4-aminophenols (Reakhim) with methyliodide in acetone in the presence of 2,6-lutidine [21]. Appropriate phenylacetates were prepared by the acylation of phenolates in water at pH 9.3 at 10° C with acetic anhydride. The structure of the iodides of 3- and 4-trimethylammonio-phenylacetates was checked by NMR spectroscopy. The ^{13}C-NMR spectra were taken on the Bruker AC 200 instrument.

The rates of the enzymatic hydrolysis of acetylthiocholine were measured by using the common spectrophotometric method of Ellmann [22] on a Perkin-Elmer 402 spectrophotometer .

The rates of the enzymatic hydrolysis of the phenylacetates in the 0.15 M KCl solution were followed titrimetrically (Radiometer Titrigraph TTT80/PHM82/ABU80, Denmark) at fixed temperatures, pH 7.5.

The enzymatic hydrolysis data have been interpreted according to the accepted three-step reaction scheme for AChE-catalyzed reactions [23-25]:

$$E + S \overset{K_s}{\rightleftharpoons} ES \xrightarrow{k_2} EA + P_1 \xrightarrow{k_3} E + P_2 \qquad [1]$$

using the steady-state kinetic parameters K_m and k_{cat}:

$$K_m = K_s\ k_3 / (k_2+k_3) \qquad [2]$$

$$k_{cat} = k_2\ k_3 / (k_2+k_3) \qquad [3]$$

The constants k_{cat} and K_m were determined from the Michaeles-Menten equation:

$$v_o = k_{cat}\,[E]\,[S]_o \,/\, (\,K_m + [S]_o\,), \qquad [4]$$

using nonlinear regression analysis.

The kinetic constants for the AChE-catalyzed hydrolysis of 3-trimethylammoniophenylacetate were determined by using the integral method, taking into account the product inhibition phenomenon. K_m and k_{cat} were determined from the following dependence [26]:

$$\frac{[P]}{t} = \frac{k_{cat}\,[E]}{1 - K_m/K_p} - \frac{K_m\,(\,1 + [S]_o\,)}{t\,(\,1 - K_m/K_p\,)}\,\ln\frac{[S]_o}{[S]_o - [P]} \qquad [5]$$

using a predetermined value for the product inhibition constant K_p.

The reversible inhibition constant for 3-trimethylammoniophenol (substrate acetylcholine) and the inhibition type were determined from the dependence of K_m and k_{cat} on the inhibitor concentration by making use of the following equations [26-28]:

$$K_m = K_m^{o}\,(\,1 + [I] \,/\, K_i\,) \qquad [6]$$

$$k_{cat} = k_{cat}^{o} \,/\, (\,1 + [I] \,/\, K_i\,) \qquad [7]$$

The apparent thermodynamic parameters from the temperature dependences of K_m and k_{cat} were determined by using the following relationships [26,28]:

$$\ln k_{cat}/T = -\,\Delta H^{\neq}/RT + A \qquad [8]$$

$$\Delta G^{\neq} = -\,RT \ln (k_{cat}h/k_BT) \qquad [9]$$

$$\Delta S^{\neq} = (\,\Delta H^{\neq} - \Delta G^{\neq}\,)/T \qquad [10]$$

$$\ln K_m = -\,\Delta H^{o}/RT + A \qquad [11]$$

$$\Delta G^{o} = -RT \ln K_m \qquad [12]$$

$$\Delta S^{o} = (\,\Delta H^{o} - \Delta G^{o})/T \qquad [13]$$

The linear and nonlinear regression analyses were performed using the "Statgraphics" programme on the IBM PC/XT.

RESULTS

The Michaeles-Menten equation holds for the AChE-catalyzed hydrolysis reaction of all the phenylacetates studied (except 3-trimethylammoniophenylacetate). The kinetic constants k_{cat} and K_m for 3-trimethylammoniophenylacetate were calculated from a plot of $[P]/t$ against $\ln(\,[S]_o/([S]_o-[P]))/t$ (Fig. 4) using Eqn. 5 and the value of $K_p = 4\ 10^{-7}$ M.

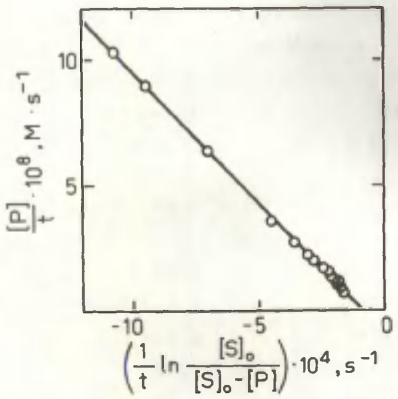


Fig. 4. Plot of [P]/t vs. $\ln([S]_o/([S]_o-[P]))/t$ for AChE-catalyzed hydrolysis of 3-trimethylammoniophenylacetate ($[S]_o$=0.1 mM) in 0.15 M KCl, pH 7.5 at 25°C.

The kinetic constants of AChE-catalyzed hydrolysis of the phenylacetates at 25° C are listed in Table 1.

Table 1.

AChE-Catalyzed Hydrolysis of Substituted Phenylacetates (0.15 M KCl, pH 7.5, t = 25 °C).

Phenyl substituent	K_m, M	k_{cat}, s^{-1}
m-$C(CH_3)_3$	$(1.6\pm0.4)*10^{-4}$	1226± 75
p-$C(CH_3)_3$	$(1.6\pm0.3)*10^{-4}$	113± 4
m-CH_3	$(2.1\pm1.1)*10^{-4}$	2296± 68
p-CH_3	$(3.1\pm0.6)*10^{-4}$	1258± 68
m-NO_2	$(7.6\pm1.4)*10^{-4}$	1450±100
p-NO_2	$(1.6\pm0.1)*10^{-3}$	827± 55
m-Cl	$(3.7\pm0.4)*10^{-3}$	2175± 97
p-Cl	$(4.8\pm0.5)*10^{-3}$	1033± 55
m-$N^+(CH_3)_3$	$(1.0\pm0.2)*10^{-5}$	6700±150
p-$N^+(CH_3)_3$	$(1.4\pm0.5)*10^{-4}$	1950±160
-H	$(9.0\pm2.9)*10^{-4}$	6900±520
Acetylcholine	$(1.4\pm0.1)*10^{-4}$	7380±410

The kinetic constants of AChE-catalyzed hydrolysis of two pairs of *meta*- and *para*-substituted phenylacetates at various temperatures are listed in Table 2.

Table 2.

AChE-Catalyzed Hydrolysis of Substituted Phenylacetates at Various Temperatures (0.15 M KCl, pH 7.5).

Temperature °C	3-*tert*-butyl-phenylacetate		4-*tert*-butyl-phenylacetate	
	K_m*10^4, M	k_{cat}, s^{-1}	K_m*10^4, M	k_{cat}, s^{-1}
10	1.60	818	1.60	68
15	1.65	961	-	-
20	1.60	1166	1.50	103
25	1.62	1226	1.62	113
30	1.60	1615	1.62	154
35	1.65	1973	1.45	195
40	2.00	2511	1.50	288
	3-methyl-phenylacetate		4-methyl-phenylacetate	
5	2.12	1407	3.01	632
20	1.70	1912	2.03	1009
25	2.12	2296	3.10	1258
30	1.97	2599	2.90	1679
35	1.90	3058	2.80	2017
40	2.30	3517	2.20	2311

The plotting of logarithms of k_{cat} and K_m vs. reciprocal of temperature yielded straight lines in all cases and apparent thermodynamic parameters calculated from Eqns.8-13 are listed in Table 3.

Table 3.

The Apparent Thermodynamic Parameters of the AChE-Catalyzed Hydrolysis of Substituted Phenylacetates (0.15 M KCl, pH 7.5).

Phenyl substituent	k_{cat} $\Delta H^{\neq}$ kJ/mol	k_{cat} $\Delta S^{\neq}$ J/mol·K	K_m ΔH^{o} J/mol	K_m ΔS^{o} J/mol·K
m-$C(CH_3)_3$	25.5±1.7	-99.9±10.2	-0.58±0.33	-92±55
p-$C(CH_3)_3$	33.5±3.8	-92.8±10.1	-0.88±0.29	-102±31
m-CH_3	22.9±1.9	-103.4±9.5	-2.60±1.55	-78±31
p-CH_3	37.6±5.8	-58.7±6.4	-2.64±1.76	-81±34

DISCUSSION

AChE reactions with derivatives of substituted phenols

Proceeding from substituted phenols, several classes of AChE substrates and inhibitors have been designed : substituted phenyl acetates as substrates [29-31], substituted phenols as reversible inhibitors [32,33], substituted phenylcarbamates [32,34-46], phenylphosphates [38,40,47,48] and phenylsulfonates [49] as irreversible inhibitors . The reactions of phenyl derivatives with AChE have been studied mainly by using the QSAR methodology from physical organic chemistry [50]. Within this approach the interpretation of the substituent effects has been realized by using inductive, resonance, steric, hydrophobic, hydrogen bonding, and charge transfer parameters for the substituted phenols in different combinations [30,33,35,38,40,41,47,48,51-56]. The main conclusion from these approaches is that in the reactions of AChE with the derivatives of substituted phenols there exists no simple Hammett-type relationship [30,33,35,40,41,47-49] and no common QSAR for the *ortho*-, *meta*- and *para*-substituted derivatives [41,52-56]. In most cases these facts have been explained by steric restrictions on the orientation of the substituted phenyl derivatives in the active site of AChE [41,47-49,53-55]. Thus, the claccical QSAR can effectively

detect the presence of steric factors in enzymatic reactions, but this approach is quite useless in explaining the steric factors on the level of spatial structure of active site, since the organic model systems forming the ground of physical organic chemistry, do not contain any parameters for modelling the steric features of the enzyme active sites [50]. Modelling the spatial structure of enzyme active sites can be realized by using the biomimetic chemistry approach [18].

Biomimetic chemistry approach

The aim of the present work was to apply the methodology of biomimetic chemistry in modelling the spatial structure of the AChE active site. The main specific feature of the biomimetic chemical approach is the exploitation for the modelling of an certain aspect of active sites of biological macromolecules (in the present case spatial structure of the active site of AChE) organic model molecules, containing cavity for binding of substrates. In the case of homology between systems, the conclusions from the studies of a model system can be extrapolated to the biological system [18].

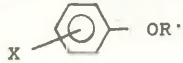
The first, and the most responsible step in this approach, is the choice of the model molecule that can properly mimic the active site structure. Owing to the unique structure of each enzyme, anyone of them needs an individual approach in model molecule design. Success at this step depends on the availability of different model molecules and on good luck.

We selected cyclodextrin molecules for the modelling of the AChE active site. Cyclodextrins are cyclic oligosaccarides consisting of α-1,4-linked D-glucopyranose rings. The interior of cyclodextrin molecules forms a cylindrical cavity, open from the both sides. α- , β- and γ-cyclodextrins contain, respectively 6, 7, and 8 glucose residues in the molecule and accordingly the inner diameters of the cavity are approximately 4.5, 7.0 and 8.5 Å. Moreover, cyclodextrins contain hydroxyl groups, interacting with a large number of acylating reagents [57]. The above-mentioned properties make cyclodextrins especially useful in modelling the action of the serine hydrolases, including AChE. Thanks

to the fruitful efforts of many authors, the properties of cyclodextrins have been studied fairly thoroughly by means of physical organic chemistry and structural chemistry approaches, and clear-cut conclusions have been drawn about the relations between the chemical specificity and the spatial structure of the cyclodextrin molecules [57,58].

In the present investigation we used substituted phenylacetates as common substrates for the comparative study of AChE and cyclodextrins. Among the former we can find differently substituted isomers having nearly equal chemical reactivity in organic chemical reactions and similar properties in partition processes between the water and organic phases [59,60]. Table 5 shows that these requirements

Table 5.

Molar Refractivity (MR), Hydrophobic (π) and Electronic (σ) Substituent Constants for Substituents in Aromatic Systems  OR·

-X	MR[a]	π [b]		σ [c]	
		para	*meta*	*para*	*meta*
-H	1.03	0	0	0	0
$-CH_3$	5.65	0.50	0.54	-0.15	-0.07
$-C(CH_3)_3$	19.62	1.90	1.77	-0.20	-0.10
$-OCH_3$	7.87	0.04	0.14	-0.27	0.12
-F	0.92	0.12	0.33	0.06	0.34
-Cl	6.03	0.85	0.87	0.23	0.37
-Br	8.88	1.01	1.09	0.23	0.39
$-NO_2$	7.36	0.30	0.23	1.24	0.71
$-N(CH_3)_2$	22.82	0.18[a]		-0.83	-0.15
$-N^+(CH_3)_3$	21.20	-5.96[a]		0.82	0.88
$-COO^-$	6.05	-4.36[a]		0.00	-0.10

[a] taken from Ref. [59].

[b] taken from Ref. [60]

[c] σ (or σ^- for *p*-NO_2) values taken from Ref. [59]

have been met in the case of the pairs of *meta*- and *para*-substituted phenyl derivatives with alkyl, halogen (except fluor) and dimethylamino substituents. At the same time *ortho*

isomers differ systematically from *meta* and *para* isomers in their partition properties [60]. Thus, as usual, the π values of the *ortho*-substituents are different from those of the *meta*- and *para*-substituents and vary considerably according to the side chain structure [60]. The different behavior of the *ortho*-substituted derivatives can be explained by additional direct steric and field effects between the *ortho* substituents [50,59,60].

The above-mentioned pairs of phenylacetates represent nearly equireactive isomeric compounds differing only in the substituent orientation relative to the acyl group. The properties listed make these pairs directly useful for fhe detection of steric aspects of the different active sites, because, as in the case of stereoisomers, the reasons for discrimination between the mentioned *meta* and *para* isomers in enzymatic and biomimetic reactions must be connected with the spatial features of the enzyme active sites.

Theoretically enzymes or biomimetic systems may express either *para*-specificity, *meta*-specificity or equireactivity toward equireactive *meta*- and *para*-substituted isomeric phenyl derivatives. On the basis of literature data [30-49] we can say that in the case of AChE there is well-expressed *meta*-specificity. On the other hand, *para*-specificity toward phenylacetates is present in the case of α - chymotrypsin [61,62] and trypsin [63].

For adequate modelling of AChE with biomimetic model molecules we must use such systems, which also express *meta*-specificity toward equireactive phenyl derivatives. Cyclodextrins, especially α - and β -cyclodextrin, meet this requirement [64] but, in principle, many different systems can express *meta*-specificity. Consequently, conclusions about the similarity of the spatial structures of two systems can be drawn only after a systematic kinetic and thermodynamic analysis of the *meta*-specificity phenomenon in the case of the both systems compared (see next paragraph).

Comparison of specificities of cyclodextrins and AChE toward phenylacetates

As concerns cyclodextrins, the *meta*-specificity phenomenon has been studied fairly thoroughly [64] and has been rewieved in a number of books [18,57,58,65]. The kinetic and thermodynamic features characteristic of the *meta*-specificity of cyclodextrines can be listed as follows:

1. In the case of a hydrolysis reaction of phenylacetates no simple Hammett-type QSAR is valid and the reactions of *meta* isomers are faster than those of *para* isomers in the case of equireactive isomers and even in the case of nitro substituent [64] (Fig. 5).

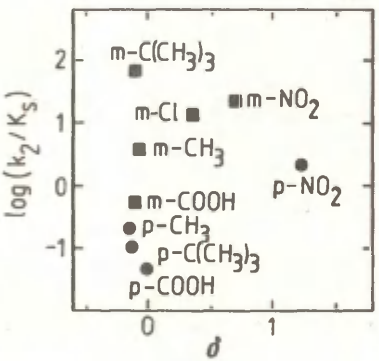


Fig. 5. Plot of logarithm of second order rate constant for reaction of α-cyclodextrin with phenylacetates (data from [64]) vs. the substituent σ constant.

2. The *meta*-specificity is revealed in the acylation step (k_2) of the hydrolysis reaction:

$$C + S \overset{K_s}{\rightleftharpoons} [\,C\,S\,] \xrightarrow{k_2} C\text{-}Ac + P_1 \xrightarrow{k_3} C + P_2 \qquad [14]$$

while the dissociation constants of the cyclodextrin-phenylacetate complex (K_s) for the *meta*- and *para*-substituted compounds differ insufficiently [64] (see Table 6).

Table 6.

The Dissociation Constants for the α-Cyclodextrin-Phenylacetate Complexes (K_s) and the Rate Constants for the Cyclodextrin Acylation (k_2) (Carbonate Buffer pH 10.6, I=0.2, 25°C) [64].

Phenyl substituent	$K_s * 10^2$, M	$k_2 * 10^2$, s^{-1}
m-CH_3	1.7±0.5	6.58
p-CH_3	1.1±0.7	0.22
m-$C(CH_3)_3$	0.20±0.08	12.9
p-$C(CH_3)_3$	0.65±0.39	0.067
m-NO_2	1.9±0.4	42.5
p-NO_2	1.2±0.4	2.43
m-COOH	10.5±3.1	5.55
p-COOH	15.5±9.0	0.67

3. The difference between the reactivity of cyclodextrine toward *meta* and *para* isomers depends on the size of the phenyl substituent. The bigger the substituent, the greater is the difference in the reactivity between the *meta* and *para* isomers [64] (Fig. 6).

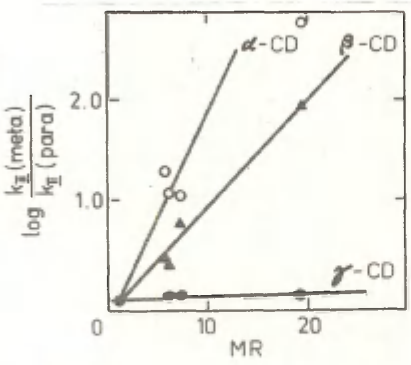


Fig. 6. Dependence of the difference in logarithms of second order rate constants of cyclodextrin (CD) mediated hydrolysis of *meta*- and *para*-substituted phenylacetates (data from [64]) on the molar refractivity of substituent.

4. The difference in cyclodextrin reactivity toward certain *meta* and *para* isomer depends on the diameter of the cyclodextrin cavity. The *meta*-specificity phenomenon is

most clearly expressed in the case of α-cyclodextrin (diameter of the cavity 4.5 A [57]) β-cyclodextrin (d = 7 A [57]) expresses weaker *meta*-specificity, and in the case of γ-cyclodextrin (d = 8.5 A [57]) *meta*- and *para*-substituted phenylacetates are equireactive [64] (see Fig. 6).

5. *Meta*-specificity of the cyclodextrins is achieved owing to the lower activation enthalpy of acylation for *meta* isomers as compared with *para* isomers, whereas activation entropy slightly compensates this difference [66] (see Table 7).

Table 7.

The Thermodynamic Parameters for Acylation (k_2) of α-Cyclodextrin with Substituted Phenylacetates [66].

Phenyl substituent	$\Delta H^{\neq}$, kJ/mol		$\Delta S^{\neq}$, J/mol·K	
	meta	*para*	*meta*	*para*
$-CH_3$	20.1	41.4	-170.2	-125.5
$-NO_2$	13.8	37.7	-165.3	-120.5

In the present work we have studied the same above-mentioned properties in the case of AChE. Comparison of the kinetic and thermodynamic data on the *meta*-specificity of cyclodextrins with the analogous data on AChE-catalyzed reactions has revealed fairly high degree of coincidence of the above-listed characteristic features.

Nor is there any simple Hammett-type relationship in the case of AChE-catalyzed hydrolysis of phenylacetates and the *meta*-substituted isomers prevail over the *para*-substituted ones even in the case of a nitro substituent (see Table 1).

The *meta*-specificity in the case of AChE-catalyzed hydrolysis of neutral phenylacetates is connected with the differences in the apparent catalytic constant of the hydrolysis reaction (see Table 1.). Although in the case of AChE-catalyzed reactions the constant k_{cat} is a complex parameter (see Eq. 3), the differences in the k_{cat} for acetates are connected only with the differences in the acylation rate constants. In the case of the AChE reactions the difference between the reactivities of *meta* and *para*

isomers increases symbatically with the increase of the size of the substituent (Fig. 7).

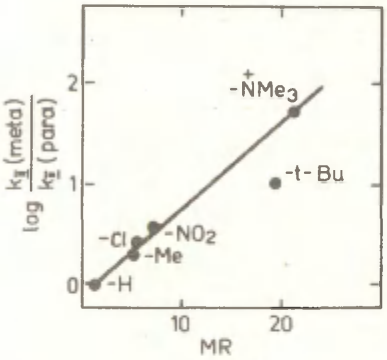


Fig. 7. Dependence of the difference between the logarithms of second order rate constants of AChE-catalyzed hydrolysis of *meta*- and *para*-substituted phenylacetates on the molar refractivity of substituent.

Comparing Figs. 6 and 7 we can conclude that on the basis of the dependence of the difference in the reactivity of *meta* and *para* isomers on the molar refractivity of the substituents, AChE is most similar to β-cyclodextrin.

From Table 4 we can see that the *meta*-specificity of AChE reactions is obtained owing to the lower apparent activation enthalpy of k_{cat} in the case of a *meta* isomers, whereas the apparent activation entropy compensates for the favorable H difference. The apparent $\Delta H^{\neq}$ and $\Delta S^{\neq}$ for k_{cat} are complex parameters [28], but as AChE-catalyzed hydrolysis of studied substrates is acylation-limited (see Table 1) the apparent $\Delta H^{\neq}$ and $\Delta S^{\neq}$ for k_{cat} reflect mainly the thermodynamic parameters of the acylation reaction. Consequently, in the case of AChE the *meta*-specificity phenomenon is similar to the *meta*-specificity of cyclodextrines in the both kinetic and the thermodynamic aspects.

Creation of AChE active site model

As the *meta*-specificity phenomenon reveals similar kinetic and thermodynamic features in the case of AChE and cyclodextrines, we can conclude that there exist similar reasons for the *meta*-specificity in the case of the two

systems studied.

In the case of cyclodextrines the origin of *meta*-specificity has been precisely investigated by determining the structure of the inclusion complexes of cyclodextrines with phenylacetates in solution by means of NMR spectroscopy [67]. It was established that in the case of *meta*-substituted phenylacetates the distance between the carbonyl carbon atom and the nucleophilic oxygen atom of the cyclodextrine 2-hydroxy-group in the inclusion complex was substantially shorter than it was in the case of the inclusion complexes with *para*-substituted compounds (see Fig. 8).

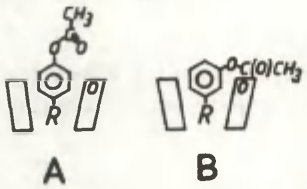


Fig. 8. Conformations of the inclusion complexes of α-cyclodextrin with *p*-nitrophenylacetate (A) and *m*-nitrophenylacetate (B) in a 1:1 (v/v) mixture of 1N DCl and DMSO from NMR measurements [67]. R denotes $-NO_2$.

Therefore, the *meta*-specificity of cyclodextrins is obtained through orientational effects and the acceleration of the reaction of *meta*-isomers compared with that of *para*-isomers is obtained via the proximity effect [18,57,58,64,67].

In summary, the reasons for the *meta*-specificity of cyclodextrins lie in the spatial structure and the conformational rigidity of the cyclodextrin molecules. The most important geometrical parameters determining the specific properties of the cyclodextrins are the shape and the diameter of the cavity plus the location and the orientation of the nucleophilic hydroxyl group to the cavity. On the basis of the conclusion that AChE and cyclodextrins

have the same origin of *meta*-specificity, in Fig. 9 we propose for the AChE active site a spatial model reflecting the most important geometric features of the β-cyclodextrin molecule causing the *meta*-specificity of the system.

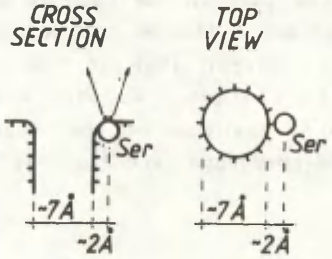


Fig. 9. Spatial model of AChE active site. The limits of orientation of electron pair of nucleophile are shown with arrows.

The model represents a cylindrical rigid cavity with a diameter of approximately 7Å (diameter of the cavity of β-cyclodextrine) and nucleophilic serine hydroxyl. The location and orientation of nucleophile has been estimated from the space-filling model of β-cyclodextrin molecule.

Proposed model explains the specificity of AChE toward *meta*- and *para*-substituted phenylacetates, phenyl N-methylcarbamates [32,34-46] and also toward *meta*- and *para*-substituted phenylphosphates [40,47,48] and phenylsulfonates [49] on the basis of spatial structure of AChE active site and this structure can serve as a framework for further development of the model on the basis of additional experimental data.

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