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STUDY OF MEDIUM EFFECT ONTO THE DECOMPOSITION RATE OF POTASSIUM 1,1-DIMETHOXY-2,4-DINITROCYCLOHEXA-2,5-DIENATE

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Kinetics of decomposition of potassium 1,1-dimethoxy-2,4-dinitrocyclohexa-2,5-dienate has been measured spectrophotometrically in binary mixtures of dimethylsulfoxide - protonic components. Aliphatic alcohols and water in temperature range 15-35° C were taken for the latter. Activation parameters of this reaction were found. It has been established that the reaction of the σ-complex decomposition proceeds according to bimolecular mechanism and substantially depends on the acidity and structure of the protonic component. This is proved by the excellent correlation between log k and pK_a of alcohols and the σ^*, E_s^c values of alcohol radicals.

At present, there can be found sufficient data in literature on the studies of medium effect on the stability of the Jackson-Meisenheimer anionic σ-complexes as well as on establishing interrelations between the structures of complexes and their reactivities[1,2]. Nevertheless, the studies of σ-complexes on the basis of aromatic dinitro compounds are very rare.

Thus, the present work is aimed at studying the effects of medium structure and acidity as well as the temperature

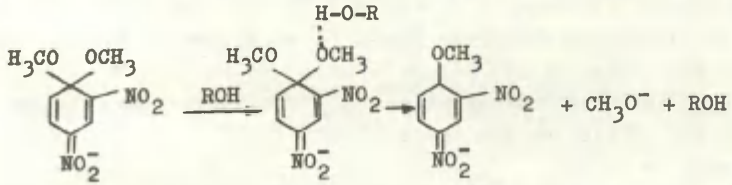
on the stability of potassium 1,1-dimethoxy-2,4-dinitrocyclohexa-2,5-dienate σ-complexes. In free form, this complex is unstable, since in the case of the dissolution in protonic solvents, it decomposes instantly. Therefore, the decomposition reaction was studied in the binary mixtures, consisting of an aprotic polar solvent - dimethyl sulfoxide (DMSO) and of one of the protonic components - water or aliphatic alcohols C_1-C_4 with either normal or iso-structure, the content of the latter being 0.1-1.2 mol/l.

The studied anionic σ-complex which has the structure of quinolonitro acid has been fully dissociated into ions in DMSO, whereas the solvents having high dielectric constants favor the formation of free ions instead of the solvent-separated ion pairs[3].

Reaction rate was determined spectrophotometrically by the optical density change of the solution at the absorption maximum (λ = 506 nm) which is characteristic of the σ-complexes of Jackson-Meisenheimer with two nitro-groups in benzene ring. The linear character of the corresponding kinetic dependences (Fig. 1,a) shows that at low concentrations in the mixture of alcohols and water the reaction follows the first order both according to the protonic components and to the decomposing complex.

Consequently, the decomposition of the σ-complex of 2,4-dinitroanizole with potassium methylate is a protolytic reaction and it proceeds according to the bimolecular mechanism, including the protonation of the oxygen atoms of σ-complex and the cleavage of the C-O[4] bond (Scheme 1).

The results of the measurements can be found in Table 1. They indicate that the rate of σ-complex decomposition



linearly depends on the acidity of the protonic component and

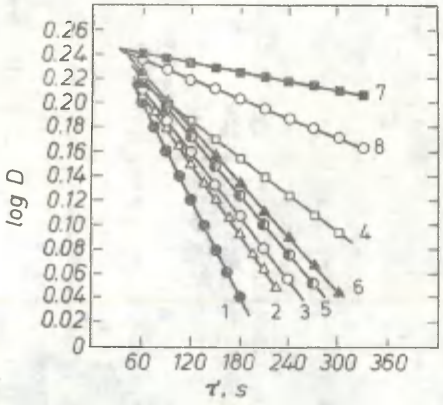


Fig. 1. Dependence of log D on the time of Б-complex decomposition at the concentration of protonic component 0.1mol/l*

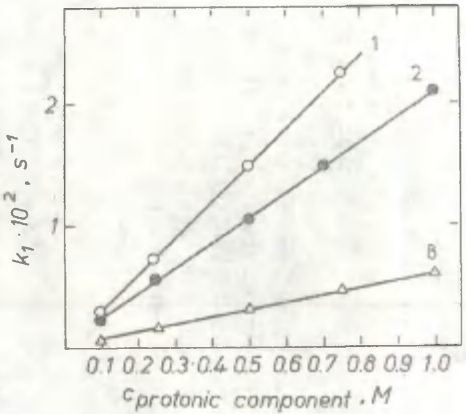


Fig. 2. Dependence of the first order constants k_1 on the concentration of protonic component*.

* Numbers of kinetic curves correspond to those of Table 1.

changes as follows: $CH_3OH > C_2H_5OH > C_3H_7OH > C_4H_9OH > i\text{-}C_4H_9OH > i\text{-}C_3H_7OH > H_2O > t\text{-}C_4H_9OH$. The point for water does not obey this relationship. Namely, in the mixtures of water and DMSO the decomposition rate is unexpectedly low and does not correspond to the pK_a of water. We believe that this phenomenon can be explained by the formation of the structures of type $DMSO \cdot 2H_2O$[5], the latter being less reactive than the free molecules of water. The observable lowering of the reaction rate is probably also due to the stabilization of the product by the formation of hydrates of nitro groups. It has been shown in the studies concerning classical Jackson-Meisenheimer complexes[6].

The calculations according to the least squares' method[7] have shown that there is an excellent correlation between the log k and pK_a of alcohols ($r = 0.999$; $s = 0.013$). As to the acidity of aliphatic alcohols, it depends on the electron-donor properties of the alkyl group, which certainly influences the rate of σ-complex decomposition. Incidentally, there is a satisfactory correlation ($r = 0.952$; $s = 0.097$) between the logarithms of decomposition rate constants and the σ-constants values of alcohol radicals (σ^*). The obtained positive values of the reaction constant ρ for the present isokinetic series in equation $\log k = -1.34 + 3.24\,\sigma^*$ give evidence of the process's electrophilic character towards the substrate. A comparatively high ρ value refers to a rather significant polarity level of the transition state[8].

The study of the kinetics of potassium 1,1-dimethoxy-2,4-dinitrocyclohexane-2,5-dienate has shown that the reaction rate does not only depend on the acidity of medium but also on the protonic component structure. The data analysis (Table 1) reveals the existence of a certain interrelation between the log k of the rate of σ-complex decomposition and steric constants of alkyl radicals E_s^c. This is also proved by the established satisfactory correlation between those two quantities ($r = 0.950$; $s = 0.100$). Evidently, the branching of the alkyl chains of alcohol diminishes the role of

specific solvation of etheric oxygen atoms and retards decomposition rate.

The study of temperature dependence of the σ-complex decomposition enabled us to find the activation parameters of the reaction. The activation energy (Table 1) is changed insignificantly by the nature of alcohol. Thus, the entropy factor which is connected with the solvation of the complex by the protonic components of binary mixture probably controles the decomposition. Fig. 3. shows that the experimental points fall well onto the straight lines within the coordinates log k - 1/T, thus justifying the application of the Arrhenius equation for the given systems.

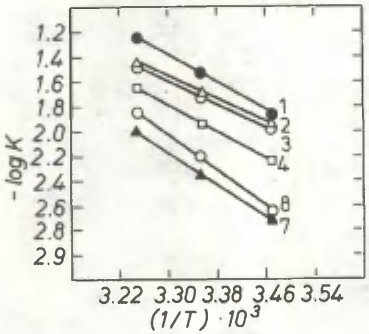


Fig. 3. Relationship log k-1/T for the potassium 1,1-dimethoxy-2,4-dinitrocyclohexane-2,5-dienate decomposition reaction in the mixtures of DMSO and protonic components. The numbers of lines correspond to those of Table 1.

The obtained negative activation entropy values agree with the earlier suggested reaction mechanism[9].

Table 1

Kinetic and Thermodynamic Parameters of Potassium 1,1-dimethoxy-2,4-dinitrocyclohexa-2,5-dienate Decomposition Reaction

	Protonic component	$k_2 \cdot 10^2$, $l \cdot mol^{-1} \cdot s^{-1}$			pK_a	δ^*	E_s^C	E	log A	$\Delta s^{\neq}$
		288°K	298°K	308°K				kJ/mol		kJ/mol·degree
1	CH_3OH	1.30	3.00	5.72	15.09	0.00	0.00	11.74	7.201	-26.01
2	C_2H_5OH	1.15	2.10	3.72	15.93	-0.10	-0.38	10.28	5.867	-31.65
3	C_3H_7OH	1.08	1.94	3.49	16.10	-0.115	-0.67	10.34	5.872	-31.63
4	$i\text{-}C_3H_7OH$	0.70	1.10	2.30	17.10	-0.19	-1.08	10.74	5.950	-31.27
5	C_4H_9OH	0.79	1.84	3.39	16.10	-0.13	-0.70	10.75	6.195	-30.15
6	$i\text{-}C_4H_9OH$	0.99	1.77	3.20	16.10	-0.125	-1.24	10.78	6.163	-30.30
7	$t\text{-}C_4H_9OH$	0.20	0.44	1.00	19.00	-0.30	-2.46	13.45	7.522	-24.08
8	H_2O	0.22	0.61	1.42	15.70	-0.49	0.32	16.90	10.198	-11.86

The results of our studies confirm that the interaction of the complex with the protonic component functions as the limiting stage of the reaction. As a result of this interaction the transition state (II) is formed with the consequent rise of the order of the whole system.

Thus, we have established that the potassium 1,1- dimethoxy-2,4-dinitrocyclohexa-2,5-dienate decomposition reaction proceeds by the bimolecular mechanism and it largely depends on the structure and acidity of the protonic component.

Experimental

The σ-complex I was obtained using methods described elsewhere[10]. The solvents used were purified according to the standard methods[11]. The technique of kinetic studies has been published earlier[12]. The constant was calculated according to the first-order equation[13]. The bimolecular constants were found by dividing the pseudofirst order constants with the concentration of the protonic component[13]. Activation parameters were calculated according to the equation given in monograph[14]. Correlation parameters were calculated using the well-known methods of mathematical statistics[7,8].

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INFLUENCE OF LEAVING GROUP NATURE AND MECHANISMS OF ORGANIC BASE CATALYSIS IN REACTIONS OF 1-X-2,4-DINITROBENZENES WITH PIPERIDINE IN BENZENE

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Received August 15,1989

Influence of leaving group nature on the kinetics of reactions of 1-X-2,4-dinitrobenzenes (F, Cl, Br, I, $OSO_2C_6H_5$) with piperidine and its deuterium analogs in benzene at 25°C has been studied spectrophotometrically. For substrate's halogen derivatives noncatalytic route of nucleophilic substitution proceeds in stages. The process includes slow decomposition of σ-complex via cyclic transition state and limiting formation of σ-complex for benzene sulfonate. Leaving group nature has a certain effect on the catalysis mechanism of those reactions by bases containing nitrogen and oxygen. Catalytic rate constants of substrates (X = F, Cl, Br, I, $OC_6H_4NO_2$-4) depending on their structures and main catalysts obey the following equations: $\log k_m = (-8.93 \pm 0.31) + (8.31 \pm 0.28)pK_{ass} + (1.24 \pm 0.08)pK_{HB}$ and $\log k_m = (-6.66 \pm 0.25) + (0.97 \pm 0.03)pK_{HB(N^+X^-)} + (1.17 \pm 0.08)pK_{HB}$. Slow decomposition of σ-complex in catalytic process is determined by NH proton group separation via cyclic transition state with participation

of leaving group and essential catalyst. In the case of benzene sulfonate leaving group, the associative mechanism of catalysis by bases is discussed.

The influence of leaving group in reactions of activated benzene derivatives with aliphatic amines has been studied in polar media mainly[1-3]. Papers[4,5] deal with the catalytic effects of the additions of organic bases in those media. It could have been expected that in the case of transition to nonpolar aprotic media (cf.[6-9]) the leaving group effect should more clearly be revealed in catalytic reaction as well.

The present paper is aimed at studying the effect of leaving group both in noncatalytic reactions and in those catalyzed by organic bases of the compounds having the following formulae: $2,4(NO_2)_2C_6H_3X$ (X=F(I), Cl(II), Br(III), I (IV), $OSO_2C_6H_5$(V), $OC_6H_4NO_2$-4 (VI)[8]) with piperidine and its deuterium analogs in benzene at 25°C.

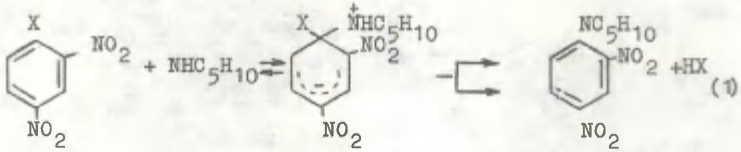
Our research into the kinetics of reactions of compounds (I)-(IV), (VI) with piperidine has shown that they proceed in two parallel routes: in the noncatalytic one with constant k_o ($l \cdot mol^{-1} \cdot s^{-1}$) and in the route catalyzed by the second amine molecule with constant k_B ($l^2 \cdot mol^{-2} \cdot s^{-1}$). In a similar reaction with participation of compound (V) no catalytic action of amine was observed (Table 1).

It was supposed that there takes place the following conversion of the limiting stage during transition from compounds (I)-(IV),(VI) to (V): for compounds (I)-(IV), the decomposition of the σ-complex is limited by (VI), in the case of (V), it is the formation of the latter that acts as a limiting stage. In keeping with that, the scheme of nucleophilic substitution proceeding in stages includes simultaneous formation of the σ-complex and then its monomolecular and bimolecular decomposition with participation of the second amine molecule.

Table 1

Noncatalytic Constants. Catalysis of Second Molecule of Amine for Reactions of Compounds (I)-(V) with Piperidine and N-Deuterium Piperidine in Benzene

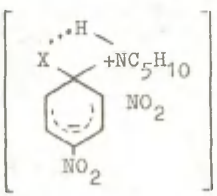
Compounds	$k_o \cdot 10^2$	$k_o^D \cdot 10^2$	k_o/k_o^D	k_B	k_B^D	k_B/k_B^D	$K_{ass} 10$
I	73.9	38.2	1.93	594	50.4	11.8	9.10
II	7.17	6.61	1.08	0.323	0.094	3.72	4.35
III	10.1	7.52	1.31	0.214	0.103	2.08	4.20
IV	2.80	2.32	1.19		-	-	3.99
V	201	201	1.00	-	-	-	



(1)

In order to confirm the existence of differences in the mechanisms of the reaction series studied it was interesting to observe the influence of another separating group - hydrogen atom, in the case of piperidine nitrogen in the very complex replacing it by a deuterium atom. The kinetic regularities of the reaction with N-deuteropiperidine are analogous with those obtained for piperidine. Rate constants k_o^D and k_B^D as well as the values of kinetic isotope effects (KIE) estimated by k^H/k^D are given in Table 1. The KIE found exceeds one both in the case of noncatalytic and catalytic reactions of substrates (I)-(IV). The effect is an essential one and, consequently, it refers to the separation of the hydrogen atom in the rate limiting stage. In the case of substrate (V) the KIE is close to one and cannot therefore be very exactly defined.

On the other hand, according to report[1], significant differences in constant values in the case of leaving groups' exchange for the reactions of substrates (I)-(IV) with piperidine and N-deuteropiperidine show that leaving group X also splits into limiting stage. The fact that both leaving groups (hydrogen atom and X) split off in the limiting stage makes us conclude[11-13] that the formation of hydrogen bond between them in cyclic four-member transition state (VIIa) favors their separation.



(VIIa)

The formation of hydrogen bond in (VIIa) agrees with the existence of correlation dependence (2) for the substrates containing halogen

$$\log k_X = \log k_X^o + \alpha \cdot pK_{ass} \qquad (2)$$

where k_X is the rate constant for leaving group X; pK_{ass} - logarithm of constant of association of cyclohexylhalogenides with phenol in CCl_4 at 25° C assessing the ability of leaving group X to form hydrogen bond; α denotes permanent sensitivity of the reaction series to a certain property of the leaving group; k_X^o - rate constant for hypothetical substrate with $pK_{ass} = 0$.

The numeric value of constants k_o in the case of variable X is

$$\log k_o = (-3.27 \pm 0.56) + (3.30 \pm 0.78) pK_{ass} \qquad (3)$$

$$s = 0.23 \qquad R = 0.95$$

Value α found in Eq. (3) equals 3.30 referring to rather high sensitivity of leaving group X toward the formation of hydrogen bond strengthening in order F>Cl>Br>I. It

is in agreement with the suggested stage-like substitution scheme (1).

Nucleophilic substitution with participation of benzene sulfonate derivative of the substrate proceeds more rapidly in the leaving group series, it has not been influenced catalytically by the second molecule of amine and the KIE does not exceed one. Those facts enable us to consider that in this case it is the formation of the σ-complex that acts as the limiting stage.

In order to establish the leaving group nature in the catalytic reactions of compounds (I)-(V) with piperidine in benzene, we studied the effect of the additions of nitrogen and oxygen-containing bases. The values of catalytic constants k_m ($l^2 \cdot mol^{-2} \cdot s^{-1}$) are given in Table 2. The data indicate that the k_m values decrease in the series of substrates (I)-(IV), (VI) parallelly to the pK_{HB} change according to Eq. (4).

$$\log k_m = \log k_m^o + \beta \cdot pK_{HB} \qquad (4)$$

where pK_{HB} denote the constant logarithm of association of a given base with p-fluoropu[illegible]ol in CCl_4 at 25° C, enabling to assess the proton-acce[illegible]or ability to form hydrogen bond; β - the coefficient of sensitivity of reaction series to this parameter.

The authors of paper[9] have noticed a similar dependence in reactions of nucleophilic aromatic substitution.

The dependence of catalytic constants on the pK_{HB} values for various leaving groups (Fig. 1) and the statistic parameters of Eq. (4) for compounds (I)-(VI) (Table 3) show that sensitivity coefficient β depends on the leaving group nature. As in the case of compounds (I)-(IV), (VI) characterized by the decisive role of the σ-complex's decomposition, the β values practically coincide. The level of proton transfer to the catalyst forms 10-20 % (cf. [14]).

Since the intensity of catalysts decreases in substrate series (I)-(IV), (VI), as well as in the case of noncatalytic processes, correlation (2) was used for the quantitative estimation of this phenomenon. The numeric values of the

Table 2

Values of Logarithms of Catalytic Constants for Reactions of Compounds (I)-(VI) with Piperidine, Catalyzed by Organic Bases in Benzene, 25° C

Base	log k_m						pK_{HB}
	I	II	III	IV	V	VI[8]	
1. Dicxane	-0.19	-	-	-	-0.64	-3.55	0.73
2. Ethylacetate	0.36	-	-	-	-0.38	-	1.08
3. Acetone	0.45	-	-	-	-0.24	-	1.18
4. Piperidine	1.43	-1.55	-1.18	-1.95	0.51	-2.08	1.88
5. Triethylamine	1.31	-	-	-	-	-	1.91
6. Dimethylformamide	-	-1.05	-0.95	-1.75	-	-	2.06
7. 2,4-dimethylpyridine	-	-0.87	-0.85	-1.63	-	-	2.17
8. Diazabicyclo octane	1.51[6]	-	-	-	-	-1.81	2.20
9. Diethylacetamide	-	-0.38	-0.55	-1.16	-	-	2.47
10. Dimethylsulfoxide	2.10	-0.47	-0.41	-1.12	1.10	-	2.53
11. Triphenylphospine cxide	1.16	-0.22	-0.16	-0.69	1.38	-	3.16

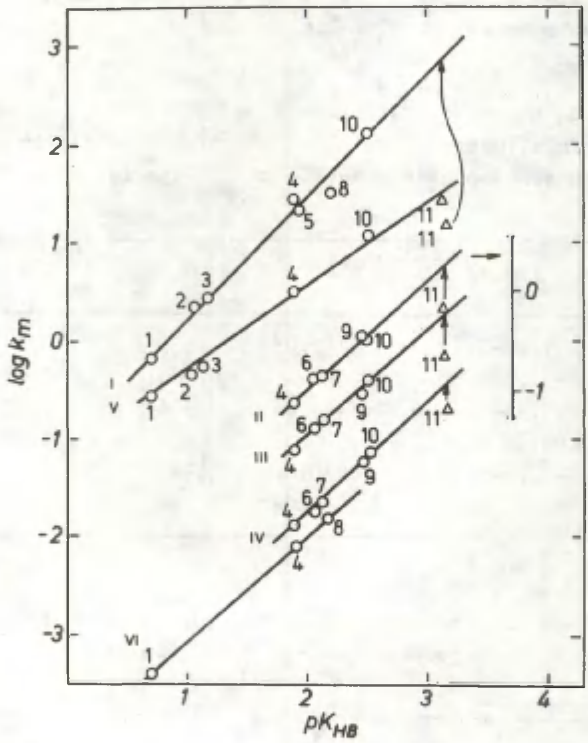


Fig. 1. Dependence of log k_m for reactions of compounds (I)-(VI) catalyzed by various bases with piperidine in benzene. Point numbers correspond to those in Table 2.

parameters of (2) are given in Table 4. It follows from those data that the α values do not actually depend on the catalyst chosen. The sensitivity value of α exceeds more than twice that of the noncatalytic process. Consequently, at the transition to the catalytic process the sensitivity of the leaving group substrate to the formation of hydrogen bond tends to increase.

Table 3

Parameters of Correlation Equation (4) for Catalytic Reactions of Compounds (I)-(VI) with Piperidine

Compound	log k_m^o	ß	R	s
I	-1.00±0.12	1.21±0.07	0.993	0.11
II	-3.22±0.03	1.23±0.15	0.980	0.08
III	-3.33±0.13	1.14±0.05	0.996	0.03
IV	-4.48±0.14	1.33±0.06	0.992	0.05
V	-1.21±0.16	0.88±0.06	0.992	0.12
VI	-4.42±0.13	1.21±0.08	0.998	0.08

Table 4

Parameters of Correlation Equation (2).for Catalytic Reactions of Compounds (I)-(VI) with Piperidine

Catalyst	log k_X^o	α	R	s
DMSO	-6.69±0.76	8.50±1.05	0.985	0.309
Pyridine*	-6.72±0.79	8.55±1.09	0.984	0.321
Piperidine	-6.23±0.77	9.31±1.08	0.987	0.343
Triphenyl-phosphin-oxide	-3.21±0.75	4.58±0.54	0.974	0.221

* On the basis of the data of this equation we have calcu-

lated the pK_{ass} values for (VI), which is equal to 0.545.

The analysis of the data of Tables 3 and 4 leads us to the consideration that the catalytic constants studied obey multi-parameter equation (5) taking into account the additive contribution of the structural parameters of substrates (I)-(IV), (VI) and the catalysts.

$$\log k_m = A_0 + A_1 \cdot pK_{ass} + A_2 \cdot pK_{HB} \qquad (5)$$

The numeric values of the parameters of this equation in both natural and normed scales are given in Eqs. (6) and (7)

$$\log k_m = (-8.93 \pm 0.31) + (8.24 \pm 0.28) pK_{ass} + (1.24 \pm 0.08) pK_{HB} \qquad (6)$$

$$s = 0.210 \qquad R = 0.987$$

$$\log k_m = (-8.06 \pm 0.57) + (1.04 \pm 0.03) pK_{ass} + (0.51 \pm 0.03) pK_{HB} \qquad (7)$$

$$s = 0.157 \qquad R = 0.988$$

Statistical parameters of Eq. (6) confirm its firmness, while the coincidence of the A_1 and A_2 with parameters α and β (Tables 3 and 4) refer to the validity of Eq. (5). Eq. (7) enabled us to draw conclusions about the prevalence of the contribution of hydrogen bond with the leaving group.

Since the pK_{ass} for Br-, Cl- and I -derivatives have but insignificant differences (Table 1), the quantitative estimation of the formation of hydrogen bond with the leaving group was based on the equation of type (4). The pK_{HB} of tetrabutylammonium halogenides were equal to[15] $I^- = 2.52$, $Br^- = 3.27$, $Cl^- = 3.60$, $F^- = 5,86^*$, yet remarkably differing in their values. In this case the numeric values of correlation equations in natural and normed scales are as follows:

$$\log k_m = (-6.66 \pm 0.25) + (0.97 \pm 0.03) pK_{HB(\overset{+-}{NX})} + (1.17 \pm 0.08) pK_{HB}$$

$$s = 0.152 \qquad R = 0.992 \qquad (8)$$

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* Calculated from relationship $pK_{HB(\overset{+-}{NX})} = 5.09 + 0.22 pK_{a(X^-, H_2O)}$

$$\log k_m = (-6.04\pm0.23)+(1.17\pm0.35)pK_{HB(\overset{+-}{NX})}+(0.51\pm0.04)pK_{HB}$$
$$s = 0.138 \qquad -R = 0.992 \qquad (9)$$

As it was expected, the parameters of Eqs. (6)-(9) agree well with each other, thus confirming the correctness of the application of parameters pK_{ass} and $pK_{HB(\overset{+-}{NX})}$ to estimate the role of the participation of leaving group in the formation of H-bond in the processes studied.

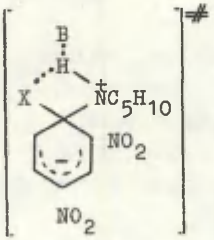
We should also like to dwell upon the nature of catalysis by the second molecule of the amine in the reactions studied. The α value for relationship (2) of its catalysis by piperidine (Table 4) is identical with other bases which do not have any active hydrogen atom. On the other hand, the pK_{HB} values for piperidine, equalling 2.95 were calculated on the basis of the data of Table 3. The catalysis by the second molecule of piperidine in the studied processes does not differ from other organic compounds. Consequently, in these catalytic processes pyridine participates as the monofunctional basic catalyst. Analogous basic character of the catalysis by the second molecule of amine in the reactions of nucleophilic aromatic substitution has also been revealed in the cases of participation of butyl amine[9] and aniline[17].

As concerns the catalysis by piperidine (Table 1), we noticed a rather strong isotope effect during the substitution of deuterium for the hydrogen atom of NH-group. For the fluoro-derivative of the substrate, the primary KIE value reaches 11.8. This permits us to consider that in the case of the catalysis of these reactions by some other bases, proton transfer takes place in the rate-determining stage.

The results of the present paper as well as the literature data characterizing similar kinetic processes[5-7,18-19] make us consider that the decomposition of the σ-complex can proceed via the transition state (VII b).

The role of base B in the decomposition of the zwitterionic complex stands in the creation of the cyclic transiti-

on state, including the atom of hydrogen, coordinated with three atoms - the X leaving group, catalyst B and the nitrogen atom of attacking nucleophile, i.e., piperidine. The afore-said is in keeping with the sensitivity to the formation of hydrogen bond with the leaving group, catalyst and data of the primary KIE.



(VII b)

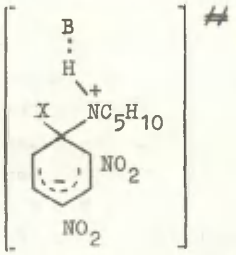
The alternative mechanism for catalytic processes in nucleophilic substitution suggested by Bunnett[20] is hardly applicable here, since its realization is possible in strongly polar media mainly. On the other hand, in this case one might expect not only the dependence of catalytic reaction series on the pK_{HB} of bases but also on the pK_a which is responsible for a full proton transfer. But the latter dependence was not found. One can presume that for the processes studied here Bannett's mechanism is realizable only in the protoinert nonpolar medium, provided that the basicity of the catalyst is at least by one order higher than that of the nucleophile (piperidine). In such a case a full proton transfer from the zwitter-ionic complex onto the catalyst and the consequtive formation of the BH^+ are highly probable. The phenomenon has been observed in the case of picrylfluoride reaction with aniline[17], catalyzed by the organic compounds whose basicities exceed that of the nucleophile - aniline.

Triphenylphosphine oxide having the largest pK_{HB} value has got a special importance among the catalysts studied. According to Eq. (4) the catalytic constants of this base are smaller than expected (Fig. 1) and the α values are also much lower than those for the sensitivity of the other ca-

talysts studied here. The causes of this stand probably in the spoilt additivity (Eq. (5)) in the border zone of transition into the isoparametric correlation (10) including the cross-effect of the structural factors of the leaving group and catalyst.

$$\log k_m = A_0 + A_1 \cdot pK_{ass} + A_2 \cdot pK_{HB} + A_3 \cdot pK_{ass} \cdot pK_{HB} \qquad (10)$$

The catalysts having high pK_{HB} values, e.g., triphenyl phosphine oxide, can like the cyclic form of transition state (VII b) realize a less reactive flow with transition state (VII c) in which leaving group X being competitive with base B for the hydrogen atom separates without any electrophilic contribution.



(VII c)

If the catalysis is carried out by such bases, the contribution of the catalytic flow via the cyclic transition state (VII b) can diminish owing to the realization of the catalytic flow via the noncatalytic state (VII c) which is connected with their affinity to the hydrogen bond formation. In the case of triphenylphosphine oxide the α sensitivity to the formation of hydrogen bond with the leaving group decreased twice.

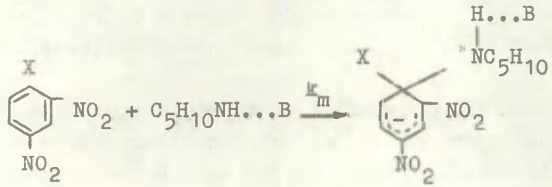
For the substrate's benzene-sulfonate derivative the sensitivity to parameter pK_{HB} is less than 1, equalling 0.88. Consequently, the level of proton transfer to the catalyst for reaction (V) is different, which actually refers to the different catalysis mechanism.

If we take into consideration that in the case of the reactions of compounds (V) with piperidine, the formation of

б-complex appears to be the limiting stage, the catalysis can be observed in this stage only, i.e., the very stage s should be accelerated by the catalyst used. Base B takes part in the equilibrium formation of the hydrogen-bonded associate with nucleophile

$$C_5H_{10}NH + B \xrightarrow{K_p} C_5H_{10}NH \ldots B \qquad (11)$$

having stronger nucleophility than the initial amine, since the electron density is localized on the nitrogen atom; thus it results in the acceleration of the б-complex formation that can be estimated by product $K_p \cdot K_m$ (in the case of the changes taking place by stages) which is rather close to or exceeds that of the noncatalytic reaction. The scheme of the catalytic route is as follows:



(12)

The fact that triphenyloxide falls onto a common relationship log k_m - pK_{KB} (Fig. 1) agrees with the mechanism suggested.

This mechanism can be classified as an associative one in the framework of the general basic mechanism. Evidently, it can be realized also in the case of the leaving group with a strong tendency towards separation. In our case this is the benzene sulfonate group.

Experimental

2,4-Dinitroderivatives of benzene were synthesized and purified according to methods[3]; benzene piperidine and organic catalysts according to those described in[21]. N-Deuteropiperidine was obtained like in handbook[13]. The content of deuterated amine was determined according to the IR-spectra

and it formed 96 %.

Reaction rate was measured in the conditions of pseudo-first order towards the substrates whose concentration was $5 \cdot 10^{-5}$ mol·l^{-1} in all experiments. Catalytic constants measurements were carried out at the following concentrations of piperidine: (I) - $2{,}5 \cdot 10^{-3}$, (II)-(IV) - $2.5 \cdot 10^{-2}$, (V) - $1.25 \cdot 10^{-3}$ mol·l^{-1}. The concentration intervals of catalysts: (I) - pyridine, triethylamine $(2.5 \div 13.3)10^{-3}$, dioxane, acetone $(0.1 \div 0.2)$, dimethylsulfoxide $(0.5 \div 2.25)10^{-3}$, ethylacetate $0.03 \div 0.125$, piperidine $(1.0 \div 2.5)10^{-3}$, triphenylphosphine oxide $(0.6 \div 2.5)10^{-2}$ mol·l^{-1}; for (II)-(IV) - pyridine $0.34 \div 1.67$, 2,4-dimethylpyridine, dimethylsulfoxide, diethylacetamide $0.1 \div 05$, dimethylformamide $0.5 \div 2.5$, piperidine $(2.5 \div 7.0)10^{-2}$, triphenylphosphine oxide $(2.0 \div 9.0)10^{-2}$ mol·l^{-1}; for (V) - pyridine $0.1 \div 0.4$, dioxane $1.0 \div 2.0$, dimethylsulfoxide $(1.26 \div 6.3)10^{-2}$, acetone, ethyl acetate $0.5 \div 2.0$, piperidine $(1.25 \div 5.0)10^{-3}$, triphenylphosphine oxide $(0.6 \div 2.5)10^{-2}$ mol·l^{-1}.

The reaction was controlled on a spectrophotometer SF-16 on the basis of the accumulation of tertiary amine of 1-piperidino-2,4-dinitrobenzene, at 375 nm; the cell thickness was 1cm.

Rate constants of pseudofirst order were calculated as follows:

$$k = \frac{1}{t} \ln \frac{D_\infty - D_o}{D_\infty - D_t} \qquad (13)$$

where D_∞, D_o, D_t are the optical densities of the solution by the termination of the reaction, at the beginning of the reaction and at time moment t, respectively.

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REACTIVITY OF DERIVATIVES OF PHENYLANTHRANILIC ACID. VIII. KINETICS OF ALKALINE HYDROLYSIS OF 2^1-DERIVATIVES OF ß-DIMETHYLAMINOETHYL ESTER OF 4-CHLORO-N-PHENYLANTHRANILIC ACID IN BINARY DIOXAN-WATER SOLVENT

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Kinetics of alkaline hydrolysis of 2^1-derivatives of ß-dimethylaminoethyl ester of 4-chloro-N-phenylanthranilic acid in water-dioxan mixture (60 vol % of dioxan) in temperature range of 298-358 K has been studied. Bimolecular constants of reaction rate have been found. Thermodynamic activation parameters have also been determined. Substituent effects of ester molecule on obtained parameters have been discussed. It has been established that the reaction series obeys the Hammett equation. Isokinetic character of the reaction is shown. By the method of multiple regression analysis the multi-parameter equation is found describing the influence of σ-constants of substituents and experiment temperature for ß-dimethyl, as well as that of ß-diethylaminoethyl esters of 4-chloro-N-phenylanthranilic acid.

We have already studied the kinetics of alkaline hydro-

lysis of 4[1]-derivatives of ß-dimethylaminoethyl ester of 4-chloro-N-phenylanthranilic acid[1]. Our interest was to investigate the effect of ortho-substituents in the nonanthranilic fragment of a molecule on the kinetic parameters of alkaline hydrolysis.

The bimolecular reaction rate constants were calculated from the variation of sodium hydroxide concentration in time by means of potentiometric titration. The methods of kinetic measurements are analogous[1].

The reaction series studied obeys the kinetic equation of second order:

$$\frac{dx}{dt} = k(a-x)(b-x) \qquad (1)$$

where a,b - initial concentrations of ester and alkali (mol/l) at time moment t (s);
x - current concentration of reaction product (mol/l) at time moment t (s);
k - reaction rate constant (l/mol·s).

The integrated version of the equation is:

$$k = \frac{1}{t(b-a)} \ln \frac{a(b-x)}{b(a-x)} \qquad (2)$$

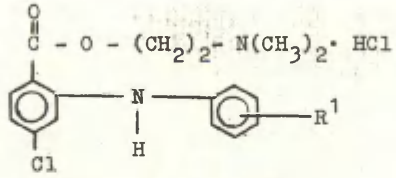
permitting to calculate the value of k at time moment t.

The obtained k value is corrected for the volume expansion of the solvent at the experiment's temperature (it changes from 25°C to t°) multiplying it by factor $\tau = d_{25}/d_t$, where d_{25}, d_t denote the densities of the binary solvent dioxan-water at 25°C and t°C.

The reaction rate constants were calculated according to Eq. (2). The changes in the concentrations of the ester and the nucleophile do not bring about any change of the bimolecular reaction rate constant value in the range of the experimental error, thus referring to the total second order, the first order in nucleophile and in substrate.

Table 1

2^1-Derivatives of ß-Dimethylaminoethyl Ester
of 4-Chloro-N-phenylanthranilic Acid



R^1	Melting point °C	% N found	Empirical formula	% N calculated	Rf
2^1- Cl	80-81	7.3	$C_{17}H_{19}Cl_3N_2O_2$	7.1	0.61
2^1- CH_3	121-122	7.6	$C_{18}H_{22}Cl_2N_2O_2$	7.5	0.65
2^1- OCH_3	141-142	7.4	$C_{18}H_{22}Cl_2N_2O_2$	7.2	0.63

Table 2

Rate Constants of Alkaline Hydrolysis of 2^1-Derivatives of β-Dimethylaminoethyl Ester of 4-Chloro-N-Phenylanthranilic Acid in Dioxan-Water Mixture at Different Temperatures

T,K \ R^1	$k \cdot 10^4$, $l \cdot mol^{-1} s^{-1}$			
	H	2^1-Cl	2^1-CH_3	2^1-OCH_3
298	2.35 ± 0.06*	4.13 ± 0.10	1.39 ± 0.04	0.73 ± 0.03
308	3.66 ± 0.03*	6.28 ± 0.08	2.28 ± 0.06	1.25 ± 0.06
318	6.05 ± 0.07*	10.57 ± 0.11	3.87 ± 0.09	2.13 ± 0.08
328	10.3 ± 0.07*	16.66 ± 0.17	6.77 ± 0.05	3.96 ± 0.12
338	16.9 ± 0.12*	26.38 ± 0.09	11.34 ± 0.11	6.86 ± 0.06
348	26,4 ± 0.11*	40.24 ± 0.21	18.17 ± 0.09	11.33 ± 0.21
358	40.6 ± 0.24*	59.57 ± 0.24	28.15 ± 0.16	18.04 ± 0.09

* from Ref.[1]

Table 3

Parameters of the Hammett Equation for 2[1]-Derivatives of
ß-Dimethylaminoethyl Esters of 4-Chloro-N-Phehylanthranilic Acid

$$\log k = \log k_o + \rho\sigma$$

T,K	ρ	$\log k_o$	r	S
298	1.276±0.032	-3.635±0.024	0.9936	0.0221
308	1.188±0.028	-3.433±0.021	0.9984	0.0249
318	1.117±0.037	-3.201±0.034	0.9944	0.0358
328	1.054±0.044	-2.989±0.017	0.9981	0.0183
338	0.987±0.025	-2.772±0.027	0.9958	0.0197
348	0.932±0.036	-2.582±0.028	0.9942	0.0317
358	0.880±0.083	-2.392±0.012	0.9931	0.0219

The introduction of an acceptor substituent (see Table 2) accelerates the reaction. This is connected with the stabilization of the acid's anion owing to a more remarkable delocalization of its charge. Donor substituents are decreasing the reaction rate.

The comparison of the data of Table 2 and those published in [2] lead us to the conclusion that the replacement of the CH_3 radical by the C_2H_5 radical in the alcoholic fragment of ester within the experiment error does not influence the value of the reaction rate constant. We can, probably, explain it with the isolating effect of the $-CH_2-CH_2-CH_2$ group[3]. This statement confirms the suggestion expressed already in Ref. [2] that the reaction proceeds according to the $B_{AC}2$ mechanism:

$$R\text{-}\overset{\overset{O}{\|}}{C}\text{-}OCH_2CH_2N(R_1)_2 + OH^- \rightleftharpoons R\text{-}\overset{\overset{O^-}{|}}{\underset{\underset{OH}{|}}{C}}\text{-}OCH_2CH_2N(R_1)_2$$

$$P\text{-}\overset{\overset{O^-}{|}}{\underset{\underset{OH}{|}}{C}}\text{-}OCH_2CH_2N(R_1)_2 \rightleftharpoons R\text{-}\overset{\overset{O}{\|}}{C}\text{-}OH + (R_1)_2NCH_2CH_2O^- \longrightarrow$$

$$\longrightarrow R\text{-}\overset{\overset{O}{\|}}{C}\text{-}O^- + (R_1)_2NCH_2CH_2OH$$

The dependence of the reactivity of the substrate on the substituent's nature in the nonanthranilic molecule fragment can be assessed by the Hammett equation (Table 3):

$$\log k = \log k_o + \rho\sigma \qquad (3)$$

The value of reaction constant ρ for the ester derivatives is positive, which also confirms the $B_{AC}2$ reaction mechanism. A rather low ρ value refers to a weak sensitivity of the reaction center to the substituent effect in the ortho position. If the temperature rises, ρ will decrease, and thus makes the electron system of the molecule less sensitive to the substituent effect.

For the 2[1]-derivatives of ß-dimethylaminoethyl ester of

Table 4

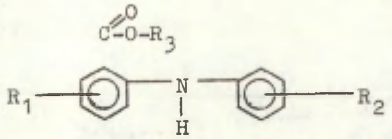
Parameters of the Hammett Equation for $2^1,4^1$-Derivatives of ß-Dimethyl- and ß-Diethylaminoethyl Esters of 4-Chloro-N-Phenylanthranilic Acid

$$\log k = \log k_o + \varrho\sigma$$

T,K	ϱ	$\log k_o$	r	S
298	1.275±0.042	-3.634±0.026	0.9931	0.0247
308	1.190±0.060	-3.328±0.061	0.9958	0.0316
318	1.118±0.054	-3.206±0.053	0.9938	0.0307
328	1.054±0.048	-2.987±0.041	0.9951	0.0231
338	0.989±0.031	-2.773±0.028	0.9932	0.0261
348	0.933±0.044	-2.583±0.019	0.9921	0.0346
358	0.881±0.094	-2.396±0.087	0.9917	0.0351

Table 5

Parameter π for Esters of Phenylanthranilic Acids



N	R_1	R_3	ρ RCOOH	ρ ester at 318 K	π
1	4-Cl	$-(CH_2)_2N(CH_3)_2$	0.73[7]	1.117	0.654
2	4-Cl	$-(CH_2)_2N(C_2H_5)_2$	0.73[7]	1.118[2]	0.653
3	4-NO_2	$-CH_3$	0.73[7]	1.110[4]	0.658
4	4-Cl-5-NO_2	$-CH_3$	0.73[7]	1.104[5]	0.661

Table 6

Kinetic Aotivation Parameters (E_A and ln A) of Alkaline Hydrolysis of 2[1]-Derivatives of ß-Dimethylaminoethyl Ester of 4-Chloro-N-Phenylanthranilic Acid

R_1	E_A kcal/mol	ln A	r	S
H	10.24±0.16[1]	8.86±0.39[1]	0.9990[1]	0.0041[1]
2[1]-Cl	9.02±0.08	7.83±0.21	0.9934	0.0071
2[1]-CH_3	10.86±0.11	9.31±0.16	0.9947	0.0052
2[1]-OCH_3	11.02±0.14	9.28±0.07	0.9981	0.0063

4-chloro-N-phenylanthranilic acid, the ρ value is identical to that of 4^1-derivatives of the same ester[1] and of the $2^1,4^1$-derivatives of ß-diethylaminoethyl ester of the same acid[2]. Proceeding from that, it was possible to find a common Hammett equation for both $2^1,4^1$-derivatives of ß-dimethyl- and ß-diethylaminoethyl esters of 4-chloro-N-phenylanthranilic acid (Table 4).

It should also be mentioned that ρ values for the derivatives studied and for the methyl esters of 4-nitro- and 4-chloro-5-nitro-N-phenylanthranilic acids[4,5] are rather close, which confirms the common mechanism of alkaline hydrolysis of those compounds. The sama is expressed by the value of parameter π[6] (Table 5), calculated by Eq. (4):

$$\pi = \frac{\rho R\text{-}COOH}{\rho R\text{-}COOS} \qquad (4)$$

The present reaction series obeys the Arrhenius equation. Thus, it was possible to calculate activation energy E_A and pre-exponential factor A (Table 6).

The introduction of the electron-acceptor substituent makes the E_A value drop, while the use of electron-donor substituents has the opposite influence. Changes in ln A are similar to those of E_A. Changes in ln A are similar to those of E_A. Relationships $E_a = A + B\sigma$, $\ln A = C + D\sigma$ are not statistically reliable.

The enthalpies ($\Delta H^{\neq}$) and entropies ($\Delta S^{\neq}$) of activation have been calculated according to the Eyring equation (see Table 7):

$$\ln \frac{k}{T} \cdot \frac{h}{K} = \frac{\Delta S^{\neq}}{R} - \Delta H^{\neq} \cdot \frac{1}{RT} \qquad (5)$$

Free activation energy ($\Delta G^{\neq}$) was found by the second law of thermodynamics (Table 7).

Negative activation entropy value also proves the $B_{AC}2$ mechanism of the reaction studied. High absolute values of activation entropy have probably been caused by the form-

Table 7

Thermodynamic Activation Parameters of Alkaline Hydrolysis of 2^1-Derivatives of ß-Dimethylaminoethyl Esters of 4-Chloro-N-Phenylanthranilic Aoid

R_1	$\Delta H^{\neq}$ kcal/mol	$-\Delta S^{\neq}$ e.u.	r	S	$\Delta G^{\neq}$ 298 kcal/mol
H	9.59±0.15[1]	43.1±0.4[1]	0.9989[1]	0.0042[1]	22.4[1]
2^1-Cl	8.37±0.26	45.5±0.8	0.9954	0.0084	21.9
2^1-CH_3	10.17±0.51	42.0±1.1	0.9967	0.0103	22.7
2^1-OCH_3	10.74±0.34	41.3±0.9	0.9969	0.0061	23.0

Table 8

Determination of Isokinetic Temperature.
Correlation Parameters of Eqs. y=a+bx of Dependences of Kinetic and Activation Parameters of Alkaline Hydrolysis of 2'-Derivatives of ß-Dimethylaminoethyl Ester of 4-Chloro-N-Phenylanthranilic Acid

x	y	a	b	r	S	ß,K
$\log k_{298}$	$\Delta H^{\neq}$	$(0.394\pm0.037)\cdot10^3$	$(-2.49\pm0.04)\cdot10^3$	0.9947	0.0071	658
$\log k_{308}$	$\Delta H^{\neq}$	$(0.398\pm0.021)\cdot10^3$	$(-2.70\pm0.07)\cdot10^3$	0.9941	0.0024	644
$\log k_{318}$	$\Delta H^{\neq}$	$(0.417\pm0.027)\cdot10^3$	$(-2.84\pm0.06)\cdot10^3$	0.9983	0.0048	652
$\log k_{328}$	$\Delta H^{\neq}$	$(0.527\pm0.017)\cdot10^3$	$(-3.02\pm0.06)\cdot10^3$	0.9962	0.0051	652
$\log k_{338}$	$\Delta H^{\neq}$	$(0.634\pm0.043)\cdot10^3$	$(-3.23\pm0.05)\cdot10^3$	0.9910	0.0036	649
$\log k_{348}$	$\Delta H^{\neq}$	$(0.743\pm0.029)\cdot10^3$	$(-3.43\pm0.04)\cdot10^3$	0.9947	0.0027	650
$\log k_{358}$	$\Delta H^{\neq}$	$(0.846\pm0.034)\cdot10^3$	$(-3.62\pm0.09)\cdot10^3$	0.9939	0.0033	654
$\Delta S^{\neq}$	$\Delta H^{\neq}$	$(38.4\pm0.6)\cdot10^3$	646 ± 21	0.9947	0.193	646
log A	E_A	-1.084 ± 0.029	296 ± 16	0.9934	0.186	682
1/T	ϱ	-1.088 ± 0.063	706 ± 11	0.9961	0.084	649

$\bar{B}$=654

Table 9

Determination of Isokinetic Temperature
According tc Eq. $\log k_{T_2} = \text{const} + x \log k_{T_1}$, $T_2 > T_1$

$$x = \frac{(T_1 - ß)T_1}{(T_2 - ß)T_2}$$

Temperature, K		x	r	S	ß,K
T_1	T_2				
298	318	0.884	0.9981	0.0077	649
298	338	0.790	0.9944	0.0096	683
298	358	0.693	0.9932	0.0041	656
318	338	0.884	0.9963	0.0132	652
328	358	0.783	0.9947	0.0117	654
338	358	0.885	0.9971	0.0139	658

ß = 658.5

Table 10

Values of Parameters of Eq. (6) and Isoparametric Values (IPV) of Parameters to be Correlated

Variables	Parameters	Numeric values of parameters	IPV	S	R
	$\log k_o$	3.840 ± 0.023	$B = 638$	0.0187	0.997
σ	a_1	-1.128 ± 0.046	$x_1 = 3.11$		
$T^{-1} \cdot 10^3$	a_2	-2.237 ± 0.043	$x_2 = 1.57$		
$\sigma T^{-1} \cdot 10^3$	a_{12}	0.720 ± 0.027			

Table 11

Values of Parameters of Eq. (6) and Isoparametric Values (IPV) of the Parameters to be Correlated for Alkaline Hydrolysis of $2^1,4^1$-Derivatives of ß-Dimethyl- and ß-Diethylaminoethyl Esters of 4-Chloro-N-Phenylanthranilic Acids

Variables	Parameters	Numeric values of parameters	IPV	S	R
	$\log k_o$	3.798 ± 0.021	ß=641	0.0218	0.996
σ	a_1	-1.114 ± 0.037	$x_1=3.12$		
$T^{-1}.10^3$	a_2	-2.221 ± 0.035	$x_2=1.56$		
$\sigma T^{-1}.10^3$	a_{12}	0.713 ± 0.024			

ation of a highly symmetrical intermediate, but the insignificant $\Delta H^{\neq}$ values by the synchronism of the reaction. The decrease in the $\Delta H^{\neq}$ values makes the absolute value of $\Delta S^{\neq}$ rise, thus permitting us to expect the existence of an isokinetic relationship. In order to check the validity of the supposition, we analyzed the reaction series according to the known tests[3]:

$$\Delta H^{\neq} - \log k_{T_i}, \quad \Delta H^{\neq} - \Delta S^{\neq}, \quad E_A - \log A, \quad \rho - T^{-1}$$

using pattern $y = a + bx$.
Calculated values of pair correlations are given in Table 8.

The values of isokinetic temperature ß in Table 8 coincide with those found using other methods[3] (Table 9).

The value ß for the reaction series studied is quite close to the ß for the alkaline hydrolysis of 4^1-derivatives of the ß-dimethyl- and $2^1,4^1$-derivatives of ß-diethylaminoethyl esters of 4-chloro-N-Phenylanthranilic acid[1,2], as well as for methyl esters of 4-nitro- and 4-chloro-5-nitrophenylanthranilic acids[4,5]. This is also confirmed by the common mechanisms of those reactions. ß stands out of the experimental temperature range, i.e., ethalpic control probably functions here.

The obtained results have been treated applying the polylinearity principle by a multiparameter equation which takes into account the effect of б-constants of substituents and temperature (Table 10):

$$\log k = \log k_o + a_1 б + a_2 \cdot T + a_{12} б \cdot T^{-1} \qquad (6)$$

Closeness of values of the parameters of Eq. (6) for the compounds studied and 4^1-derivatives of ß-dimethyl- and $2^1,4^1$-derivatives of ß-diethylaminoethyl esters of 4-chloro-N-phenylanthranilic acid, enabled us to derive a general multiparameter equation (6), describing those three reaction series (Table 11).

Experimental

Reagents. The purification of solvents and testing of their purity levels have been described in[1]. ß-dimethylesters of 4-chloro-N-phenylanthranilic acids were synthesized using known methods[7,8]. Compounds' purity was tested in system propanol-water 1:1 by means of element analysis (Table 1). The solution of sodium hydroxide which did not contain any carbonates was prepared in keeping with methods[9].

Kinetic measurements have been described in[1]. Changes in the sodium hydroxide concentration depending on the duration of the reaction were determined by means of potentiometric titration on a pH-meter EV-74 with glass ESP-43-074 and chlorosilver EVL-1M electrodes. The aqueous solution of HCl was used as the titrant. Linear correlations were calculated on a computer Elektronika MK-52, using standard programs[10]. Multiparameter equation (6) was calculated on a EC-1045 computer.

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EFFECT OF LIGAND VOLUME ON AFFINITY OF MUSCARINIC ANTAGONISTS

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The applicability of hydrophobicity constants log P and molar refractivity parameters MR in QSAR for muscarinic ligands is compared on the basis of binding data for a series of classical muscarinic antagonists. These compounds involve esters, ethers and alkylammonium ions. It has been found that the molecular refractivity parameters give a common linear dependence of pK_d upon MR for all of these types of ligands, except benzilic and tropic acid esters, for which the mechanism of the receptor-ligand interaction is different from all other ligands. In the case of hydrophobicity parameters the reaction series is split into subgroups reflecting their different chemical structure.

Proceeding from the structure of acetylcholine molecule important role of the structural fragment NCCOCC has been postulated for muscarinic ligands[1-5], including both agonists and antagonists of this receptor. As a rule the ligands of the latter type possess extra bulky substituents at the both ends of the NCCOCC backbone. The influence of these apolar fragments on binding affinity pK_d of ligands has been quantified by means of the hydrophobicity constants log P[6,7] :

$$pK_d = c + \gamma \cdot \log P \quad . \qquad (1)$$

For several groups of muscarinic antagonists these studies

have revealed linear correlations between the pK_a and log P values yielding similar slopes f but different intercepts c[6,7]. As a rule these subseries of antagonists involve different polar groups or different number of electronegative atoms in ligand molecule. This means that there are two possible explanations of the different intercepts found from Eqn (1). Firstly, Tropsha et al[7] took this as an indication of different binding modes of muscarinic antagonists to the receptor site. On the other hand, however, the similar slopes of pK_a vs log P plots were taken as evidence for the common mechanism of hydrophobic binding of ligands[6], and thus the different intercept values can be related to different solvation effects on processes of ligand binding to receptor site and the partition of the ligands between water and octanole used as the reference system for determining the hydrophobicity parameters.

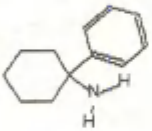
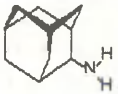
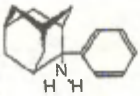
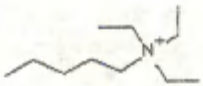
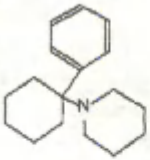
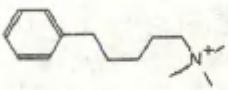
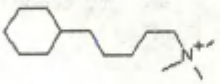
In the present analysis the mechanism of the antagonist binding to muscarinic receptor is further analyzed by making use of the molecular refractivity parameters MR, which also characterize the "bulkiness" of ligand molecule, but differently from the log P values do not reflect the solvation effects of the polar groups in their structure.

DATA AND METHODS

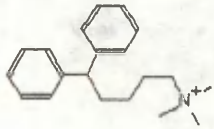
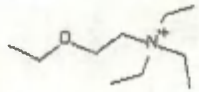
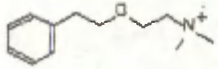
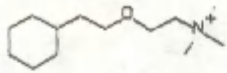
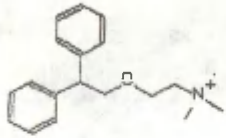
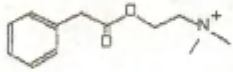
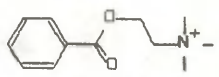
The Table contains the binding data for muscarinic antagonists compiled from literature and used for the present analysis. Besides the ammonium group these compounds involve ester or ether groups or are simple alkylammonium salts without polar moieties. The log P values for these ligands were calculated according to the additive scheme by making use of the Rekker fragmental constants[8,16] and the PRO LOGP program ver. 2.0 from CompuDrug LTD (Budapest). As all the compounds used in the following analysis involve quaternary nitrogen atom at pH 7.5, its contribution was not taken into account and thus all calculated log P'-constants are equally shifted relatively to the actual log P values for ligands.

The MR values were calculated by means of the same program and the fragmental constants published by Hansch et al[16].

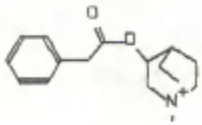
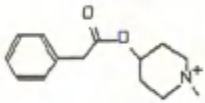
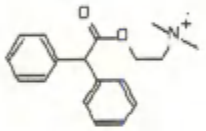
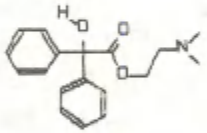
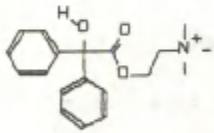
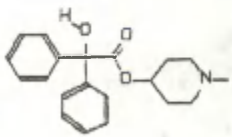
Table.
The set of muscarinic antagonists used for QSAR.

No	Ligand	pK_d	log P'	MR	Ref.
1.		3.53	4.95	58.5	9
2.		3.57	4.64	48.5	9
3.		4.45	6.48	72.8	9
4.		4.59	5.73	59.3	10
5.		5.04	7.19	79.6	9
6.		5.18	6.54	69.8	10
7.		5.39	7.63	71.2	10

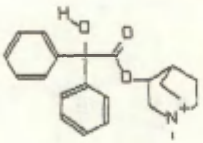
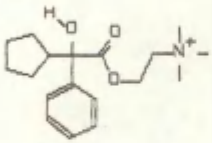
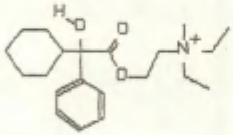
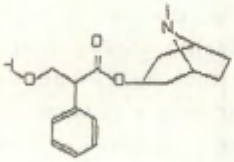
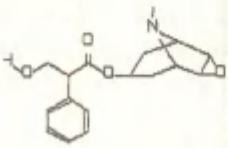
Continuation of Table

No	Ligand	pK_a	log P'	MR	Ref.
8.		7.03	8.53	94.0	9
9.		7.02	8.22	94.1	10
10.		3.97	4.32	56.9	10
11.		4.70	4.43	67.3	10
12.		5.28	5.53	68.8	10
13.		6.41	6.11	91.6	10
14.		5.34	4.25	67.7	11
15.		5.43	4.60	63.0	11

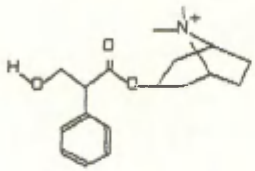
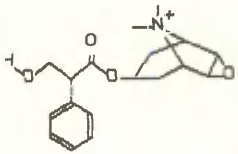
Continuation of Table

No	Ligand	pK_a	log P'	MR	Ref
16.		5.80	5.08	77.5	12
17.		6.34	4.91	74.9	12
18.		7.20	5.92	92.0	12
19.		8.02	3.74	88.9	13
20.		8.64	4.25	93.5	13
21.		9.40	4.41	96.1	14

Continuation of Table.

No	Ligand	pK_a	log P'	MR	Ref.
22.		9.89	5.08	103.3	13
23.		8.07	4.83	90.3	13
24.		9.58	6.38	104.3	15
25.		9.70	3.94	83.6	13
26.		9.85	1.97	83.7	13

Continuation of Table.

No	Ligand	pK_d	log P'	MR	Ref.
27.		9.96	4.46	88.2	13
28.		10.1	2.50	88.3	14

RESULTS AND DISCUSSION

The parameters log P' and MR for the set of antagonists used in the present analysis are plotted in Fig 1. It can be seen that the ligands were split into different subgroups reflecting the negative hydrophobicity increments for -COO- and -O- groups which were used for calculating the log P' values. Thus there exists no simple correlation between the log P' and MR values for the present reaction series. The latter fact allows differentiation between the hydrophobicity and volume effects on antagonist binding to muscarinic receptor.

The values of pK_a for muscarinic antagonists are plotted against log P and MR in Figs.2 and 3. It can be seen that a common linear relationship was obtained for alkylammonium ions, ethers and esters if the MR constants are used to characterize the ligand structure:

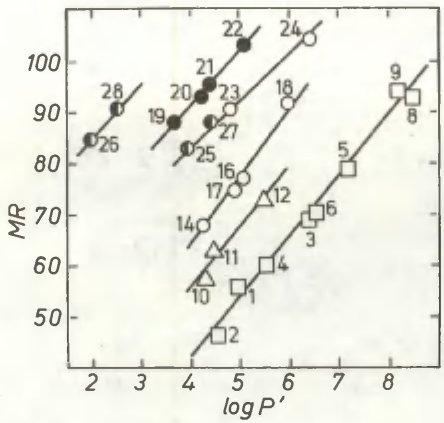


Fig.1. Plot of MR versus log P' for the set of muscarinic antagonists used for QSAR. Data from Table 1, □ -alkylammonium ions, △ -ethers, ● -benzilates, ◐ -tropates, ○ -other esters.

$pK_d = c' + \psi MR$ (2)

where $c' = -0.3 \pm 0.6$ and $\psi = 0.077 \pm 0.008$ (correlation coefficient 0.913). Benzilic and tropic acid esters deviate from this linearity, showing either larger or smaller slopes $\psi = 0.12 \pm 0.03$ (correlation coefficient 0.947) and 0.048 ± 0.005 (correlation coefficient 0.990), respectively.

Differently from the data shown in Fig.2 the plot of pK_d against log P gives several parallel linear dependences, as identified in the previous reports[6,7]. The changes in the intercept c in Eqn (1) are proportional to the negative fragmental constants for the polar functional groups of the ligands. Thus a conclusion can be drawn that the affinity of muscarinic antagonists is governed by the volume of the ligand molecules rather than by their hydrophobicity, quantified by the constants log P. That also means that the splitting of the pK_d versus log P plot into different parts cannot be regarded as evidence of different binding modes of these ligands because

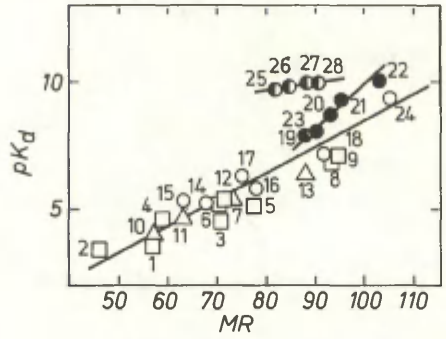


Fig.2. Plot of pK_d versus MR for muscarinic antagonists listed in Table. Definition of points is given in the Legend to Figure 1.

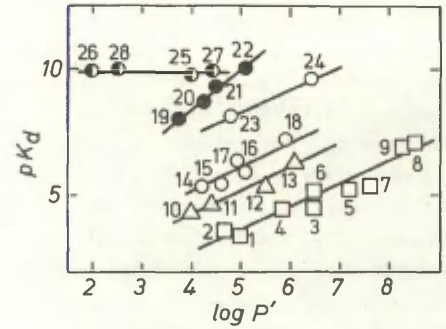


Fig.3. Plot of pK_d versus log P for muscarinic antagonists listed in Table. Definition of points is given in the Legend to Figure 1.

this phenomenon is due to the disparate log P values for esters, ethers and alkylammonium ions.

The benzilic esters involved in the present analysis are characterized by a steeper plot of pK_d versus log P', as has been shown previously[6]. The similar phenomenon can also be followed in Fig. 2 where the plot of pK_d versus MR is given. The latter fact confirms the idea of different mechanisms governing the interaction of these ligands with the receptor site in comparison with the rest of the reaction series.

Another deviation of the affinity data from the general correlation for the pK_d values is revealed in the case of esters of tropic acid. In spite of the variations in "bulkiness" of these ligands these pK_d values are quite similar pointing to the absence of the appropriate structural effect. It is noteworthy that similar phenomenon can be observed in the QSAR when log P constants are used (Fig.3).

In summary, the affinity of muscarinic antagonists seems to depend upon the volume of ligands, quantified by molecular refractivity constants MR. In a rather good approximation the application of these parameters provides a common interrelationship between the structure and potency of muscarinic antagonists although the physical meaning of the effects quantified by MR is not clear yet. For further analysis of the different binding mechanisms found in the case of benzilic and tropic acid esters a more thorough kinetic analysis of the ligand binding process will be carried out.

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KINETIC ANALYSIS OF INTERACTION OF ESTER ANTAGONISTS WITH MUSCARINIC RECEPTOR

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The kinetic parameters for interaction of several non-radioactive antagonists with muscarinic receptor from rat brain cortex were measured by using N-methyl-[^{3}H]scopolamine as radioactive reporter ligand at 25°C and pH 7.4. It has been found that esters of benzilic and tropic acids initiate conformational isomerization of the receptor-ligand complex, while some variations of the structure of the acyl part of these esters result in alteration of the reaction mechanism. The data obtained were analyzed by means of quantitative structure-activity relationships.

Kinetic studies on binding of several radioactive antagonists to muscarinic receptor have revealed complex mechanism of this process, the most characteristic feature of which is the isomerization of the initial receptor-antagonist complex into a slowly dissociating form (RA)[1,2,3]:

$$R + A \underset{}{\overset{K_A}{\rightleftharpoons}} RA \underset{k_{-i}}{\overset{k_i}{\rightleftharpoons}} (RA) \quad . \qquad (1)$$

The latter complex can be determined by the filtration or centrifugation methods, generally used for the detection of membrane-bound radioligand[1].

According to this reaction scheme the overall process of the ligand binding is a reversible process and thus it can be characterized by the dissociation constant K_d, which has the

same meaning as the appropriate parameter determined from the equilibrium binding experiments. However, this constant is an apparent parameter:

$$K_d = K_A \cdot K_i \ , \qquad (2)$$

where $K_i = k_{-i}/k_i$. The constants K_A and K_i can be separately detected by means of kinetic analysis of ligand association to the receptor.

Until recently such kinetic analysis was feasible only in the case of radioactively labelled ligands that complicated a wider use of this approach. In our previous paper[4] of this series we offered an experimental procedure to investigate the kinetic mechanism of interaction of non-radioactive ligands with muscarinic receptor by making use of one radioactive "reporter ligand". In the present study by means of this experimental procedure the mechanism of interaction of several muscarinic antagonists with the membrane-bound receptor from rat brain cerebral cortex is analyzed.

EXPERIMENTAL

N-methyl-[^{3}H]scopolamine (72 Ci/mmole) was obtained from "Amersham". Atropine, N-methylatropine, scopolamine and benzoylcholine were commercial products from "Sigma" and they were used without any additional purification. N-Methylquinuclidinyl benzilate, choline benzilate, N,N-dimethylaminoethyl benzilate and choline ester of phenylcyclopentylhydroxyacetic acid were synthesized and kindly donated for kinetic studies by Prof. N.Godovikov, the Institute of Elementoorganic Compounds, Moscow.

Choline ester of phenylacetic acid was synthesized proceeding from dimethylaminoethanole and phenylacetyl chloride and the product was methylated by CH_3I by conventional procedures[5]. The structure of the compound obtained was verified by the NMR spectrum and its purity was checked by the HPLC analysis (solvent tetrahydrofuran:H_2O 7:3, column "Zorbax ODS", 4.6x250 mm).

All the other chemicals of analytical grade were obtained from Reachim, USSR.

The membranes from rat cerebral cortex were prepared as

described by Langel et al[6]. The membrane-bound radioligand was determined by the filtration method using Whatman GF/B filters. The kinetic experiments were carried out in 0.05 M K-phosphate buffer, pH 7.40, at 25°C.

The theoretical background and experimental procedures for kinetic measurements were described in detail by Eller et al[4]. N-Methyl-[^{3}H]scopolamine was used as the "reporter ligand". The experiments were made at the excess of radioligand (InM) over the receptor concentration (50-100 pM) to meet the pseudo-first-order conditions and the kinetic curves were measured at different concentrations of non-radioactive antagonists. These kinetic data were fitted to the rate equation consisting of either one or two exponential terms depending upon the nature of the process:

$$B_t = B_{ns} + \sum_i B_{spi} \cdot \exp(-k_i t) \qquad (3)$$

where B_t - concentration of the membrane-bound radioligand at time t, B_{ns} - concentration of the non-specifically bound radioligand, B_{spi} - maximal concentration of the specifically bound radioligand to fraction i and i=1 or 2. Further the plots of the observed rate constants against the concentration of non-radioactive antagonist were analyzed to calculate the appropriate kinetic parameters. The experimental data were processed on a PC/XT computer by means of a nonlinear regression program.

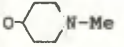
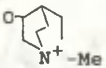
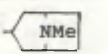
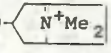
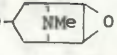
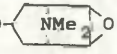
RESULTS

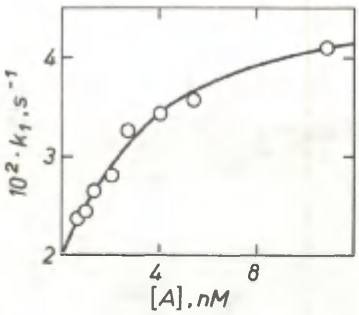
1. Kinetic analysis

The non-radioactive antagonists listed in Tables 1 and 2 had two types of effects on the kinetics of binding of N-methyl-[^{3}H]scopolamine to membrane-bound muscarinic receptor (Figs. 1 and 2). Some of these antagonists caused the increase in the observed rate of radioligand association that gives evidence of the isomerization of the receptor-ligand complex, as it was shown in[4]. In these cases the kinetic curves were analyzed by rate equation (3) containing two exponential terms.

Table 1

Kinetic data for antagonist interaction with muscarinic reoeptor, 25°C, pH 7.40

Antagonist	K_A nM	$10^2 k_i$ s^{-1}	$10^4 k_{-i}$ s^{-1}	K_d nM	K_i	MR	MR_{alk}	Notes
1. Ph HOCC(O)$OC_2H_4N(CH_3)_2$ Ph	38 ±13	3.4±C.6	68 ±10	9.6 ±1.7	0.20	87.9	24.9	-
2. Ph HOCC(O)$OC_2H_4N^+(CH_3)_3$ Ph	9.2±2.2	3.3±0.5	50 ± 9	2.3 ±0.2	0.15	92.0	28.9	-
3. Ph HOCC(O)O-  Ph	5.5±3.1	1.4±0.3	6.7±0.8	0.40±0.03	0.05	95.1	32.1	Ref.[2]
4. Ph HOCC(O)O- Ph 	5.0±2.3	4.6±0.5	14 ±4	0.13±0.03	0.03	103.3	40.3	Hef.[4]
5. Ph HOCC(O)O- Ph 	1.3±0.5	1.2±0.3	1.3±0.4	-	0.01	97.7	34.7	Hef.[9]
6. Ph $HOCH_2CHC(O)O$- 	6.3±2.0	6.0±1.0	10 ± 1	0.20±0.03	0.017	82.6	39.3	-
7. Ph $HOCH_2CHC(O)O$- 	3.0±1.0	6.1±1.0	21 ± 3	0.11±0.02	0.034	88.2	44.9	-
8. Ph $HOCH_2CHC(O)O$- 	3.7±1.2	3.0±0.5	30 ± 7	0.14±0.03	0.05	84.8	41.5	-
9. Ph $HOCH_2CHC(O)O$- 	9.7±2.1	11.9±0.8	9 ± 4	0.082±0.008	0.008	90.4	47.1	Ref.[3]



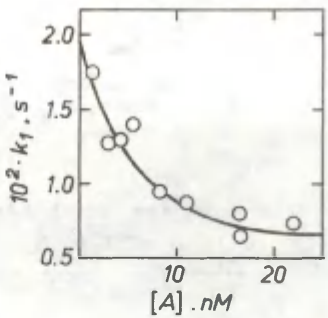


Fig.1 (left). Influence of scopolamine on the apparent rate constants of N-methyl-[^{3}H]scopolamine binding to muscarinic receptor from rat cerebral cortex, 0.05 M K-phosphate buffer, pH 7.4, 25°C.

Fig.2 (right). Influence of choline ester of phenylcyclopentylhydroxyacetic acid on the apparent rate constants of N-methyl-[^{3}H]scopolamine binding to muscarinic receptor from rat cerebral cortex, 0.05 M K-phosphate buffer, pH 7.4, 25°C.

The hyperbolic plot of the rate constant obtained from the first exponential term against antagonist concentration,

$$k_1 = \frac{k_i[A]}{K_A + [A]} \qquad (4)$$

allows the calculation of the K_A and k_i values. The second exponent allows the estimation of the k_{-i} values[4]. The results obtained by this method are listed in Table 1.

Some other antagonists caused the inhibition of radioligand (A^*) binding, resulting in the decrease in the apparent rate constants as shown in Fig.2. In this case only the reversible binding constant for non-radioactive antagonist A can be calculated[4]:

$$k_1' = \frac{k_i[A^*]}{(1 + [A]/K_d)K_A^* + [A^*]} \qquad (5)$$

The results obtained are listed in Table 2.

Table 2

Binding data for antagonist interaction with muscarinic receptor, 25°C, pH 7.4.

	Antagonist	K_A nM	K_d nM	MR	Notes
10.	$HOCC(O)OC_2H_4N^+(CH_3)_3$ (Ph, cyC_5H_9)	8,5±0,8	9.0±0.3	90.2	-
11.	$PhC(O)OC_2H_4N^+(CH_3)_3$	3760±540	3550±160	63.0	-
12.	$PhCH_2C(O)OC_2H_4N^+(CH_3)_3$	4530±380	4010±730	67.7	-
13.	$PhCH_2C(O)O$-(quinuclidine)-N^+Me_2	-	457	74.9	Ref.[9]
14.	$HCC(O)O$-(quinuclidine)-N-Me (Ph, Ph)	-	1.0	99.2	Ref.[9]
15.	$HOCC(O)OC_2H_4N^+Et_2Me$ (Ph, cyC_6H11)	-	0.26	105.6	Ref.[10]

2. Structure-Activity Relationships

Besides the compounds studied in the present report the binding data for some other esters were compiled from literature (see Table 1 and 2). Among these compounds there are several radioligands for which the direct kinetic analysis of the binding mechanism was made previously[1,2,3].

The molecular refractivity parameters were applied for correlation of the binding data for muscarinic antagonists. These parameters for the whole ester molecule as well as for

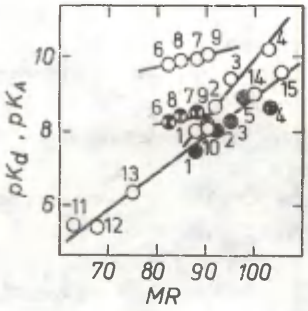


Fig.3. The plot of pK_d ○ and pK_A ● (benzilates), ⊗ (tropates) for muscarinic antagonists upon the parameter of molecular refractivity, MR. Numbers of the points correspond to Tables 1 and 2.

its alkyl part were calculated by making use of the appropriate fragmental constants[8] (see Tables 1 and 2).

The correlation of the pK_d values with the MR-constants yields linear dependences as shown in Fig.3,

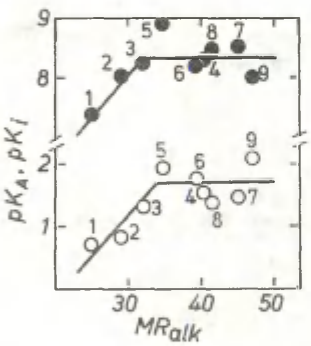
$$pK_d = \text{const} + \psi\, MR \qquad (6)$$

It can be seen that three different groups of antagonists are revealed from the pK_d vs MR plot, which involve tropic esters ($\psi = 0.046 \pm 0.004$), benzilic esters ($\psi = 0.14 \pm 0.02$) and the rest of esters involved in this analysis ($\psi = 0.10 \pm 0.01$). Further constants pK_A were built up into the analysis. In the case of benzilic esters these data fit the correlation between pK_d and MR for other esters, while the data for tropates still form a separate series pointing to the fact that the affinity of these ligands is almost independent of their structure.

The muscarinic antagonists which initiate the isomerization of the receptor-ligand complex are characterized also by the second equilibrium constant, $K_i = k_{-i}/k_i$. This parameter, which was calculated from the rate constants k_i and k_{-i}, also depends upon the ligand structure. However, in this case a more clear picture was obtained if the pK_i values were

analyzed by making use of the MR values for the alkyl groups of these esters (Fig.4). It can be seen that for smaller substituents a linear dependence can be obtained while beginning from some MR-value this parameter has no influence on the pK_i values and a clear break reveals in the plot. Application of same parameters MR_{alk} for correlation of the pK_A-values yielded a rather similar plot.

In both directions the rate of the conformational isomerization process of the receptor-ligand complex achieves minimum and the further inrease in the bulkiness of the substituent leads to some increase in the values of rate constants k_i and k_{-i} (Fig.5). In summary, these effects are similar in the case of both rate constants.



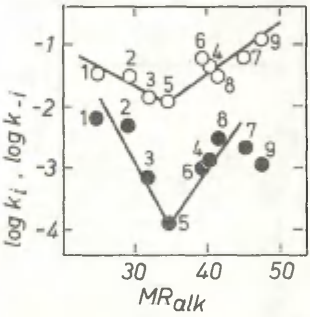


Fig.4. Dependence of pK_A ● and pK_i ○ upon structure of the alkyl part of the ester antagonists. Numbers of the points correspond to Table 1.

Fig.5. Effect of structure of alkyl groups of ester antagonists upon the rate of the conformational isomerization of the receptor-ligand complex, k_i ○ and k_{-i} ● . Numbers of the points correspond to Table 1.

DISCUSSION

In the present study the kinetic data for seven muscarinic antagonists were obtained by making use of a single radioactive ligand as proposed by Eller et al[4]. The results obtained allow to differentiate the classical muscarinic antagonists by the kinetic mechanism of their binding to the receptor site. At least two subclasses can be found. For the first group of antagonists the kinetic evidence of the isomerization process of the receptor-antagonist complex can be easily obtained and dissociation constant K_A as well as the isomerization rate constants can be calculated from these data.

In the case of the second subclass of antagonists the overall process of ligand association can be fitted to a simple binding isotherm formally corresponding to a single-step mechanism of ligand association.

There can be two explanations for such a kinetic behavior of the muscarinic antagonists of the latter type. Firstly, it is possible that these ligands do not initiate the isomerization process and thus the formation of the receptor-ligand complex obeys the simple mechanism,

$$R + A \overset{K_d}{\rightleftharpoons} RA \qquad (8)$$

where $K_d = k_{-1}/k_1$. On the other hand, the mechanism of binding of these compounds may involve also the isomerization step, which is, however, too fast to be followed by the experimental methods used. In the latter case the observed dissociation constant K_d is a complex parameter having the same meaning as given by Eqn (2).

As these two possibilities cannot be differentiated proceeding from the results of direct kinetic experiments, quantitative structure-activity relationships were used as tools to analyze the mechanism of ligand binding to muscarinic receptor in the present study. Some additional kinetic data from previous publications on the same topic were also involved in the analysis.

It can be seen in Fig.3 that the constants pK_d and pK_A

for benzilic esters form two separate lines of different slopes, corresponding to different mechanisms of the receptor-ligand interaction: the single step binding (K_A) and the two step scheme involving isomerization (K_d). The pK_d-values for the esters # 10, 11 and 12 fit the plot for pK_A, giving evidence of a single-step binding mechanism (8) for these esters.

The picture is more complex in the case of tropic esters, for with the plots of pK_d and pK_A vs the MR-constants have slopes, different from that obtained for other esters. This means that the effects, which seem to be governed by the ligand volume as the specificity determining factor, are saturated in the case of these ligands. The apparent binding effectiveness of these ligands, quantified by the constant K_d, can be, however, remarkably increased through the isomerization steps, shifted to the right. The difference between the pK_d and pK_A values, equal to the value of pK_i (see Eqn(2)), clearly points to the importance of the isomerization process in the case of these specific muscarinic antagonists.

Until now the isomerization step has been detected in the case of benzilates and tropates. Even a small modification of the acyl part of these ligands results in the alteration of this binding mechanism. At the same time the alkyl group of the ester antagonists can be widely varied without alteration of the reaction mechanism. These variations in ligand structure result in a change of binding affinity as well as the isomerization equilibrium. The latter correlation can be analyzed if the MR-constants for the alkyl part of esters are used. In this case the data for the tropic and benzilic esters can be analyzed within the framework of a common reaction series.

It is noteworthy that the same specificity determining factor, quantified by MR, is revealed two-fold in the following each other steps of the receptor-ligand interaction. Previously similar phenomena were found in the case of enzyme reactions where the same structural factor of substrate (hydrophobicity) reveals in both non-covalent binding and

following reaction steps, pointing most probably to some conformational changes of the enzyme molecule in the bond-breaking step of catalysis. However, until now we can point only to a formal similarity between the processes of ligand binding to receptor and enzyme catalysis, because there is no solid explanation of the LFE relationships between the binding affinity and the MR-constants as structural parameters. Thus the physicochemical background of the phenomemon of "double specificity", described in the present study, is not clear yet.

The latter part of this discussion concerns the structure-activity relationships for the rate constants k_i and k_{-i}. It can be seen in Fig. 5 that a clear minimum appears in the log k_i and log k_{-i} vs MR_{alk} plots pointing to the importance of structural fit of the ester alkyl group to the receptor site. For quinuclidinyl moiety the rate of the conformational transition of the receptor-ligand complex is the smallest in the reaction series studied. On the other hand, this means that for this structure the activation barrier of the conformational transition is the highest.

The isomerization step of the receptor-antagonist complex involves most probably a conformational change of the system, for which the following schematic representation can be proposed.

R RA (RA)

In these Schemes the main difference between the receptor-ligand complexes RA and (RA) is the "depth" of uptake of the ligand molecule into the receptor molecule. We propose that this principle of receptor-antagonist interaction can have a more general meaning and lead to the "isomerization" of the complexes of other cellular receptors with their specific ligands. The site, responsible for the

"uptake" of ligand molecule, can be either the ordinary binding site of the receptor or a putative channel system integrated with the receptor. In the latter case the receptor-bound antagonist also inhibits the process of signal transmission by the receptor.

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QUANTUM-CHEMICAL INVESTIGATION OF THE REACTION FIELD EFFECTS ON THE POLAR RESONANCE IN DISUBSTITUTED ETHYLENES.

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A quantum-chemical study of four model disubstituted ethylenes was carried out using the AM1 SCF and SCRF semi-empirical models. Remarkable dependance of the resonance energies on the polarity of solvent was observed.

1. Introduction.

Polar resonance plays an important role in the explanation of such phenomena as chemical structure and reactivity, various spectra of molecules and polarity of compounds. In recent years certain experimental evidence has been collected, indicating that polar resonance is not purely an intramolecular electronic effect, but it also depends on the medium. For instance, the cross terms between the solvent and electronic resonance parameters appear in the formal schemes based on linear free energy relationships (LFER), showing that the resonance and solvent effects are not independent of each other /1/. Therefore a theoretical study of the solvent effects on the electronic structure of molecules is of essential importance.

In this paper we present the results of the quantum-chemical study of solvent effects on the polar resonance energies in model disubstituted ethylenes. The solvent influence on the molecular electronic structure was simulated theoretically using the self-consistent reaction field (SCRF) model /2,3/.

The essence of the SCRF quantum-chemical method is summarized in the use of a modified Hamiltonian $\hat{H}'$ in the Schroedinger equation for the polar solute molecules in the following form /2/:

$$\hat{H}' = \hat{H}_0 + \Gamma\langle\Phi|\hat{\mu}|\Phi\rangle \quad , \qquad (1)$$

where Φ is the electronic wave function of the molecule, $\hat{\mu}$ is the dipole moment operator and $\hat{H}_0$ - the Hamiltonian for the isolated molecule. The multiplier Γ in the last term (the reaction field tensor) is a function of the dielectric properties of the solvent and the size of the solute molecule. According to the Kirkwood-Onsager theory /4,5/:

$$\Gamma = \frac{2(\epsilon + 1)}{(2\epsilon-1)V_0} \quad , \qquad (2)$$

where ϵ denotes the dielectric constant of the medium and V_0 is the volume of the cavity into which the solute molecule is embedded. The use of the macroscopic dielectric constant of the solvent in the last formula is justified in the case of the time-averaged orientational polarization of the solvent molecules in the field of solute molecule.

The electronic energy of the solute molecule in the dielectric medium is calculated then by the solution of the respective one-electron Fock equations

$$\hat{h}'_i y_i = e_i y_i \qquad (3)$$

using the self-consistent field procedure [2,3]. Here y_i denotes a molecular orbital of the energy e_i, and $\hat{h}'_i$ is the one-electron Hamiltonian corresponding to the $\hat{H}'$. The electronic energy of the molecule is given by expression

$$E_{el} = \sum_{ij} P_{ij}H_{ij} + 1/2 \sum_{ijkl} P_{ij}P_{ij}(\langle ij|kl\rangle - 1/2\langle ik|jl\rangle), \qquad (4)$$

where P_{ij} and P_{kl} denote the corresponding density matrix elements, H_{ij} is the one-electron modified core hamiltonian element, and $\langle ij|kl\rangle$ and $\langle ik|jl\rangle$ - the two-electron repulsion integrals. The total energy is calculated as follows:

$$E_{tot} = E_{el} + \sum_{k>l} \frac{Z_k * Z_l}{R_{kl}} + \Gamma \sum_k Z_k * R_k * \langle \Phi | \hat{\mu} | \Phi \rangle \qquad (5)$$

where the sums are taken over all the nuclei in the molecule, Z_k and Z_l are the core charges of the nuclei, R_{kl} - internuclear distance, and R_k denote their radius-vectors.

The method described above was realized by us as a modification of the MOPAC program package /6/.

2. The system used.

We chose one of the simplest objects where polar resonance is involved: 1,2-disubstituted ethylenes. The substituents used were -OH and $-NH_2$ representing +R and -CHO and -CN as -R-groups, respectively. This choice results in the following four compounds involving polar resonance at the double bond: HO-CH=CH-CHO, H_2N-CH=CH-CHO, HO-CH=CH-CN, and H_2N-CH=CH-CHO. Since intramolecular hydrogen bonds may be present in the cis-forms of the compounds, only trans-forms were investigated for the sake of elimination of this side effect difficult to take into account in the resonance energy analysis.

Recent quantum-chemical calculations of some substituted ethylenes /7-10/ have been published, however due to the different quantum-chemical methods used, and to the exclusion of solvent effects in study, these results are not directly comparable to ours.

Resonance energy in disubstituted ethylene is defined by us as the change of enthalpy in the following hypothetic reaction:

1/2 X-CH=CH-X + 1/2 Y-CH=CH-Y = X-CH=CH-Y ,

where X and Y are any of the substituents quoted previously.

The definition of the polar resonance energy is given then by formula

$$E_{R,XY} = H_{f,XY} - 1/2 (H_{f,XX} + H_{f,YY}) \quad , \quad (6)$$

where $E_{R,XY}$ is the resonance energy, H_f is the calculated heat of formation of a compound, and X and Y represent different substituents.

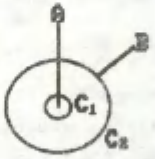
A separate problem arises with this definition of resonance energy: the homosubstituted ethylenes (XX or YY in our notation) may be composed by "cutting" the heterosubstituted one (XY) into two parts along the C=C bond and adding a mirror image to the half of the molecule obtained so. The XX and YY compounds' energies are then calculated using optimized bond lengths and angles for heterosubstituted compounds. Another possibility is to optimize further also the geometries of the homosubstituted ethylenes and use their calculated entalphies of formation in evaluation of the resonance energy. The first definition proposed here should give a more "theoretical" view on the resonance as no geometric stabilization effects are encountered. On the other hand, definition of resonance on the basis of optimized geometries should yield results more comparable to the experimental data. Both variants were used in this study and the results are given in parallel. They will be referred to, as "symmetric", and "optimized", respectively.

In order to investigate the solvent effects, two calculation series were carried out. In the first of them the standard SCF procedure (gas-phase calculation) was used, the second one involved the reaction field model with the solvent dielectric constant ϵ=78.5 . The latter will be referred to below as the "solution" calculation. The AM1 semiempirical parametrization for the elements by Dewar /11/ was used in calculations. The cavity volumes V_0 (cf. Eq.2) were calculated from the additive molecular refractions R_0 of the bonds present in the molecules. Geometries were optimized for each molecule both in the gas and solution phases, except for the homosubstituted ethylenes used in the calculation of the "symmetric" resonance energies.

3. Results and discussion.

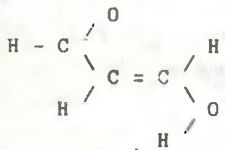
The heats of formation, dipole moments, cavity radii used, and optimum geometries of the compounds investigated are given in Table 1. The conformational (dihedral) angle between bonds was defined as follows:

Dihedral angle
A - C_1 - C_2 - B

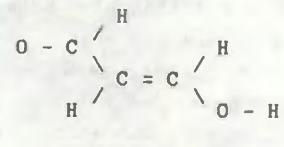


All unspecified dihedral angles were set to 0 or 180 degrees in order to guarantee the complanarity of the molecule.

These results indicate significant solvent influence on the electronic structure of several molecules. In all compounds, where a substantial redistribution of electron density is possible, i.e. in the heterosubstituted compounds, the dipole moments tend to increase in polar solvent, resulting also in a lower heat of formation than in the gas phase. In most cases the geometrical variables (bond lenghts and bond angles) of the molecules are rather insensitive to the change of environment into which the molecule is embedded. However, the geometries of some molecules tend to change in solution towards the more polar conformations, resulting in an additional increase of the dipole moment and consequent decrease of the heat of formation due to the solute-solvent polarization effects, e.g.



gas phase



solution

It could also be noticed, that while in the gas phase the NH_2-group is almost in the tetrahedral form (sp^3 hybridization), in the solution the optimal geometry is planar (sp^2). Various geometric effects can also be observed in homosubstituted ethylenes, if the geometries are optimized. A trend towards more asymmetric geometries in solution can be observed, compared to the symmetric ones in gas phase.

One can also see in Table 2 that the resonance energies tend to increase with the increase of the dielectric constant of the solvent. This should be considered as one of the main results of this work: <u>energies of polar resonance are substantially different in the gas phase and in a solution of high dielectric permittivity</u>. In various formal solvent effect theories /11-15/ a linear relationship between the reaction energies, free energies or activation energies and the observable solvent polarity parameters is postulated. Our calculations indicate that this assumption may be acceptable for resonance energies in substituted ethylenes only if the "symmetric" geometries are assumed for the reference compounds (see Fig. 1). However, if the optimal geometries for the reference compounds are used ("experimental" situation), no smooth dependence between the resonance energies in different phases for a series of compounds can be observed (Fig. 1). This also means, that any predictions of the electronic effects in compounds with direct polar resonance by the quantum-chemical calculation should involve solvent effects (e.g. SCRF procedure should be used instead).

Another important question is the validity of the linear relationships between the resonance energies in series of compounds with one constant substituent (e.g. X_1Y and X_2Y). If entropy effects are small enough, which should be the case for our model compounds, the free energy relationships for different reactions involving these compounds should also look quite similar. To test this assertion, the following procedure was carried out: using different values

of ϵ, enthalpies of formation of the compounds were calculated for both gas-phase and solution geometries without additional optimization. The lower of these two values was used for each compound to calculate the resonance energy. The resonance energies for different compounds were then compared to each other (see Fig. 2). Each point on these graphs refers to a pair of calculations with different ϵ (and, consequently, Γ) value. It can be seen even on the basis of the small set of compounds used, that the relationships can be either linear (Fig. 2a) or nonlinear (Fig. 2b). Consequently, the use of linear relationships on Kirkwood-Onsager parameters for description of experimental solvent effects in resonance-affected systems is unjustified in some cases.

In order to generalize the conclusions obtained in this paper, more extensive investigation of other systems (e.g. disubstituted benzenes and 1,3-butadienes) is needed.

Table 1: The AM1 Calculated Heats of Formation (H_f , kcal/mol), Dipole Moments (D), and Geometries of Disubstituted Ethylenes.

Note: all unspecified dihedral angles are set to 0 or 180 degrees in order to keep the molecule planar.

HO-CH=CH-CN

Variable	Gas	Solution
Heat of Formation	-2.51	-8.56
Dipole Moment	3.60	3.69
Cavity Radius, A	n/a	3.038
bond lengths, A		
C = C	1.35	1.35
C - H (at CN)	1.10	1.10
C - H (at OH)	1.10	1.11
C - O	1.37	1.36
O - H	0.97	0.97
C - C (at CN)	1.41	1.41
C ≡ N	1.16	1.16
bond angles, deg		
C - C - H (at CN)	121.4	121.8
C - C - H (at OH)	124.6	125.7
C - C - O	118.1	125.5
C - O - H	107.5	111.4
C - C - C (at CN)	122.3	122.9
C - C - N	179.5	175.7
dihedral angles, deg		
H - C - O - H (at OH)	3.6	179.8

"n/a" means that cavity radius is not applicable for gas phase.

H_2N-CH=CH-CN

Variable	Gas	Solution
Heat of Formation	37.66	28.69
Dipole Moment	5.14	6.64
Cavity Radius, A	n/a	3.148
bond lengths, A		
C = C	1.36	1.37
C - H (at CN)	1.10	1.10
C - H (at NH_2)	1.11	1.11
C - N (at NH_2)	1.37	1.36
N - H	0.99	0.99
N - H	0.99	1.00
C - C (at CN)	1.41	1.41
C ≡ N	1.17	1.17
bond angles, deg		
C - C - H (at CN)	123.0	121.6
C - C - H (at NH_2)	120.5	121.5
C - C - N (at NH_2)	125.1	124.9
C - N - H	120.1	122.0
C - N - H	118.1	121.4
C - C - C (at CN)	121.5	122.4
C - C - N (at CN)	178.1	175.6
dihedral angles, deg		
H - N - C - H (at NH_2)	-174.0	176.9
H - N - H (in NH_2)	160.7	-174.9

HO-CH=CH-CHO

Variable	Gas	Solution
Heat of formation	-68.47	-71.54
Dipole moment	3.10	5.81
Cavity Radius, Å	n/a	3.049
bond lengths,Å		
C = C	1.35	1.35
C - H (at CHO)	1.10	1.10
C - H (at OH)	1.11	1.11
C - O (at OH)	1.36	1.36
O - H	0.97	0.98
C - C (at CHO)	1.46	1.45
C - H (in CHO)	1.11	1.12
C - O (in CHO)	1.24	1.24
bond angles, deg		
C - C - H (at CHO)	121.7	120.6
C - C - H (at OH)	124.6	124.7
C - C - O (in OH)	125.1	118.2
C - O - H (in OH)	109.7	108.6
C - C - C (in CHO)	121.3	121.6
C - C - H (in CHO)	114.5	114.0
C - C - O (in CHO)	123.9	123.7
dihedral angles,deg		
H - C - O - H (H in OH)	178.2	3.3
H - C - C - H (C in CHO)	10.1	176.8

H_2H-CH=CH-CHO

Variable	Gas	Solution
Heat of formation	-25.73	-33.30
Dipole moment	4.30	6.94
Cavity Radius, A	n/a	3.158
bond lengths,A		
C = C	1.36	1.36
C - H (at NH_2)	1.10	1.10
C - H (at CHO)	1.11	1.11
C - N	1.36	1.36
N - H	0.99	0.99
N - H	0.99	0.99
C - C (at CHO)	1.45	1.46
C - H (in CHO)	1.12	1.12
C - O (in CHO)	1.24	1.23
bond angles, deg		
C - C - H (at NH_2)	121.8	122.2
C - C - H (at CHO)	119.3	120.3
C - C - N	125.6	126.0
C - N - H	120.6	120.0
C - N - H	119.6	122.7
C - C - C (at CHO)	121.6	124.0
C - C - H (in CHO)	114.8	111.3
O - O - O	124.7	127.7
dihedral angles, deg		
H - C - N - H	-175.2	0.0
H - C - N - H	163.9	180.0
H - C - C - H (in CHO)	1.2	180.0

NC-CH=CH-CN

Variable	Gas	Solution
Heat of formation	76.03	76.09
Dipole moment	0.03	0.06
Cavity Radius, Å	n/a	2.500
bond lengths, Å		
C = C	1.34	1.34
C - H (ethylene	1.11	1.11
C - H hydrogens)	1.11	1.11
C - C	1.42	1.42
C - N	1.16	1.16
C - C	1.42	1.42
C - N	1.16	1.17
bond angles, deg		
C - C - H	122.5	123.3
C - C - H	122.6	122.6
C - C - C	122.2	122.1
C - C - N	178.4	178.8
C - C - C	122.9	121.1
C - C - N	178.4	178.4

OHC-CH=CH-CHO

Variable	gas		
	symmetric geometries for NH_2	for OH	optimal
Heat of formation	-47.20	-47.16	-47.47
Dipole moment	0.00	0.00	0.84
bond lengths, Å	0.00	0.00	0.00
C = C	1.34	1.34	1.34
C - H (ethylene	1.10	1.10	1.10
C - H hydrogens)	1.10	1.10	1.10
C - C	1.47	1.48	1.47
C - H	1.11	1.11	1.11
C - O	1.23	1.23	1.23
C - C	1.47	1.48	1.48
C - H	1.11	1.11	1.11
C - O	1.23	1.23	1.23
bond angles, deg			
C - C - H	121.2	121.3	122.6
C - C - H	121.2	121.3	122.6
C - C - C	122.6	122.3	122.2
C - C - H	115.1	115.4	115.4
C - C - O	123.5	123.1	122.8
C - C - C	122.6	122.3	121.8
C - C - H	115.1	115.4	115.6
C - C - O	123.5	123.1	122.6
dihedral angles,deg			
H - C - C - C	180.0	180.0	180.0
H - C - C - H	0.0	10.1	168.2
H - C - C - O	180.0	180.0	180.0
H - C - C - C	180.0	180.0	180.0
H - C - C - H	0.0	-10.1	164.1
H - C - C - O	180.0	180.0	180.0

OHC-CH=CH-CHO (continued)

Variable	solution	
	symmetric for both	optimal
Heat of formation	-47.62	-50.43
Dipole moment	0.00	4.44
Cavity Radius, A	3.224	3.224
bond lengths, A		
C = C	1.34	1.34
C - H (ethylene	1.10	1.10
C - H hydrogens)	1.10	1.11
C - C	1.47	1.47
C - H	1.11	1.12
C - O	1.23	1.24
C - C	1.47	1.48
C - H	1.11	1.12
C - O	1.23	1.24
bond angles, deg		
C - C - H	122.6	122.6
C - C - H	122.6	120.3
C - C - C	122.2	124.4
C - C - H	115.4	116.4
C - C - O	122.8	121.0
C - C - C	122.2	121.5
C - C - H	115.4	115.3
C - C - O	122.8	121.6
dihedral angles,deg		
H - C - C - C	180.0	180.0
H - C - C - H	180.0	166.4
H - C - C - O	180.0	180.0
H - C - C - C	180.0	180.0
H - C - C - H	180.0	15.2
H - C - C - O	180.0	180.0

HO-CH=CH-OH

Variable	gas			solu-tion
	flat geometries for CN	for CHO	optimal	
Heat of formation	-75.48	-79.79	-79.73	-79.63
Dipole moment	0.00	0.00	0.12	2.77
Cavity Radius, A	n/a	n/a	n/a	2.852
bond lengths,A				
C = C	1.35	1.35	1.35	1.35
C - H (ethylene	1.10	1.10	1.10	1.10
C - H hydrogens)	1.10	1.10	1.10	1.10
C - O	1.38	1.37	1.38	1.38
O - H	0.97	0.97	0.97	0.97
C - O	1.38	1.37	1.37	1.37
O - H	0.97	0.97	0.97	0.97
bond angles, deg				
C - C - H	124.2	126.2	126.0	124.5
C - C - H	124.2	126.2	126.2	124.4
C - C - O	117.4	123.9	123.3	117.8
C - O - H	106.2	108.7	108.4	106.1
C - C - O	117.4	123.9	123.9	124.1
C - O - H	106.2	108.7	108.6	108.5
dihedral angles,deg				
H - C - O - H	0.0	180.0	-173.4	0.0
H - C - O - H	0.0	180.0	178.1	180.0

$H_2N-CH=CH-HH$

Variable	gas	
	symmetric (for both)	optimal
Heat of formation	13.13	8.63
Dipole moment	0.00	0.09
bond lengths, Å		
C = C	1.36	1.36
C - H (ethylene	1.11	1.11
C - H hydrogens)	1.11	1.11
C - N	1.38	1.40
N - H	0.98	1.00
N - H	0.98	1.00
C - N	1.38	1.40
N - H	0.98	1.00
N - H	0.98	1.00
bond angles, deg		
C - C - H	121.6	121.7
C - C - H	121.6	121.6
C - C - N	124.2	124.4
C - N - H	119.8	112.3
C - N - H	118.7	113.8
C - C - N	124.2	124.2
C - N - H	119.8	113.8
C - N - H	118.7	111.9
dihedral angles,deg		
H - C - C - N	180.0	180.0
H - C - N - H	-174.0	36.4
H - C - N - H	162.0	127.5
H - C - C - N	180.0	180.0
H - C - N - H	174.0	-165.6
H - C - N - H	-162.0	126.4

N_2N-CH=CH-NH_2 (continued)

Variable	solution	
	symmetric for CN	optimal
Heat of formation	13.75	8.31
Dipole moment	0.00	3.24
Cavity Radius, A	3.090	3.090
bond lengths,A		
C = C	1.36	1.36
C - H (ethylene	1.11	1.11
C - H hydrogens)	1.11	1.11
C - N	1.38	1.40
N - H	0.98	1.00
N - H	0.98	1.00
C - N	1.38	1.41
N - H	0.98	1.01
N - H	0.98	1.01
bond angles, deg		
C - C - H	121.7	121.8
C - C - H	121.7	121.8
C - C - N	124.1	123.7
C - N - H	119.1	111.7
C - N - H	120.5	113.0
C - C - N	124.1	125.0
C - N - H	119.1	109.3
C - N - H	120.5	111.7
dihedral angles, deg		
H - C - C - N	180.0	180.0
H - C - N - H	12.0	17.6
H - C - N - H	169.0	125.2
H - C - C - N	180.0	180.0
H - C - N - H	-12.0	52.2
H - C - N - H	-169.0	119.0

Table 2: Heats of Formation H_f, Resonance Energies E_R and the Dipole Moments μ of the Compounds.

X	Y	ϵ	H_f kcal/mol	μ D	E_R(sym) kcal/mol	E_R(opt) kcal/mol
-OH	-CN	1.0	-2.5	3.60	-2.8	-0.6
		78.5	-8.6	3.69	-6.7	-6.8
$-NH_2$	-CN	1.0	37.7	5.14	-6.9	-4.7
		78.5	28.7	6.84	-16.4	-13.5
-OH	-CHO	1.0	-68.5	3.10	-5.0	-4.9
		78.5	-71.5	5.81	-10.0	-6.5
$-NH_2$	-CHO	1.0	-25.7	4.30	-8.7	-6.3
		78.5	-33.3	6.94	-17.6	-12.2

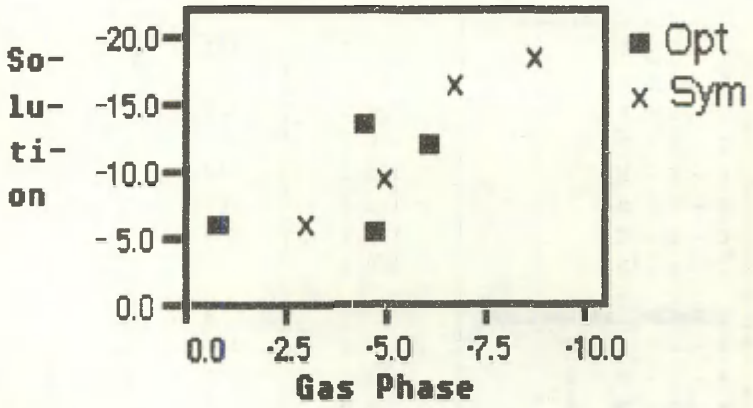


Figure 1: Gas Phase Resonance Energies vs. Solution Resonance Energies in 1,2-Heterosubstituted Ethylenes.

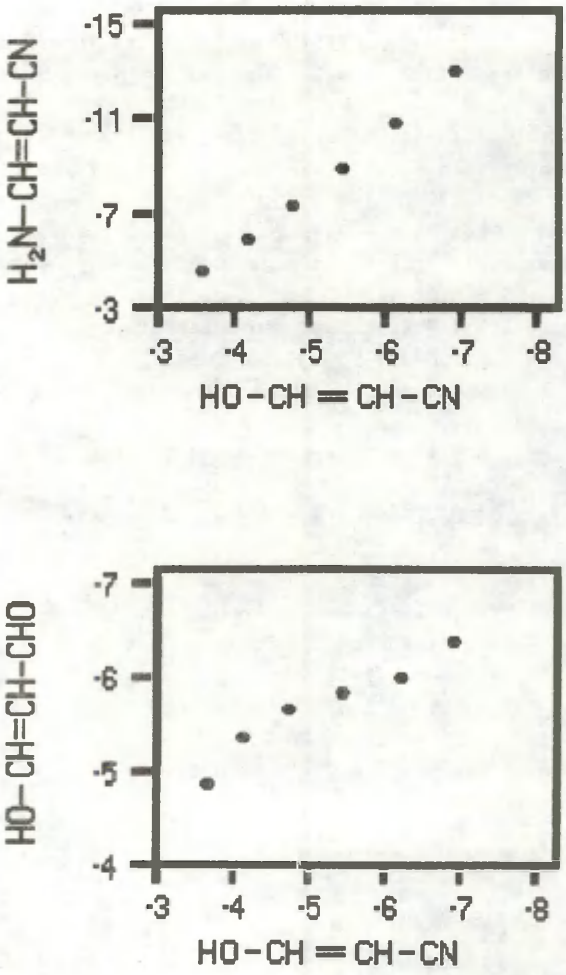


Figure 2: Dependence of Resonance Energies in Different Dielectric Media.

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KINETIC STUDY OF BENZOATE HYDROLYSIS
XVII ALKALINE HYDROLYSIS OF o-SUBSTITUTED BENZOATES IN CONCENTRATED AQUEOUS n-Bu_4NBr SALT SOLUTION

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The kinetics of the alkaline hydrolysis of five o-substituted phenyl benzoates $C_6H_5COOC_6H_4$-X (X = 2-NO_2, 2-Cl, 2-F, 2-CH_3, 2-OCH_3) in 1M and 2.25M n-Bu_4NBr solutions has been studied at 50° C.

The statistical treatment of the log k values for the alkaline hydrolysis of o-substituted phenyl benzoates in the case of 1 and 2.25M n-Bu_4NBr solutions and water at different temperatures was performed with simultaneous use of the data of m- and p-substituted derivatives.

Besides σ^o constants, additional inductive σ_I and steric E_s^B scales were used as substituent parameters in the case of o-substituted derivatives ($E_s^B = \log k^X_{H^+} - \log k^H_{H^+}$ where k_{H^+} is the rate constant of the acidic hydrolysis for o-substituted phenyl benzoate in water at 50° C).

In the previous papers it was found on the bases of the data of the acidic dissociation of benzoic acids and al-

kaline hydrolysis of phenyl tosylates[1,2], that the ortho-effect considerably decreases and the difference log k_o/k_p becomes minimal (k_o and k_p denote the rate constants for ortho-and para-substituted derivatives) when passing from water to the concentrated n-Bu_4NBr solutions.

The purpose of the present study was to check whether an analogical situation can take place also in the case of the alkaline hydrolysis of substituted phenyl benzoates.

In the previous paper[3] on the same theme we presented the values of the rate constants k ($M^{-1} \cdot s^{-1}$) for the alkaline hydrolysis of phenyl benzoates with substituents in metha- and para-positions, in 1 and 2.25 molar tetra-n-butylammonium bromide solution at 50° C.

In the present paper the values of log k for the alkaline hydrolysis of five ortho-substituted phenyl benzoates in 1 and 2.25 M n-Bu_4NBr solution at 50° C are given. The results of the statistical treatment of log k values and the data for ortho-, metha-, and para-substituted derivatives, using the method of multiple regression analysis, are also reported.

Experimental

The kinetics of the alkaline hydrolysis of substituted phenyl benzoates $C_6H_5COOC_6H_4$-X (X = 2-NO_2, 2-Cl, 2-F, 2-CH_3, 2-OCH_3) was investigated in 1M and 2.25M tetra-n-butylammonium bromide solution at 50° C. In the case of 2-OCH_3-phenyl benzoate the kinetics was measured for water solution at 50°C as well.

As alkali, 0.0223 molar tetra-n-butylammonium hydroxide was used.

The purification of alkali and tetrabutylammonium bromide, the preparation and the characteristics of phenyl benzoates studied (besides the 2-OCH_3-substituted one) have been given in our previous publications[4,5].

2-OCH_3-phenyl benzoate was synthesized from benzoyl chloride and guaiacol in the aqueous NaOH solution. The substance was recrystallized several times from 50 % aqueous

ethanol and dried in vacuo over P_2O_5 m.p. 57-57.5° C.

Kinetic measurements were carried out under pseudomonomolecular conditions with alkali excess. For the kinetic measurements the spectrophotometric method was applied using a device equipped with a photoelectric multiplier and a recorder of the LP-type.

Second-order rate constants k_2 were calculated dividing pseudomonomolecular rate constants by the alkali concentration. The measurements at each salt concentration were repeated and the arithmetic means of the corresponding second order rate constants k_2 were calculated. The k_2 values found like this and the number of measurements at each salt concentration are given in Table 1.

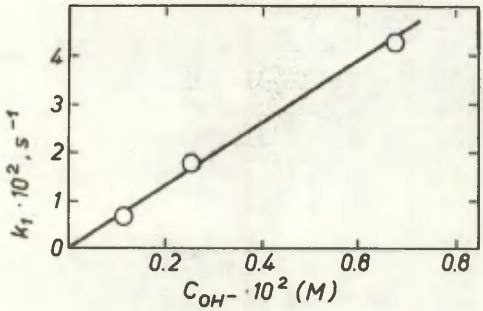

Fig. 1. Relationship between k_1 and C_{OH^-} for 2-methoxyphenyl benzoate at 50° C in water.

The kinetics of the alkaline hydrolysis of 2-OCH_3-phenyl benzoate in water without salt additions, was measured at three alkali concentrations at 50° C (see Fig. 1). The second order rate constant was calculated from relationship (1)

$$k_1 = k_2 \cdot C_{OH^-} + \text{const} \qquad (1)$$

where k_1 is the rate constant of the pseudomonomolecular reaction and k_2 - the second order rate constant (see Table 2).

Table 1

Rate Constants k ($M^{-1} \cdot s^{-1}$) for Alkaline Hydrolysis of 2-Substituted Phenyl Benzoates $C_6H_5CO_2C_6H_4$-X in Presence of n-Bu_4NBr Additions (C_{OH^-} = 0.0223) at 50°C

X	Salt (M)	k ($M^{-1} \cdot s^{-1}$)	n*	λ_{nm}
2-NO_2	2.25	2.32 ±0.04	6	427
	1.00	1.21 ±0.02	6	
2-Cl	2.25	0.471 ±0.006	5	303
	1.00	0.295 ±0.008		
2-F	2.25	0.422 ±0.004	6	292.5
	1.00	0.272 ±0.005		
2-CH_3	2.25	0.0633±0.0019	6	298
	1.00	0.0721±0.00016		
2-OCH_3	2.25	0.0416±0.0008	4	298
	1.00	0.0509±0.0008		
3-Cl	2.25	1.31 ±0.04	6	303
		1.08 ±0.13**		
	1.00	0.622 ±0.013		
		0.749 ±0.080**		

n* - Number of measurements of the salt concentration considered; ** - in paper[3].

Table 2

Values of k_1 (s^{-1}) at Various n-Bu_4NOH Concentrations and k_2 ($M^{-1} \cdot s^{-1}$) for Alkaline Hydrolysis of 2-OCH_3-Phenyl Benzoate in Water at 50°C

C_{OH^-} (M)	$k_1 \cdot 10^3 \cdot s^{-1}$	n*	k_2 ($M^{-1} \cdot s^{-1}$)
0.0116	6.82±0.19	4	0.668±0.032
0.0256	17.80±0.44	3	
0.0640	42.13±1.14	3	

n - Number of measurements at alkali concentration con-

sidered.

Discussion

Fig. 2 illustrates the plots of log k values vs. tetrabutylammonium bromide concentration at 50° C. During transition from water to 1 M tetrabutylammonium bromide solution, negative salt effect was discovered in the case of all phenyl benzoates studied. But in the case of ortho-substituted

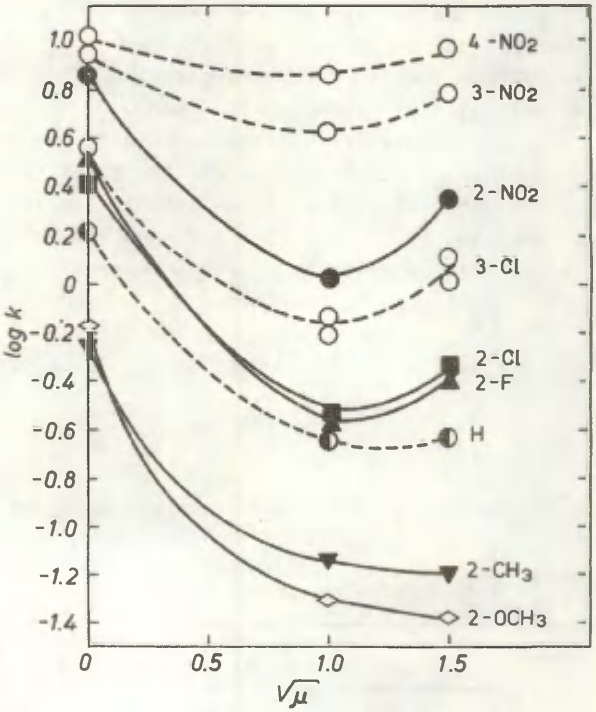

Fig. 2. Dependence of log k_2 on $\sqrt{\mu}$ for alkaline hydrolysis of substituted phenyl benzoates at 50° C.

derivatives the negative salt effects are stronger than in the case of the corresponding metha and para-substituted derivatives. An analogous situation was observed in the case of the alkaline hydrolysis of substituted phenyl tosylates[2]. In the case of the alkaline hydrolysis of phenyl tosylates, the positive ortho effect detected for water solution, decreases considerably during transition to 1 and 2.25 M n-Bu_4NBr solutions. When studying the alkaline hydrolysis of ortho-substituted phenyl benzoates in water, such negative ortho effects were observed which did not weaken during transition to the concentrated tetrabutylammonium bromide solutions but became even stronger.

The same phenomenon demonstrate the σ^{o}_{ortho} values calculated from the log k for the alkaline hydrolysis of ortho-substituted phenyl benzoates (Table 3).

Using the method of multiple regression analysis, the common treatment of log k values for the alkaline hydrolysis of ortho-substituted and metha- and para-substituted phenyl benzoates in 1 and 2.25 molar n-Bu_4NBr solution at 50° C as well as in water at various temperatures was carried out according to the equation:

$$\log k^{X}_{m,p(ortho)} = \log k^{H}_{0} + \rho^{o}_{m,p(ortho)}\sigma^{o} + \rho_{I(ortho)}\sigma_{I} + \delta_{(ortho)}E^{B}_{s} \qquad (2)$$

Table 3

Values of σ^{o}_{ortho} Calculated from log k Values for Alkaline Hydrolysis of Substituted Phenyl Banzoates $C_6H_5CO_2C_6H_4$-X at 50° C

Substituent X	H_2O	1 M Bu_4NBr	2.25 M Bu_4NBr
2-NO_2	0.628	0.414	0.504
2-Cl	0.171	0.079	0.162
2-F	0.312	0.060	0.137
2-CH_3	-0.539	-0.251	-0.272
2-OCH_3	-0.441	-0.338	-0.360
2-$N(CH_3)_2$	-0.486	-	-

In the data processing we also included the term $\rho^{o}_{R(ortho)}\sigma^{o}_{R}$, but afterwords it was excluded as an insignificant one.

For comparison the data treatment was carried out according to the following equations as well:

$$\log k^{X}_{(ortho)} = \log k^{H}_{O} + \rho_{I(ortho)}\sigma_{I} + \rho^{o}_{R(ortho)}\sigma^{o}_{R} + \delta_{(ortho)}E^{B}_{s} \qquad (3)$$

and

$$\log k^{X}_{m,p} = \log k^{H}_{O} + \rho^{o}_{m,p}\sigma^{o} \qquad (4)$$

The treatment of the log k values according to Eq. (4) also embraced the log k value for an unsubstituted derivative.

The results of the statistical data treatment according to Eqs. (2)-(4) are given in Tables 4 and 5.

The statistical data processing was carried out on a "Nord-100" computer. The program of multiple regression analysis composed by V. Palm[7,8] was used. The "recommended" σ^{o} values from Tables[9] and the σ_{I} and σ^{o}_{R} constants from publication[10] were used. In the case of 2-$N(CH_3)_2$-substituent it was assumed that the resonance term was absent and in the common data treatment for this derivative the correction for $\rho^{o}_{p}\sigma^{o}_{R}$ was included.

For ortho-substituted derivatives the corresponding σ^{o} values for para-substituents were used.

As steric constants E_s the difference $E^{B}_{s} = \log k^{X}_{H^+} - \log k^{H}_{H^+}$ was used, where $k^{X}_{H^+}$ is the rate constant of the acidic hydrolysis for ortho-substituted phenyl benzoate in water at 50° and $k^{H}_{H^+}$ is the same constant for unsubstituted derivative[11].

In the statistical data treatment we used the $(E^{B}_{s})_{calc}$ values, calculated from the linear relationship between the log k values for the alkaline hydrolysis of phenyl tosylates and values of $(\log k^{X}_{OH^-} - \log k^{X}_{H^+})_{m,p(ortho)}$ for the alkaline hydrolysis of phenyl benzoates at 50° C[11] (k_{OH^-} and

k_{H^+} are the rate constants for the alkaline and acidic hydrolysis, respectively).

Substituent	E_s^B	$(E_s^B)_{calc}$
2-NO_2	-0.374	-0.374
2-Cl	-0.378	-0.243
2-F	-0.155	-0.155
2-CH_3	-0.264	-0.264
2-OCH_3	-	-0.308
2-$N(CH_3)_2$	-	-0.425
H	0	0

It follows from the results of the statistical data treatment given in Tables 4 and 5 that the log k values for 2.25 and 1 M n-Bu_4NBr solutions as well as for water could be satisfactorily correlated by equations (2)-(4).

During transition from water to the 2.25 M n-Bu_4NBr solution term $\rho^o_{m,p(ortho)}$ increases by about one unit but the contribution of the $\rho_{I(ortho)}\sigma_I$ term became insignificant. Since the contribution of the steric term practically does not depend on the nature of the solvent, the negative ortho effect still increases during transition to the 2.25 M solution of n-Bu_4NBr. When passing from water to the concentrated tetrabutylammonium bromide solution the total effect of ortho-substituents (NO_2, Cl, F) is twice smaller than that in the case of metha- and para-substituents.

It was found that in the case of alkaline hydrolysis of phenyl benzoates the effect of ortho-substituents $\Delta\log k^X$ changes equally to that in the case of the alkaline hydrolysis of phenyl tosylates when passing from water to the 2.25 M n-Bu_4NBr solution. It should be remembered that a similar situation has already been observed in the case of metha- and para-substituents[2].

In Fig. 3. the relationship between the values of $\Delta\log k^X$ (2.24 M Bu_4NBr) - $\Delta\log k^X(H_2O)$ (where $\Delta\log k^X = \log k^X - \log k^H$) for the alkaline hydrolysis of phenyl tosylates and the same values for the alkaline hydrolysis of phenyl benzoates at 50° C is presented. One can see that the

Table 4

Results of Statistioal Data Treatment of log k Values at 50° C According to the Following Equations:

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

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

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

Equation	Parameters	H_2O	1M Bu_4NBr	2.25M Bu_4NBr
1	2	3	4	5
(1)	$\log k^{H}_{0}$	0.242±0.024	-0.680±0.068	-0.654±0.030
	$\rho^{o}_{m,p}$	0.945±0.047	1.84 ±0.13	2.02 ±0.06
	r	0.995	0.990	0.998
	s	0.039	0.089	0.041
	s_o	0.099	0.141	0.067
	n/n_o	5/5	5/5	5/5
(2)	$\log k^{H}_{0}$	0.246±0.020 0.246±0.022*	-0.602±0.049	-0.607±0.030
	$\rho^{o}_{m,p(ortho)}$	0.939±0.028 0.936±0.030*	1.65±0.088	1.93±0.055
	$\rho_{I(ortho)}$	0.562±0.055 0.544±0.062*	0	0
	$\delta_{(ortho)}$	1.41 ±0.084	1.57±0.21	1.42±0.13

Table 4 continued

1	2	3	4	5
		1.37 ±0.11*		
	r	0.998 0.997*	0.991	0.997
	s	0.031 0.032*	0.094	0.060
	s_o	0.056 0.072*	0.136	0.080
	n/n_o	10/10 9/9*	10/10	10/10
(3)	$\log k_0^H$	0.193±0.040 0.199±0.055*	-0.657±0.089	-0.641±0.074
	$\rho_{I(ortho)}$	1.69 ±0.063 1.70 ±0.088*	1.79 ±0.14	2.39 ±0.12
	$\rho^o_{R(ortho)}$	0.781±0.061 0.801±0.090*	1.41 ±0.15	1.66 ±0.12
	$\delta_{(ortho)}$	1.59 ±0.12 1.63 ±0.19*	1.81 ±0.31	2.18 ±0.25
	r	0.997 0.993*	0.989	0.995
	s	0.040	0.078	0.065

Table 4 continued

1	2	3	4	5
		0.048 *		
	s_o	0.075	0.159	0.101
		0.113 *		
	n/n_o	7/7	6/6	6/6
		6/6*		

* - log k value for 2-$N(CH_3)_2$ derivative was excluded before data processing.

Table 5

Results of Statistical Data Treatment of log k Values at 40°, 25° and 15° C in Water According to Equations (1), (2) and (3) (see Table 4)

Equation	Temperature	40°C	25°C	15°C
1	2	3	4	5
(1)	$\log k_o^H$	0.024±0.041	-0.352±0.044	-0.606±0.036
	$\varrho^o_{m,p}$	0.961±0.081	1.03 ±0.09	1.05 ±0.070
	r	0.986	0.986	0.993
	s	0.068	0.072	0.058
	s_o	0.167	0.166	0.132
	n/n_o	5/5	5/5	5/5
(2)	$\log k_o^H$	0.011±0.034	-0.347±0.042	-0.632±0.034
		0.012±0.041*	-0.343±0.040*	-0.632±0.041*
	$\varrho^o_{m,p(ortho)}$	0.995±0.051	1.04 ±0.06	1.11 ±0.051
		0.988±0.057*	1.01 ±0.06*	1.10 ±0.057*
	$\varrho_{I(ortho)}$	0.476±0.096	0.536±0.118	0.528±0.095
		0.454±0.113*	0.453±0.112*	0.516±0.114*
	$\delta_{(ortho)}$	1.28 ±0.15	1.26 ±0.18	1.25 ±0.15
		1.22 ±0.20*	1.03 ±0.20*	1.22 ±0.21*
	r	0.995	0.993	0.996
		0.991*	0.991*	0.992*
	s	0.053	0.066	0.053

Table 5 continued

1	2	3	4	5
		0.057*	0.057*	0.058*
	s_o	0.097	0.116	0.089
		0.136*	0.134*	0.124*
	n/n_o	10/10	10/10	10/10
		9/9 *	9/9 *	9/9*
(3)	$\log k_o^H$	0.031±0.071	-0.391±0.013	-0.717±0.095
		0.022±0.004*		-0.655±0.072*
	$\rho_{I(ortho)}$	1.66 ±0.12	1.76 ±0.020	1.86 ±0.15
		1.85 ±0.06*		2.09 ±0.12*
	$\rho^o_{R(ortho)}$	0.889±0.125	0.952±0.021	0.984±0.158
		1.18 ±0.08 *		1.33 ±0.16*
	$\delta_{(ortho)}$	1.47 ±0.24	1.45 ±0.04	1.38 ±0.30
		1.08 ±0.014*		1.98 ±0.28*
	r	0.991	0.999	0.988
		0.999*		0.995*
	s	0.077	0.013	0.097
		0.025*		0.049*

Table 5 continued

1	2	3	4	5
	s_o	0.134 0.059*	0.028	1.154 0.102*
	n/n_o	6/6 5/5 *	6/6	6/6 5/5*

* - Data for 2-$N(CH_3)_2$-derivative were excluded before data processing.

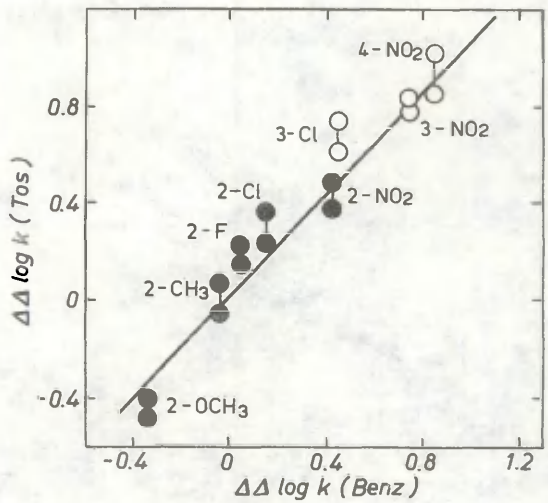

Fig. 3. Relationships between $\Delta\Delta \log k(Tos)_{m,p(ortho)}$ and $\Delta\Delta \log k(Benz)_{m,p(ortho)}$ at 50° C.
$\Delta\Delta \log k^X = \Delta \log k^X(2.25M Bu_4NBr) - \Delta \log k^X(H_2O)$
$\Delta \log k^X = \log k^X - \log k^H$.

points for ortho-substituents fall onto the same straight line with metha- and para-substituents,

$$\Delta\Delta \log k^X(Tos)_{m,p(ortho)} = 0.060(\pm 0.07) + 1.09(\pm 0.08)\,\Delta\Delta \log k^X(Benz)_{m,p(ortho)}$$
$$s = 0.126$$

$$\Delta\Delta \log k^X(Tos)_{(ortho)} = 0.042(\pm 0.013) + 1.16(\pm 0.17)\,\Delta\Delta \log k^X(Benz)_{(ortho)}$$
$$s = 0.132$$

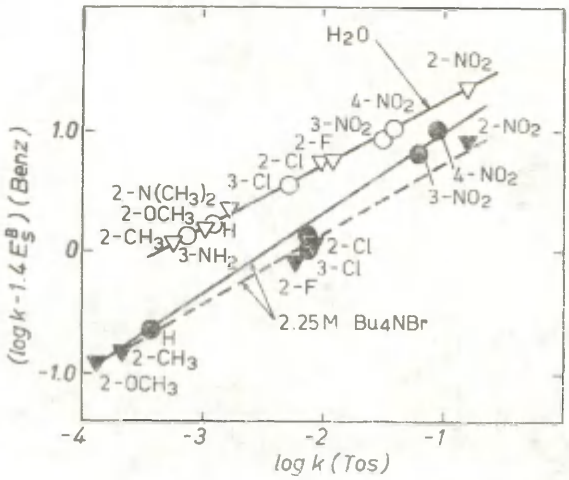

Fig. 4. Relationship between (log k - 1.4 E_s^B) for alkaline hydrolysis of substituted phenyl benzoates and log k for alkaline hydrolysis of substituted phenyl tosylates in water and 2.25 M n-Bu_4NBr solution at 50° C.

In the case of phenyl tosylates both the experimental values of log k and those calculated from the activation parameters were embraced[12].

Fig. 4. presents the dependence of Δlog k - 1.4 E_s^B values for the alkaline hydrolysis of substituted phenyl benzoates on the log k values for the alkaline hydrolysis of

substituted phenyl tosylates in the case of water and the 2.25 M solution of n-Bu_4NBr at 50° C.

While in the case of water solution the points for ortho substituents fall on the same straight line with metha and para-substituents, then passing to the 2.25 M solution of n-Bu_4NBr the points for ortho substituents to some extent deviate from the straight line for metha- and para-substituents.

For water at 50° C we have (see Table 6):

$$\frac{\Delta \log k^X(\mathrm{Tos})_{m,p}}{\Delta \log k^X(\mathrm{Benz})_{m,p}} = \frac{\rho^o_{m,p}(\mathrm{Tos})}{\rho^o_{m,p}(\mathrm{Benz})} = \frac{1.840}{0.945} = 1.95 \qquad (5)$$

$$\frac{\Delta \log k^X(\mathrm{Tos})_{(ortho)}}{(\Delta \log k^X - 1.4E_s^B)(\mathrm{Benz})_{(ortho)}} =$$

$$= \frac{(\rho^o_{m,p(ortho)}\sigma^o + \rho_{I(ortho)}\sigma_I)(\mathrm{Tos})}{(\rho^o_{m,p(ortho)}\sigma^o + \rho_{I(ortho)}\sigma_I)(\mathrm{Benz})} = \frac{1.88\sigma^o + 0.98\sigma_I}{0.945\sigma^o + 0.55\sigma_I} =$$

$$= \frac{1.88(\sigma^o + 0.521\sigma_I)}{0.945(\sigma^o + 0.55\sigma_I)} = 1.99 \qquad (6)$$

where $\Delta \log k^X = \log k^X - \log k^H$

When passing to 2.25 M solution of n-Bu_4NBr the slopes of straight lines in Fig. 4. somewhat change:

$$\frac{\Delta \log k^X(\mathrm{Tos})_{m,p}}{\Delta \log k^X(\mathrm{Benz})_{m,p}} = \frac{3.01}{2.02} = 1.49 \qquad (7)$$

$$\frac{\Delta \log k^X(\mathrm{Tos})_{(ortho)}}{(\Delta \log k^X - 1.4E_s^B)(\mathrm{Benz})_{(ortho)}} = \frac{3.11\sigma^o + 0.59\sigma_I}{1.93\sigma} =$$

$$= 1.60(\sigma^o + 0.19\,\sigma_I)$$

If $\sigma_I \longrightarrow 0$, then the points for ortho substituents fall on one and the same straight line with metha and para substituents.

Table 6

Values of log k_o^H, $\rho^o_{m,p}$, $\rho^o_{m,p(ortho)}$, $\rho_{I(ortho)}$ and δ for Alkaline Hydrolysis of Substituted Phenyl Benzoates and Phenyl Tosylates at 50° C [13]

Parameters	Phenyl benzoates		Phenyl tosylates	
	H_2O	2.25M Bu_4NBr	H_2O	2.25M Bu_4NBr
log k_o^H	0.242 ± 0.024	-0.654 ± 0.030	-2.917 ± 0.013	-3.381 ± 0.109
$\rho^o_{m,p}$	0.945 ± 0.047	2.02 ± 0.06	1.84 ± 0.04	3.01 ± 0.19
$\rho^o_{m,p(ortho)}$	0.939 ± 0.028	1.93 ± 0.06	1.88 ± 0.04	3.11 ± 0.17
$\rho_{I(ortho)}$	0.562 ± 0.055	0	0.98 ± 0.07	0.59 ± 0.29
$\delta_{(ortho)}$	1.41 ± 0.08	1.42 ± 0.13	0	0

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CODING OF BENZENOID AROMATIC COMPOUNDS AND THEIR DERIVATIVES

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Technique for canonical coding of benzenoid aromatic compounds, their substituents and heteroderivatives is suggested. It is relatively simple, compact and universal to be applied in relation to the indicated class of compounds. The procedure of obtaining the canonical code is described. Examples of codes for a series of compounds of this class are given. The suggested coding technique is compared to those used before.

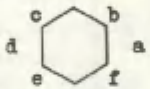
The progress made in the chemical information theory has called for working out the coding system of chemical compounds. Unfortunately, there are several problems to be solved yet in connection with coding of polycyclic compounds[1].

The present paper deals with a rather important group of polycyclic compounds - benzenoid aromatic compounds (BAC), their substituted and hetero derivatives. The structures of the BAC molecules can be well described on a hexagonal network by means of polymino hexagons[2] (which is a contiguous part of a planar hexagonal mosaic). For the computer input, storage and processing of the information on polyminos, we need such a method of their formal description

which would satisfy all the following requirements: 1) unambiguity of polymino restoration from the description; 2) compactness of description; 3) relatively simple and structurally understandable description; 4) convenience of its input, storage and processing.

In order to identify the polyminos it is necessary to introduce a canonical description which would adequitely correspond to the polymino. It is suggested that there is a certain formal description (one of polymino determiners) that can be built using conventional means, while the more complicated task of canonization of the description should be performed automatically, using a computer.

Here we give a possible formal description of hexagonal polymino embracing all these requirements. The sides of an equal-sided hexagon corresponding to the benzene ring are marked as follows:



Certainly, this is not the only possibility of marking.

A random hexagon in the polymino is chosen as the starting point; then the graph of continuity of the hexagons is built as an oriented tree with its roots at the initial hexagon chosen.*

When proceeding along the tree, we mark each hexagon with a letter corresponding to that inside the previous one to which the next one is connected. The branching routes, with an exception of the last one, will be put into the brackets. As a result, we get linear succession of letters a,.....,f and brackets, which is actually meant to be the formal description of polymino.

Such a description depends on the orientation of the polymino of the plane, choice of the route covering the tree, as well as on the way of passing through it, and there certainly are several possibilities for doing it.

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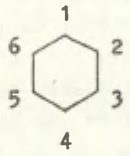
* For explanations of theoretical and graph terms, see Ref.3.

Thus, for instance, anthracene can be described as aa, (d)a, (a)d, dd; triphenylene - a(f)b, e(f)d, c(d)b, but also (f)(d)b, a(b)f, e(d)f, c(b)d, (f)(b)d, (b)(d)f, (b)(f)d, (d)(f)b, (d)(b)f.

One way for obtaining the canonical description of the hexagonal polymino can be created as follows. Polymino is orientated on a surface in accordance with the nomenclature of IUPAC[4]. For cases when those regulations do not ensure the unambiguity of the orientation, we have worked out an algorithmic modification of the nomenclature regulation A22, guaranteeing the unambiguity of the BAC orientation on the plane[5].

As the root, the first hexagon on the left in the basic horizontal line is taken. In order to create the covering tree, first, we number, from left to right the adjacent hexagons of the basic horizontal line. After that the hexagons adjacent to the first root that have not been numbered yet, will be numbered and connected to it in the lexicographical order of the side of adjacency. The procedure is repeated for the second, third, etc. hexagons until all the hexagons are connected to the tree. The branchings will be written in the order which is contrary to the lexicographical one. The canonical descriptions of a few BAC are given in Table 1.

The derivatives of BAC can be coded as follows. The vertices of an equilateral hexagon, corresponding to the benzene ring are marked as:



In the case of homo substitution (substituents of a similar type) the code of the BAC derivative will be obtained by insertion of the set of numbers corresponding to the places of substitution of the benzene ring into the fragment of the BAC code that represents this ring. At the same

time we suppose that the substitution type is known from the context, otherwise one must follow the procedure of hetero substitution described below.

In the case of hetero substitution (the substituents belong to different types), in the code of a derivative the substituted atom (group) should be marked after each number.

Canonical descriptions (codes) of a set of BAC are given in Table 2.

In comparison with the line-formulae of Wiswesser[1] that have been applied for BAC our canonical descriptions meant specially for BAC, are to our mind more definite, easier to use in automatic treatment, as well as more descriptive.

Parametric coding is an even simpler and more compact coding technique[6]. Nevertheless, the means of coding that we have suggested can have a wider range of application. Unlike perimetric coding, this technique enables one to code quite easily the compounds with "holes", i.e. non-contiguous compounds (e.g. circulenes), as well as any substituents and hetero derivatives (it does not depend on the closeness of the atom to the perimeter). This can be explained by the fact that, when moving along the covering tree, we can choose any hexagon of polymino (which would not be possible in the case of moving along the perimeter).

The method of coding of cycling systems by E.A. Geivandov[7] appeals because of its simplicity, although unlike our method, it does not ensure the canonical character of the code.

The canonical description of polimino can be used for solving the problems of isomorphism[8]. It can be used quite successfully in the case of computerized creation of the structural formulae of BAC. We have worked out a computer program that allows us to create a canonical description of a benzenoid aromatic compound from its formal description, which is also checked against being unrealistic, during the coding process.

Table 1

Canonical Description of Some Benzenoid Aromatic Compounds

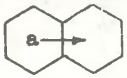
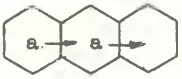
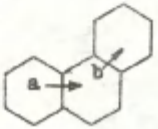
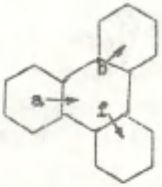
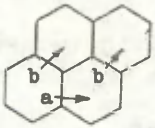
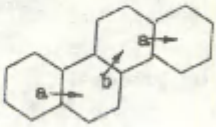
BAC	Canonical description	Explanation
1	2	3
Naphthalene	a	
Anthracene	aa	
Phenanthracene	ab	
Triphenylene	a(f)b	
Pyrene	(b)ab	
Chrysene	aba	

Table 1 continued

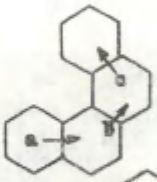
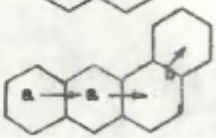
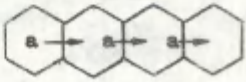
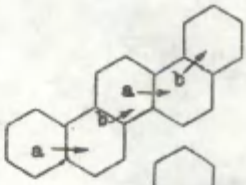
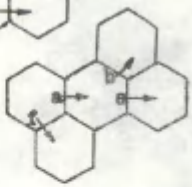
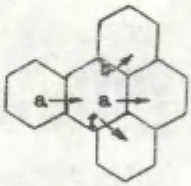
1	2	2
Benzo[c]phenathrene	abc	
Benz[a]anthracene	aab	
Naphthacene	aaa	
Picene	abab	
Perylene	(f)a(b)a	
Benzo[e]pyrene	a(f)(b)a	
Pentacene	aaaa	

Table 1 continued

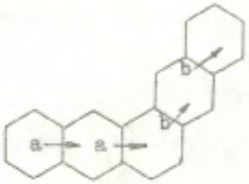
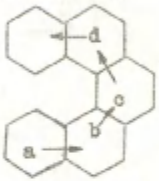
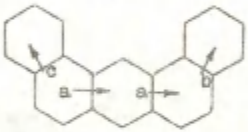
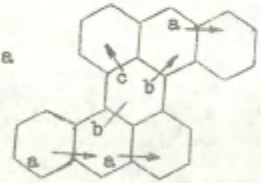
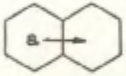
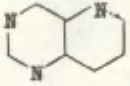
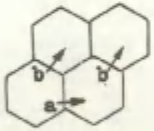
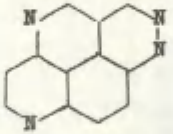
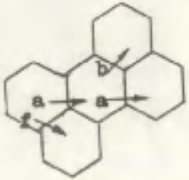
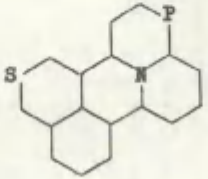
1	2	3
Pentaphene	aabb	
Dibenzo[c,g]-phenanthrene	abcd	
Dibenz[a,j]-anthracene	(c)aab	
Dibenzo[a,k]-perylene	a(b(c)ba)a	

Table 2

Canonical Description of Some Substituted and Hetero Derivatives of BAC

BAC and its canonical description		Derivative	Canonical description of derivatives
	a		4 6 a 1
	(b)ab		4 (b 6) a b 2 3
	(f)a(b)a		6 S (f) a 2 N (b 2P)a

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C O N T E N T S

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