STERIC EFFECTS IN ALKALINE SOLVOLYSIS OF DIARYL ANILIDOPHOSPHATES

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Analysis of the products of solvolysis of aryl esters of anilidophosphoric acids in water–2-propanol mixture excludes that the reaction proceeds via E1cB mechanism. Analysis of the reaction products of solvolysis of methyl-substituted compounds made it possible to evaluate the importance of the reported steric hindrance by CH_3 group. The dependence of rate constants of the solvolysis on solvent system has been established.

Alkaline solvolysis of diaryl esters of anilidophosphoric acids in water–ethanol mixture was postulated to proceed via S_N2 mechanism[1]. This assumption has been based on the values of activation entropies and Hammett ϱ constants as well as on the presence of delay on conversion curves at the beginning of the reaction[1]. These conclusions were confirmed by the optical inversion accompanying alkaline methanolysis of phenyl ethyl anilidophosphate[2]. The proposed mechanism is also supported by the selectivities of the alkaline solvolysis in the system water–alcohol[3]. All the experiments mentioned above demonstrate unambiguously dominant effect of the reaction proceeding by S_N2 mechanism but they do not exclude a parallel reaction via E1cB mechanism, even though proceeding to a small extent. Recently, equilibrium constants of the acid-base equilibrium in water–alcohol mixtures for alkoxide ions of different size have been calculated[4,5], which gives an opportunity to make the above conclusions more accurate by studying steric effects of nucleophiles and electrophiles on the composition of reaction products. Such an approach provides experimental data needed for more detailed analysis of the above question.

EXPERIMENTAL

Compounds

Diaryl esters of substituted anilidophosphoric acids of the formula $(R^1O)_2P(O)NHR^2$: $R^1 = R^2 = C_6H_5$ (*Ia*, ref.[6]); $R^1 = C_6H_4-CH_3(o)$, $R^2 = C_6H_5$ (*Ib*, ref.[7]), $R^1 = C_6H_4-CH_3(p)$, $R^2 = C_6H_5$ (*Ic*, ref.[7]); $R^1 = C_6H_5$, $R^2 = C_6H_4-CH_3(o)$ (*Id*, ref.[8]), $R^1 = R^2 = C_6H_4-$

$-CH_3(o)$ (*Ie*, ref.[8]); $R^1 = C_6H_5$, $R^2 = C_6H_4-CH_3(p)$ (*If*, ref.[8]); $R^1 = R^2 = C_6H_4-CH_3(p)$ (*Ig*, ref.[8]) were prepared by reported procedures as indicated.

For purposes of chromatographic analysis of the reaction systems also sodium salts of aryl anilidophosphates of the formula (*II*) $(NaO)(R^1O)P(O)NHR^2$ were synthesized, using the general method of hydrolysis of diaryl anilidophosphates[9]. The following compounds were obtained: $R^1 = R^2 = C_6H_5$(*IIa*, ref.[9]); $R^1 = C_6H_4-CH_3(o)$, $R^2 = C_6H_5$(*IIb*); $R^1 = C_6H_4-$ $-CH_3(p)$, $R^2 = C_6H_5$ (*IIc*, ref.[10]); $R^1 = C_6H_5$, $R^2 = C_6H_4-CH_3(o)$ (*IId*); $R^1 = R^2 =$ $= C_6H_4-CH_3$ (*o*) (*IIe*); $R^1 = C_6H_5$, $R^2 = C_6H_4-CH_3$ (*p*) (*IIf*, ref.[10]); $R^1 = R^2 = C_6H_4-$ $-CH_3(p)$ (*IIg*).

Finally, also for analysis of the reaction systems, the series of methyl aryl esters (*III*) of the formula $(R^1O)(CH_3O)P(O)NHR^2$ and of 2-propyl aryl esters (*IV*) $(R^1O)(C_3H_7O)P(O)NHR^2$ were prepared by transesterification (partial alcoholysis) of diaryl esters of anilidophosphoric acids at room temperature for 1 to 14 days, depending on the compound used. If the condition of equimolar concentrations of alkoxide and the diaryl ester in the medium of anhydrous methanol, ethanol (resp. 2-propanol) is ensured, the transesterification would proceed predominantly to the first step, as depicted by Eq. (*A*)

$$(R^1O)_2P(O)NHR^2 + YO^- \rightarrow (R^1O)(YO)P(O)NHR^2 + R^1O^- \qquad (A)$$
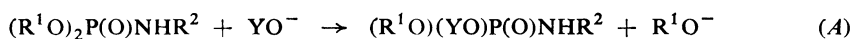
in which R^1, R^2 denote aryl groups and Y is methyl or isopropyl. The pure alkyl aryl anilido-phosphates were obtained by chromatographic separation on a silica gel column with the use of diethyl ether. This method afforded the following compounds: $R^1 = R^2 = C_6H_5$ (*IIIa*); $R^1 = C_6H_4-CH_3(o)$, $R^2 = C_6H_5$ (*IIIb*); $R^1 = C_6H_4-CH_3(p)$, $R^2 = C_6H_5$ (*IIIc*); $R^1 = C_6H_5$, $R^2 = C_6H_4-CH_3(o)$ (*IIId*); $R^1 = R^2 = C_6H_4-CH_3$ (*o*) (*IIIe*); $R^1 = C_6H_5$, $R^2 = C_6H_4-CH_3$. $.(p)$ (*IIIf*); $R^1 = R^2 = C_6H_4-CH_3(p)$ (*IIIg*); $R^1 = R^2 = C_6H_5$ (*IVa*, ref.[2]); $R^1 = C_6H_4-$ $-CH_3(o)$; $R^2 = C_6H_5$ (*IVb*); $R^1 = C_6H_4-CH_3(p)$, $R^2 = C_6H_5$ (*IVc*); $R^1 = C_6H_5$, $R^2 =$ $= C_6H_4-CH_3(o)$ (*IVd*); $R^1 = R^2 = C_6H_4-CH_3(o)$ (*IVe*); $R^1 = C_6H_5$, $R^2 = C_6H_4-CH_3(p)$ (*IVf*); $R^1 = R^2 = C_6H_4-CH_3(p)$ (*IVg*).

Dimethyl anilidophosphates were prepared earlier[11]. The purity of the above compounds was checked by C, H, N, P analysis. The results of these analyses, along with melting points of novel compounds are presented in Table I.

Procedure

Solvolysis of diaryl anilidophosphates was carried out at $25 \pm 0.1°C$ in water–methanol mixtures containing $w = 60$, 70, 80, and 90 wt.% methanol and in a water–2-propanol mixture ($w = = 70$ wt.% 2-propanol). In these mixtures $2 . 10^{-3}$ mol dm^{-3} solutions of the diaryl esters *Ia—Ig* and their solvolytic products were prepared (except for $w = 60$ wt.% methanol where due to low solubility of the esters only $1 . 10^{-3}$ mol dm^{-3} solutions were obtained) and in the same solvents also 0.2 mol dm^{-3} NaOH (Lachema, per analysis) solutions. After mixing the same volumes of solutions of a given diaryl ester and sodium hydroxide, the solvolytic reaction was followed for 1 to 3 h (depeding upon the reactivity of the ester) until the distinct indication of the presence of dimethyl ester of anilidophosphoric acid has appeared. Samples for chromato-graphic analysis were withdrawn at time intervals from 3 to 20 min and the reaction was stopped by mixing with the same volume of 0.1 mol dm^{-3} HCl. The content of the methanol–water mixture in HCl solution was chosen such that the composition of the resulting mixture injected into the column be the same as the composition of the mobile phase (for supressing system peaks). Analyses were made on Spectra-Physic chromatograph, using the set: pump SP 8700, UV-vis detector SP 8840, and integrator SP 4100. Column LiChrosorb RP-8, 10 μm, 4 × 250 mm,

TABLE I

Novel compounds

Compound	M.p., °C solvent	Formula M.w.	Calculated/Found			
			% C	% H	% N	% P
IIb	—	$C_{13}H_{13}NNaO_3P$	54·75	4·60	4·91	10·84
	acetone	285·20	54·71	4·59	4·35	10·70
IId	—	$C_{13}H_{13}NNaO_3P$	54·75	4·60	4·91	10·84
	acetone	285·20	54·70	4·64	4·52	10·99
IIe	—	$C_{14}H_{15}NNaO_3P$	56·07	5·05	4·68	10·35
	ethanol	299·23	55·91	5·12	4·08	10·32
IIg	—	$C_{14}H_{15}NNaO_3P$	56·07	5·05	4·68	10·35
	ethanol	299·23	56·36	5·14	4·74	10·27
IIIb	79—80	$C_{14}H_{16}NO_3P$	60·65	5·82	5·05	11·17
	methanol–water	277·25	60·53	5·63	5·00	11·04
IIIc	67	$C_{14}H_{16}NO_3P$	60·65	5·82	5·05	11·17
	methanol–water	277·25	60·65	5·92	5·09	10·98
IIId	80	$C_{14}H_{16}NO_3P$	60·65	5·82	5·05	11·17
	methanol–water	277·25	60·71	5·93	4·96	11·05
IIIe	90—92	$V_{15}H_{18}NO_3P$	61·85	6·23	4·81	10·63
	methanol–water	291·27	61·98	6·14	4·25	10·44
IIIf	71—72	$C_{14}H_{16}NO_3P$	60·65	5·82	5·05	11·17
	methanol–water	277·25	60·41	5·71	5·16	11·02
IIIg	69—71	$C_{15}H_{18}NO_3P$	61·85	6·23	4·81	10·63
	methanol–water	291·27	61·98	6·24	5·07	10·49
IVb	77—78	$C_{16}H_{20}NO_3P$	62·95	6·60	4·59	10·15
	hexane	305·30	63·16	6·53	4·60	10·17
IVc	55—57	$C_{16}H_{20}NO_3P$	62·95	6·60	4·59	10·15
	methanol–water	305·30	63·52	6·92	4·60	9·98
IVd	80—81	$C_{16}H_{20}NO_3P$	62·95	6·60	4·59	10·15
	methanol–water	305·30	63·17	6·52	4·65	9·41
IVe	65—66	$C_{17}H_{22}NO_3P$	63·94	6·95	4·39	9·70
	methanol–water	319·33	63·41	6·96	4·57	9·76
IVf	124	$C_{16}H_{20}NO_3P$	62·95	6·60	4·59	10·15
	methanol–water	305·30	62·41	6·34	4·71	10·02
IVg	85—87	$C_{17}H_{22}NO_3P$	63·94	6·95	4·39	9·70
	methanol–water	319·33	63·71	6·79	4·40	9·52

mobile phase methanol–water (80 : 20), flow rate 1·5 ml/min, injected volumes of samples 10 μl, detection wavelength 230—233 nm. Determination was made by the method of external standard, calibration was performed at five concentration levels. Results of chromatographic analyses are presented in Table II.

RESULTS AND DISCUSSION

In the basic medium of the solvent formed by the mixture of two protogenic components, the equilibrium is established according to Eq. (B).

$$YOH + OH^- \rightleftarrows YO^- + H_2O \qquad (B)$$
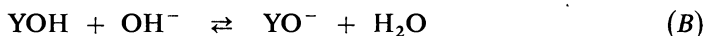
The solvolysis of diaryl esters of anilidophosphoric acids takes place only in the basic region. Based on the present knowledge, the reaction proceeds predominantly by S_N2 mechanism[1,3]. The compounds prepared in this work make it possible to detect even very small amounts of the products which would indicate the parallel occurence of E1cB mechanism. In general, the reaction under study can be depicted by Scheme 1 in which L^- is the lyate ion shown in Eq. (B). The upper branch of Scheme 1 corresponds to S_N2 mechanism with the intermediate in the form of trigonal bipyramid, the lower one to E1cB mechanism involving the planar intermediate. Unfortunately, sufficient information is not available concerning the question whether the planar intermediate reacts with the lyate ion L^- or rather with the molecule HL to form the final product. However, according to Eq. (B), in the basic medium there are present both molecules of 2-propanol and 2-propoxide ions, the concentration of the latter being given by the total concentration of the

TABLE II

Results of chromatographic analyses of products of solvolysis of difenyl anilidophosphates in the system water–methanol (MeOH)

Compound	$c_{methyl\,aryl\,ester}/c_{Na\,salt}$			
	90% MeOH	80% MeOH	70% MeOH	60% MeOH
Ia	23·4	11·6	9·1	6·98
Ib	4·0	2·6	2·3	3·0
Ic	10·7	7·5	6·2	3·98
Id	93·1	77·1	28·6	18·4
Ie	6·1	3·9	5·5	2·1
If	10·9	7·5	7·2	6·3
Ig	16·7	7·2	6·2	3·8

base and by the known ratio of 2-propoxide to hydroxide ions concentrations[5]. Their concentration thus in alkaline region is not zero. Although in the reaction mixture there is sufficient amount of nucleophile (both 2-propanol and also 2-propoxide ions), in none of the cases studied we have found among the reaction products of alkaline solvolysis in the system water–2-propanol the aryl 2-propyl ester of anilidophosphoric acid. The reaction was exclusively hydrolytic. However, in the system water–methanol and water–ethanol there proceeds transesterification[3]. This fact indicates that the bulky 2-propoxide ion or 2-propanol does not participate in the reaction according to Scheme 1. Such a steric hinderance should manifest itself

$$(R^1O)_2P(O)NHR^2 \ + \ L^{(-)}$$
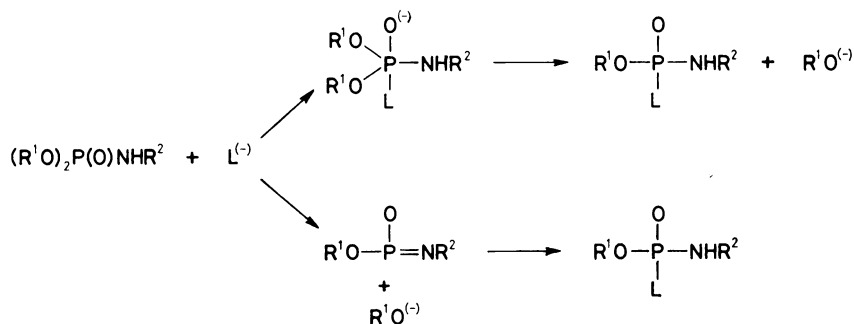
SCHEME 1

only in the case of trigonal bipyramidal intermediate and not in the case of planar intermediate. This finding thus confirms the earlier formulated S_N2 mechanism of this reaction[1] and at the same time it excludes the presence, even in traces, of the reaction proceeding via E1cB mechanism.

Reported data[12] and our previous experiments[2] combined with the already mentioned optical inversion allow to conclude that the attack of nucleophile is stereospecific and takes place at the plane of trigonal bipyramid of the substrate which is opposite to the leaving group. These experiments are contradicted by the assumption according to which the methyl group in the ortho position of dialkyl aryl phosphates exhibits steric effects. As the leaving group is here the phenoxide ion, one can expect that the atack of nucleophile is not stereospecific and takes place also at the planes in the vicinity of the leaving group. This view[13] is supported by change in the rate constant of alkaline hydrolysis of dialkyl aryl esters in the system water–dioxane. Data presented in this work allow to evaluate the steric effect of the *ortho* methyl group on reaction rate. For this purpose the solvolysis of compounds *Ia* to *Ig* in the system water–methanol had been made and the reaction products were determined quantitatively by chromatography. The previous experiments along with the results of chromatographic analyses lead to Scheme 2 where

$k_3 \ll k_5$, since it is known that cleavage of aryl esters proceeds at much faster rate compared to the reaction of alkyl esters[14,15]. The presence of monomethyl ester of anilidophosphoric acid was not detected chromatographically earlier then the peak of dimethyl ester of anilidophosphoric acid has appeared. This demonstrates that the reaction characterized by the rate constant k_4 is a slow process.
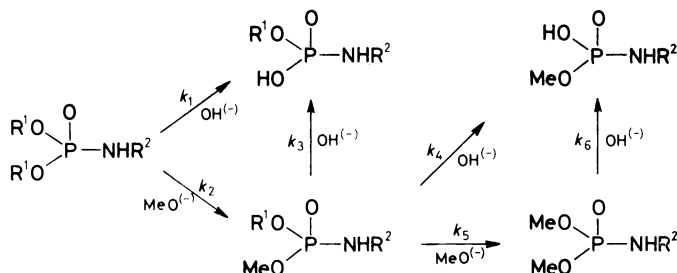
Scheme 2

The ratio of concentration of the salt of phenyl ester of anilidophosphoric acid to methyl phenyl anilidophosphate is given by the expression $k_1[OH^-]/k_2[CH_3O^-]$. At the given and known ratio of concentrations of lyate ions (Table II) its value is thus determined by the k_1/k_2 ratio. It is worthy of mentioning that concentrations of solvolytic products were determined with the less than 5% error. Comparison of concentrations of the salt formed $(c(II))$ and of the methyl aryl ester $(c(III))$ of compounds Ia, Ib or Id and Ie shows that the introduction of methyl group into *ortho* position of the aryl ester group supresses methanolysis in favour of hydrolysis. This, at first sight, could be taken as support for the conclusions drawn from kinetic measurements[13] since methoxide ion is bulkier than OH^- ion. However, as follows from comparison of concentration proportions of the reaction products Ia and Id or Ib and Ie, the *ortho*-methyl group in the anilide supresses markedly hydrolysis in favour of methanolysis, or its effect is not uniform. Also introduction of methyl group to *para* position of the aryl ester group results in non-uniform effect. In some cases it supresses methanolysis (as follows from comparison of Ia and Ic), in the other cases it essentially shows no effect on their composition or even supports methanolysis (as follows from comparison of If and Ig). However, in none of the above cases the methyl group in *para* position can be expected to exhibit steric effects. From the above results it can be concluded that the reactivity of the substrate is not affected by the steric effect of methyl group. The different reactivity observed can most likely be attributed to the electron defficiency on the phosphorus atom of the electrophile and to its polarisability, similarly to other S_N2 reactions[16], rather then to the steric effect of the *ortho*-methyl group.

Finally, from Table II one important piece of information can be extracted. In literature there exist two approaches to calculating the activities of lyate ions. One procedure is based on the measurement of the ratio of concentrations of reaction products of parallel hydrolysis and alcoholysis, assuming that the ratio of the rate constants is independent of the reaction medium[17]. The other procedure is based on the mutual linear dependence of Gibbs energies for transfer of anions[4]. In our previous communication[5] we have assumed, reasoning by analogy to neutral solvolysis, that the rate constants of alkaline solvolysis depend on the solvolytic medium in different way and that the first method thus cannot be utilized[17]. Data in Table II corroborate this conclusion.

For the ratio of concentrations of the salt to the ester it holds that

$$c(II)/c(III) = k_K c(OH^-)/k_E c(MeO^-),\qquad (1)$$

where k_K and k_E are rate constants of hydrolysis and alcoholysis, $c(OH^-)$ and $c(MeO^-)$ are concentrations of the hydroxyl and alkoxide ions. As diaryl anilidophosphates are essentially insoluble in water, k_K cannot be measured. However, Eq. (1) should be valid in general. Therefore, for solvolysis of two starting compounds in the same medium the following relation has to hold:

$$\frac{c(II)/c(III)}{c'(II)/c'(III)} = \frac{k_K/k_E}{k_K'/k_E'} = P,\qquad (2)$$

where concentrations and rate constants for the second compound are dashed Providing that the ratios of rate constants do not depend on the medium, as required by the mentioned method[17], the parameter P would be independent of the alcohol concentration. In Table III are presented some P's obtained from data of Table II

TABLE III

P's calculated from ratios of reaction product concentrations for different compounds at $25°C$ in dependence on methanol concentration

P^a	$w, \% CH_3OH$			
	90	80	70	60
Ia/Id	0·25	0·15	0·32	0·38
Ia/Ic	2·1	1·55	1·26	1·11
If/Ig	0·65	1·04	1·11	1·66

^{a} Eq. (2).

as an example. It becomes evident that P's are not constant and thus the independence of the ratio of rate constants on reaction medium cannot be expected. This demonstrates that the discussed method[17] gives only approximate results.

Summarizing, the knowledge of the ratio of activities of lyate ions has not yet been fully appreciated in literature. Based on this knowledge, one can explain e.g. the efficiency of drying of alcohols by sodium or magnesium[18] or the composition of products of solvolytic reactions in alkaline region (see cf. studies by Murto[19,20]). The present work demonstrates that the method can provide further information which would be otherwise available with difficulty or would get away from experimental evidence.

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