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Some Aspects of Isokinetic Law and Compensation Effect in Organophosphorus Compounds. Part II. Correlation Analysis of *O*-Alkyl-*S*-2-Dimethylaminoethyl Methylphosphonothiolates and Their Tetraalkylammonio Derivatives

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The correlation analysis of alkaline hydrolysis and inhihibition of BuChE with *O*-alkyl-*S*-2-dimethylaminoethyl methyl phosphonothiolates and their tetraalkylammonio derivatives are described.

The logarithm dependence of the rate constants of these reactions at two different temperatures confirms that reactions of OH^- ion and of BuChE with these esters show isokinetic functions i. e. these esters form isokinetic series.

The correlation analysis with different Hammets constants showed that alkoxy groups bonded to phosphours^{IV} have somewhat greater resonance effect ($\alpha = 1.21$) in comparison to the inductive effect in alkaline hydrolysis reaction.

The application of correlation equations represents an important part in the evaluation of electronic and steric effects of substituents bonded to tetrahedral phosphorus in nucleophilic substitution reactions. It is also common that in studying these reactions the question of isokinetic relations is considered on basis of the exsistence of one or more reactions series in examining series of compounds.

Studying the alkaline hydrolysis of *O*-alkyl-*S*-2-dimethylaminoethyl methylphosphonothiolates and *O*-alkyl-*S*-2-trimethylammonioethyl methylphosphonothiolates methyl sulfato[1], and the inhibition of pseudocholinesterase (BuChE)[2,3] it can be confirmed that the rate constant of these reactions does not change proportionally with the activation energy. Simultaneously with the increase of carbon atom number in alkyl radicals of RO group, activation energy and l gA are changed paralelly, and the free energy of activation shows small changes (Figures I and II).

Similar compensation effects are noticed in alkaline hydrolysis of phosphorofluoridates, phosphonofluoridates and phosphinofluoridates esters[4], as well as of esters of phosphinochloridates[5], and of *p*-nitrophenolyc derivatives of phosphoric acid[6,7].

Let us consider the parameters of linear equation $E_a = a + b \lg A$ and correlation coeficient for *O*-alkyl-*S*-2-dimethylaminoethyl methylphosphonothiolates and their tetraalkylammonio derivatives which are given in Table I.

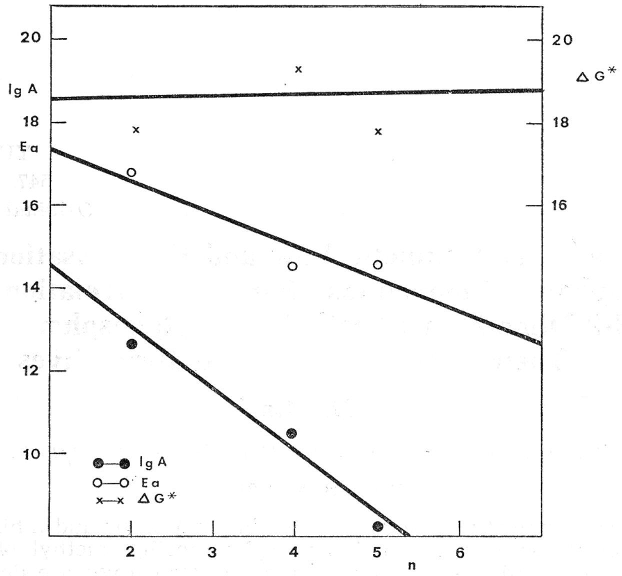

Figure 1. The dependence of activation parameters with carbon number in alkyl radicals RO group of *O*-alkyl-*S*-2-dimethylaminoethyl methylphosphonothiolates

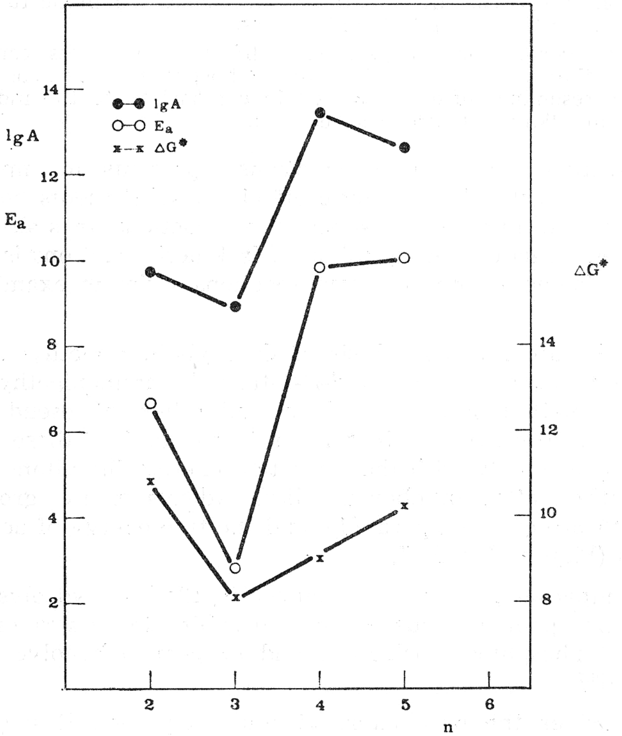

Figure 2. The dependence of activation parameters with carbon number in alkyl radicals RO group of *O*-alkyl-*S*-2-trimethylammonioethyl methylphosphonothiolates methyl sulfato.

TABLE I

Linear Equation Parameters of $E_a = a + b\,\mathrm{lg}A$ $CH_3(RO)P(O)SCH_2CH_2X$

№	X	reaction	*a*	*b*	*r*
1.	$N(CH_3)_2$	with OH^- ion	4.5766	0.9781	0.87
2.	$\overset{+}{N}(CH_3)_3 \cdot CH_3\,SO^-_4$	,,	—6.3427	1.9786	0.99
3.	$N(CH_3)$ and $\overset{+}{N}(CH_3)_3 \cdot CH_3\,SO^-_4$	,,	5.2984	0.8780	0.77
4.	$N(CH_3)_2$ and $\overset{+}{N}(CH_3)_3 \cdot CH_3\,SO^-_4$	inhibition BuChE	—7.6556	1.3661	0.94

From the above results it is obvious that with alkaline hydrolysis reactions of these esters weak correlation of activation energy and lgA is noticed, while the reaction of inhibition BuChE with these esters shows a satisfactory correlation.

However, Pal'm[8] and Exner[9-11] proved that isokinetic relation of enthalpy and entropy activation are more correctly to studyed in linear correlation, in the real dependence of $\mathrm{lg}k^1$ and $\mathrm{lg}k^2$ at two different temperatures. The rate constant of alkaline hydrolysis in its logarithm expression showed a linear correlation in coordinates $\mathrm{lg}k_2{}^1 — \mathrm{lg}k_2{}^2$. From linear equation we calculated by the least square method

$$\mathrm{lg}k_2{}^2 = a + b\,\mathrm{lg}k_2{}^1 \tag{1}$$

its parameters and correlation coeficient (r), whereby a very good correlation of rate constant of alkaline hydrolysis of *O*-alkyl-*S*-2-dimethylaminoethyl methylphosphonothiolates, as well as their tetraalkylammonio derivatives is noticed. (Table II)

It is especially interesting to point out that good linear correlation is noticed for the whole series of examined compounds with amino and ammonio derivatives of the esters of phosphonothiolic acid. The obtained linear equation of logarithm rate constant at 30 °C is described as follows.

$$\mathrm{lg}k_2{}^{40} = 0.3169 + 0.9961\,\mathrm{lg}k_2{}^{30} \tag{2}$$

TABLE II

Linear Equation Parameters and Correlation Coeficient of $l\,gk_2{}^2 = a + b\,l\,gk^1{}_2$ *of* $CH_3(RO)P(O)SCH_2CH_2X$

№	X	temperature		reaction	*a*	*b*	*r*
		t_1/°C	t_2/°C				
1.	$N(CH_3)_2$	30	40	with OH^-	0.3035	0.9840	0.998
2.	,,	30	50	,,	0.6237	1.0131	0.995
3.	,,	40	50	,,	0.3158	1.0433	0.997
4.	$\overset{+}{N}(CH_3)_3 \cdot CH_3SO^-_4$	30	40	,,	0.3381	0.9110	0.999
5.	,,	20	40	,,	0.6384	0.8302	0.998
6.	,,	20	30	,,	0.3315	0.9407	0.998
7.	$N(CH_3)_2$ and $\overset{+}{N}(CH_3)_3 \cdot CH_3SO^-_4$	30	40	,,	0.3169	0.9961	0.999

with the correlation coeficient r = 0.999. The logarithm diagram of the rate constant of alkaline hydrolysis in examined compounds is shown on Figure 3.

The very high grade of correlation coeficient confirms that *O*-alkyl-*S*-2-dimethylaminoethyl methylphosphonothiolates and *O*-alkyl-*S*-2-trimethylammonioethyl methylphosphonothiolates methyl sulfato make one reaction series with a similar alkaline hydrolysis mechanism.

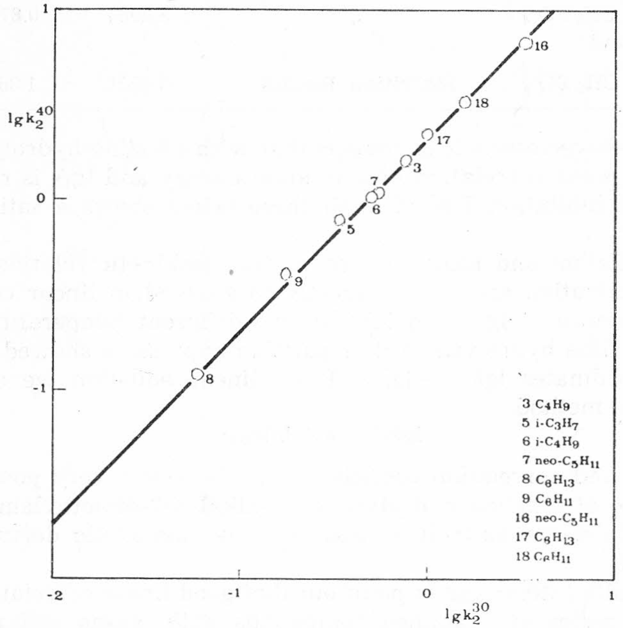

Figure 3. The dependence of alkaline hydrolysis rate constant ($\lg k_2$) at temperatures 30° and 40 °C of *O*-alkyl-*S*-2-dimethylaminoethyl methylphosphonothiolates (3,5—9) and their tetraalkilammonio derivatives (16—18).

In these coordinates a linear relationship is obtained also for the reactions of *O*-alkyl-*S*-2-dimethylamionethyl methylphosphonothiolates with BuChE (Figure 4).

The parameters and the correlation coeficient of the linear equation

$$\lg k_i^2 = a + b \lg k_i^1 \qquad (3)$$

Calculated by the least square method are given in Table III. In these examples good correlation of $\lg k_i$ at two different temperatures is also noticed, confirming that the inhibition of a ferment in the examined compounds undergoes a similar mechanism.

At last, the correlation $\lg k_2$ and $\lg k_i$ with the examined compounds of these two series at temperatures 20 °C* and 30 °C yield the linear equation

$$\lg k^{30} = -0.3270 + 1.0167 \lg k^{20} \qquad (4)$$

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* The rate constants of alkaline hydrolysis at this temperature are calculated from the Ahrrenius equation[2].

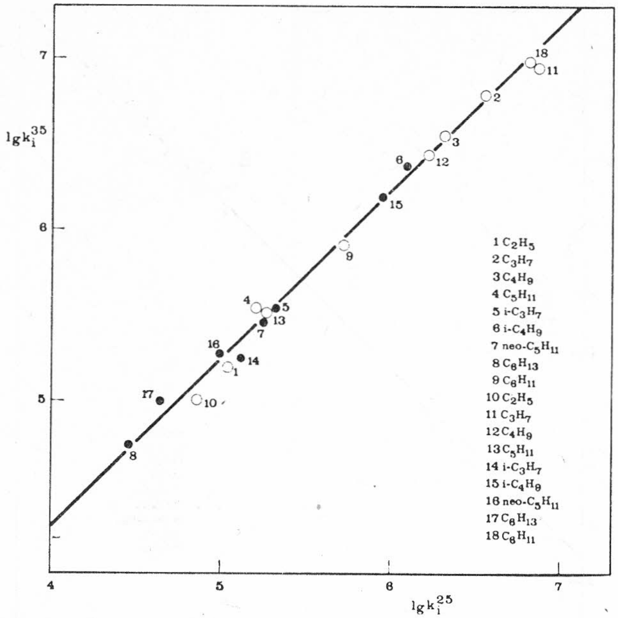


Figure 4. The dependence of inhibition rate constant ($\lg k_i$) at temperatures 25⁰ and 35 ⁰C of *O*-alkyl-*S*-2-dimethylaminoethyl methylphosphonothiolates (**1—9**) and their tetraalkilammonio derivatives (**10—18**).

TABLE III

Linear Equation Parameters and Correlation Coeficient of $l\,gk_i^2 = a + b\,l\,gk_i^1$ *of* $CH_3(RO)P(O)SCH_2CH_2X$*

№	temperature t_1/⁰C	 t_2/⁰C	*a*	b	*r*
1.	20	25	0.2214	0.9829	0.999
2.	20	30	0.3922	0.9721	0.996
3.	20	35	0.6635	0.9419	0.991
4.	25	30	0.1645	0.9906	0.999
5.	25	35	0.4309	0.0619	0.996
6.	30	35	0.2634	0.9724	0.998

* $X = N(CH_3)_2$ and $\overset{+}{N}(CH_3)_3 \cdot CH_3SO_4^-$

with a correlation coeficient $r = 0.995$, confirming that these compounds reacting with OH ion and esteratic part of the ferment represent most likely a hydroxilic group of serine that make isokinetic series (Figure 5).

Based on the equation $\lg k^{T_2} = a + b \lg k^{T_1}$, we have calculated the isokinetic temperature[11]. For the reaction of alkaline hydrolysis of *O*-alkyl-*S*-2-dimethylaminoethyl methylphosphonothiolates (β = 52.9 K) and of *O*-alkyl-*S*-2-trimethylammonioethyl methylphosphonothiolates methylsulfato (β = 469.7 K), the isokinetic temperatures confirmed that the reactivities of these compounds increase when changing the activation enthalpy. The reaction inhibition BuChE with these esters, also, confirmed that the rate constant is controled by the activation enthalpy (β = 65.3 K). The same results we have obtained from equation (4), with a isokinetic temperature β = 96.5 K that means in both

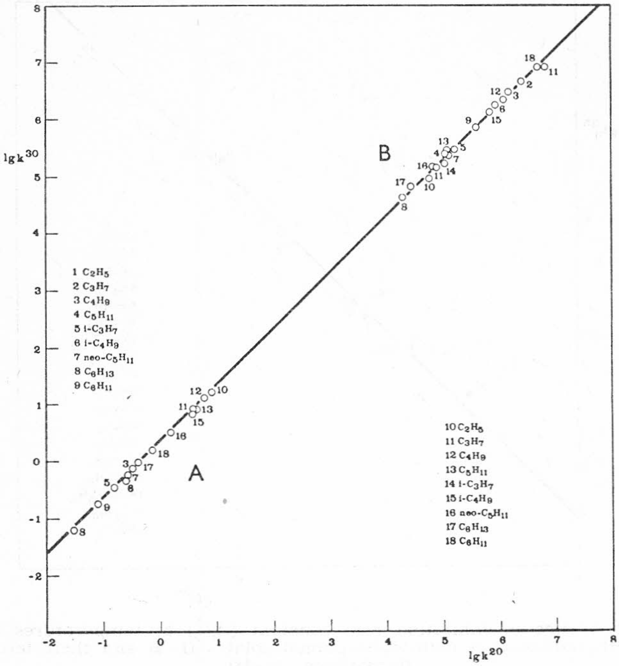


Figure 5. The dependence of alkaline hydrolysis rate constant (A) and inhibition rate constant (B) (lg*k*) at temperatures 20⁰ and 30 ⁰C of *O*-alkyl-*S*-2dimethylaminoethyl methylphosphonothiolates and their tetraalkylammonio derivatives.

reaction alkaline hydrolysis and inhibition BuChE the rate constants are controled by activation enthalpy.

We have calculated a very similar isokinetic temperature from the linear equation (5) (Figure 6 and 7).

$$\Delta H^* = \Delta H^0 + \beta \Delta S^* \tag{5}$$

confirming isokinetic series of examined esters.

Thus, the reaction of alkaline hydrolysis and reaction inhibition BuChE are based on a similar mechanism, which is described in the literature as bimolecular process $S_N2(P)^{12-19}$. Based on these results, we examined the correlation of the structure of alkyl radicals in RO group with different Hammetts constants.

Tafts inductive constant σ^* gives relatively good correlation with $\lg k_2$ of alkaline hydrolysis *O*-alkyl-*S*-2-dimethylaminoethyl methylphosphonothilates and their tetraalkylammonio derivatives (Figure 8 and 9) (Table IV).

The correlation coeficient ($r = 0.76 — 0.91$) indicates the complex behavior of RO group in alkaline hydrolysis reactions of examined esters, probably, because of specific structure of aminomercapto group atached to phosphorus.

Kabachnik and Mastrjukova[20] have shown that RO, RS and R_2N groups of phosphoric and phosphonic halidates (fluoridates and chloridates) and *p*-nitrophenol derivatives of different phosphorus acids show a resonance effect in solvolysis reactions. The coeficient α in equation (6)

$$\lg k/k^0 = \varrho \, \Sigma \, (\sigma_I{}^{\varphi} + \alpha \sigma_R{}^{\varphi} \tag{6}$$

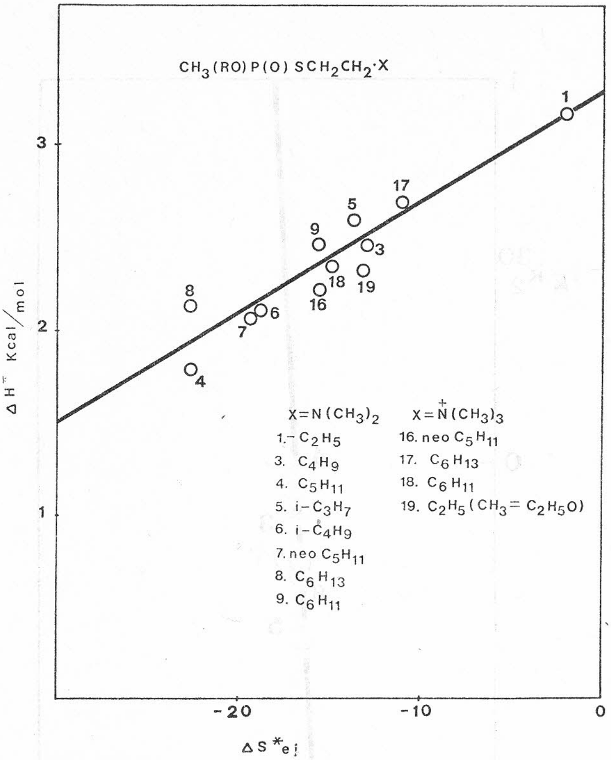


Figure 6. The correlation ΔH^* and ΔS^* of reaction alkaline hydrolysis of *O*-alkyl-*S*-2-dimethylaminoethyl methyl phosphonothiolates and their tetraalkylammonio derivatives and *O,O*-diethyl-*S*-2-dimethylaminoethyl phosphorothilate (point 19) ($\beta = 56$ K, r = 0.93)

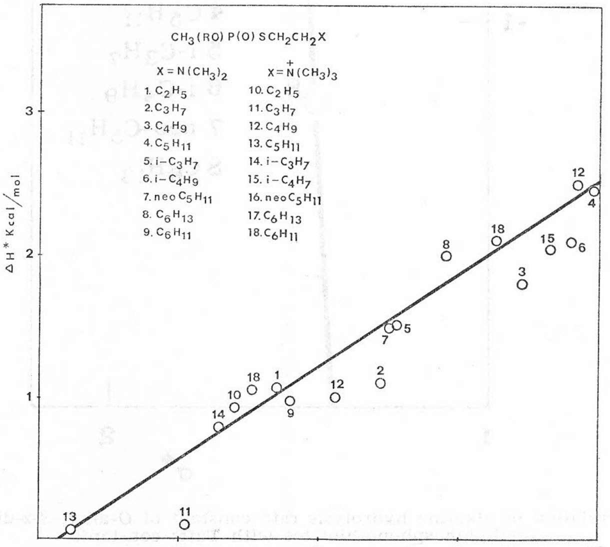


Figure 7. The correlation ΔH^* and ΔS^* of reaction inhibition BuChE with *O*-alkyl-*S*-2-dimethylaminoethyl methylphosphonothiolates and their tetraalkylammonio derivatives ($\beta = 65.3$ K, $r = 0.95$).

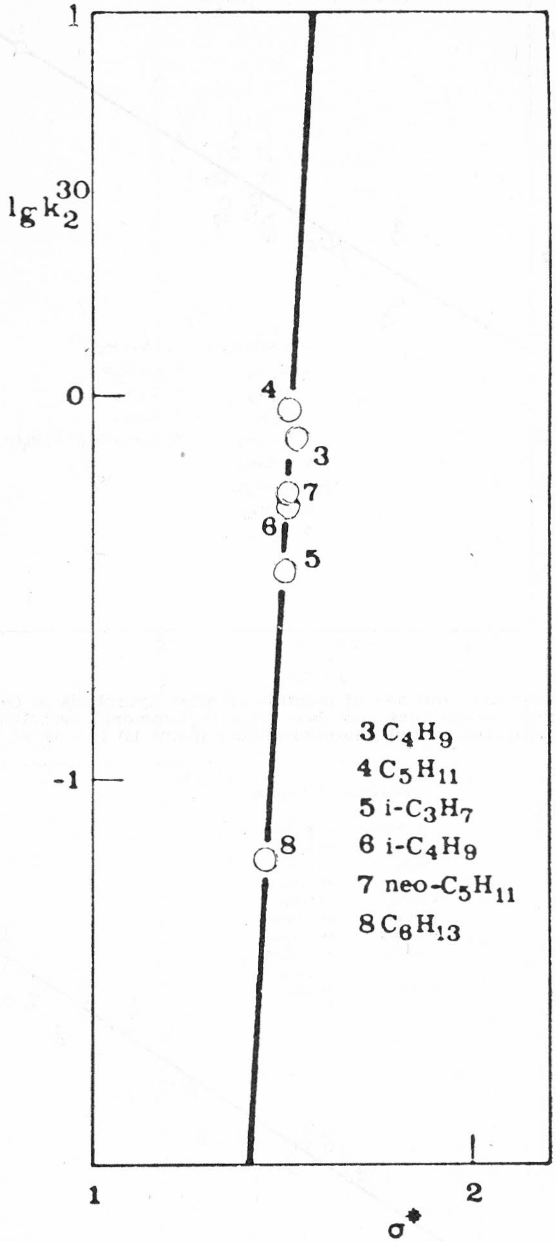


Figure 8. The correlation of alkaline hydrolysis rate constant of *O*-alkyl-*S*-2-dimethylaminoethyl methylphosphonothiolates with Tafts constants.

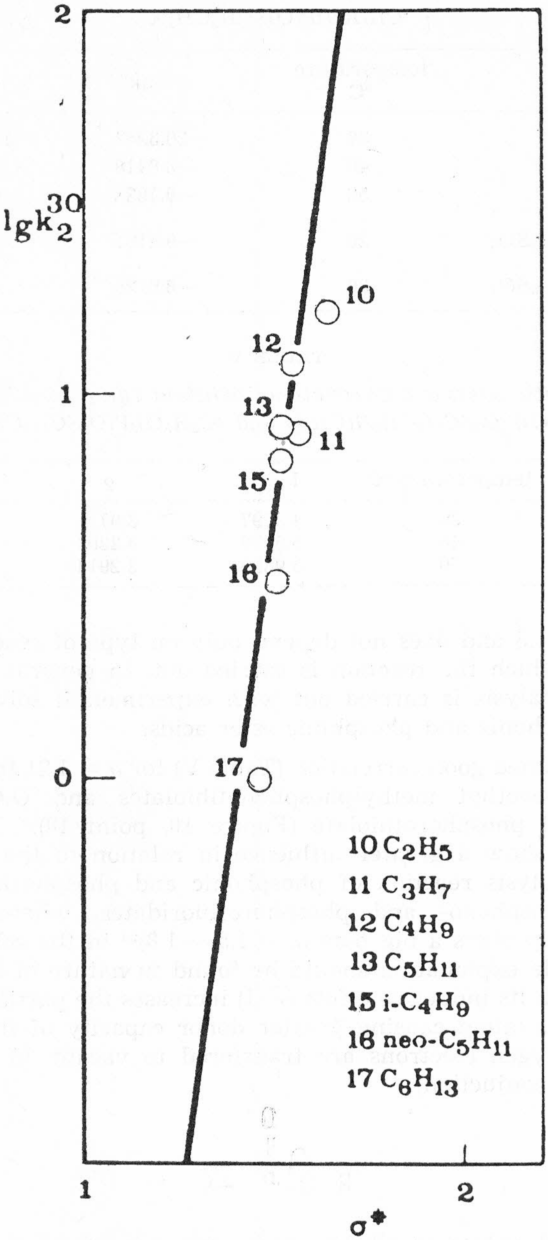


Figure 9. The correlation of alkaline hydrolysis rate constant of *O*-alkyl-*S*-2-trimethylammonioethyl methylphosphonothiolates methyl sulfato with Tafts constants.

TABLE IV

Linear Equation Parameters and Correlation Coeficient of $l\,gk = l\,gk^0 + \rho\sigma^*$ for $CH(RO)P(O)SCH_2CH_2X$

№	X	temperature ^0C	$l\,gk^0$	ρ	r
1.	$N(CH_3)_2$	30	—20.3262	13.1839	0.91
2.	$N(CH_3)_2$	40	—8.8418	5.7611	0.76
3.	$N(CH_3)_2$	50	—9.7833	6.5448	0.85
4.	$\overset{+}{N}(CH_3)_3 \cdot CH_3SO_4^-$	20	—9.3191	6.3604	0.83
5.	$\overset{+}{N}(CH_3)_3 \cdot CH_3SO_4^-$	30	—8.6128	6.0994	0.85

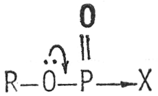
TABLE V

Linear Equation Parameters and Correlation Coeficient $l\,gk^0_2 = l\,gk^0_2 + \rho\Sigma\,(\sigma_I^{\Phi} + \alpha\sigma^{\Phi}_R)$ *for* $CH_3(RO)P(O)SCH_2CH_2N(CH_3)_2$ *and* $(C_2H_5O)_2P(O)SCH_2CH_2N(CH_3)_2$

№	temperature/^0C	$l\,gk^0$	ρ	r
1.	30	4.9297	3.0711	0.96
2.	40	5.5579	3.2209	0.93
3.	50	5.9899	3.2914	0.92

goes from 1.3 to 1.8 and does not depend only on type of reaction but also on the medium in which the reaction is carried out. In general, best results are obtained if $\sigma\rho$ analysis is carried out with experimental solvolysis results of phosphoric, phosphonic and phosphinic ester acids.

We have obtained good correlation (Table V) for $\alpha = 1.21$ for series *O*-alkyl-*S*-2-dimethylaminoethyl methylphosphonotihiolates and *O,O*-diethyl-*S*-2-dimethylaminoethyl phosphorothiolate (Figure 10, point 19).* Thus, this effect does not clearly show a greater influence in relation to the inductive effect in alkaline hydrolysis reaction of phosphonic and phosphoric thioester acids compared to phosphono- and phosphorofluoridates, where the resonance effect of RO group plays a big part ($\alpha = 1.5 — 1.8$)[20] in the solvolysis reaction. The most probable explanation should be found in nature of acyl radical. The halogen atom with its inductive effect (— I) increases the partial positive charge of the phosphorus atom causing greater donor capacity of the alkoxy group, while free 2p oxygen electrons are transfered to vacant 3d orbitals of phosphorus ($p_\pi — d_\pi$ conjuction).



$$R-\ddot{O}-\overset{\overset{O}{\|}}{P}\rightarrow X$$

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* Experimental values of alkaline hydrolysis rate constant for *O*-butyl- and *O*-pentyl-*S*-2-dimethylaminoethyl methyl phophonothiolate are obtained with a greater relative error (±5%). For these RO groups the constants are also calculated with less accuracy (±0.1 unit), so we did not take them for the calculation of the correlation coeficient.

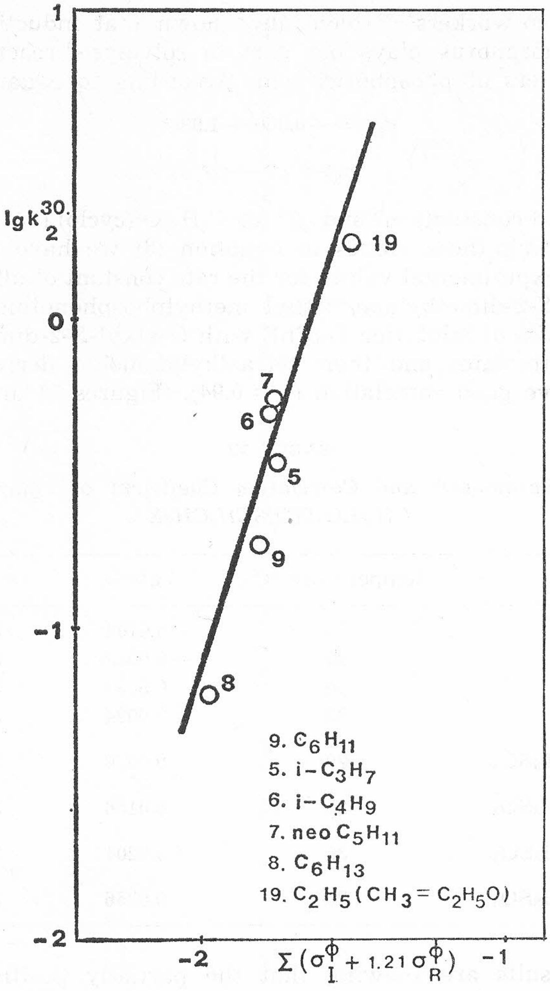

Figure 10. The correlation of alkaline hydrolysis rate constant of *O*-alkyl-*S*-2-dimethylaminoethyl methylphosphonothiolates and *O*,*O*-diethyl-*S*-2-dimethylaminoethyl phosphorothiolate (point 19) with $\Sigma(\sigma_I^\Phi + 1.21\,\sigma_R^\Phi)$

As the same time, the thioalkyl group in *O*-alkyl-*S*-2-dimethylaminoethyl methylphosphonothiolates and in *O*,*O*-diethyl-*S*-2-dimethylaminoethyl phosphorothiolate as well as in other thioesters of phosphorus acid[15–17,20] also shows an inductive effect, much weaker than the inductive effect of the halogen atom. That is why RO group in the series of examined compounds show weaker resonance effect in alkaline hydrolysis reaction compared to ester fluorides of phosphorus acids. This explains faster alkaline hydrolysis of *O*,*O*-diethyl-*S*-2-dimethylaminoethyl phosphorothiolate compared to *O*-ethyl-*S*-2-dimethylaminoethyl methyl phosphonothiolate (about 1.6 times) opposite to fluoridates of phosphorus acids, where phosphates show weaker reactivity than phosphonates.

Bel'skii and co-workers[21,22] have also shown that inductive effect of RO group around phosphorus plays big part in solvolysis reaction of different esters and thioesters of phosphorus acid. According to equation (7) and (8)[20]

$$\sigma_I^\varphi = -0.960 + 1.99\sigma^* \tag{7}$$

$$\sigma_R^\varphi = \sigma^\varphi - \sigma_I^\varphi \tag{8}$$

we have calculated constants σ_I^φ and σ_R^φ for $C_6H_{11}O$ (cyclo) ($\sigma_I^\varphi = 1.98$ and $\sigma_R^\varphi = -2.33$)*. Inserting these values in equation (6) we have obtained a good correlation with experimental values for the rate constant of alkaline hydrolysis of *O*-cyclohexyl-*S*-2-dimethylaminoethyl methylphosphonothiolate (Figure 10, point 8). The results of inhibition BuChE with *O*-alkyl-*S*-2-dimethylaminoethyl methylphosphonothiolates and their tetraalkylammonio derivatives with the Tafts constant give good correlation ($r = 0.94$). (Figures 11 and 12; Table VI).

TABLE VI

Linear Equation Parameters and Correlation Coeficient of $l\,gk_i = l\,gk_i^0 + \varrho\,\sigma^*$ *for* $CH_3(RO)P(O)SCH_2CH_2X$

№	X	temperature °C	$l\,gk_i^0$	ϱ	r
1.	$N(CH_3)_2$	20	—0.0104	3.5162	0.94
2.	$N(CH_3)_2$	25	—0.0089	3.6099	0.95
3.	$N(CH_3)_2$	30	—0.0034	3.6874	0.95
4.	$N(CH_3)_2$	35	—0.0024	3.7594	0.95
5.	$\overset{+}{N}(CH_3)_3 \cdot CH_3SO_4^-$	20	0.0070	3.5900	0.94
6.	$\overset{+}{N}(CH_3)_3 \cdot CH_3SO_4^-$	25	0.0156	3.6539	0.95
7.	$\overset{+}{N}(CH_3)_3 \cdot CH_3SO_4^-$	30	0.0201	3.7124	0.95
8.	$\overset{+}{N}(CH_3)_3 \cdot CH_3SO_4^-$	35	0.0356	3.7668	0.95

The obtained results are showing that the partially positive electricity of the phosphorus atom depends on the complex influence of alkoxy radicals in alkaline hydrolysis and in reaction of the inihibition ferment with *O*-alkyl-*S*-2-dimethylaminoethyl methylphosphonothiolates and their tetraalkylammonium derivatives on inductive effect.

It is interesting that only a drastic deviation of ethoxy radical are shown in reaction of inhibition BuChE. This case is probably connected with the very nature of fermentative reactions where the nucleophile is a part of the complex structure of the BuChE surface. Using the Kabachniks hypothesis[23] we could assume that in the case of BuChE inhibition of the examined esters only in *O*-ethyl-*S*-2-dimethylaminoethyl methylphosphono thiolate and its tetraalkylammonio derivatives, the electronic and steric factors have opposite effects (Figure 11, point 1, Figure 12, point 10). In the examined reactions high

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* We have calculated the tafts inductive constant ($\sigma^* = 1.48$) for $C_6H_{11}O$ from experimental results of alkaline hydrolysis of *O*-cyclohexyl-*S*-2-dimethylaminoethyl methylphosphonothiolate[1] and the linear equation $\lg k_2 = \lg k_2^0 + \varrho\sigma^*$ (Table IV).

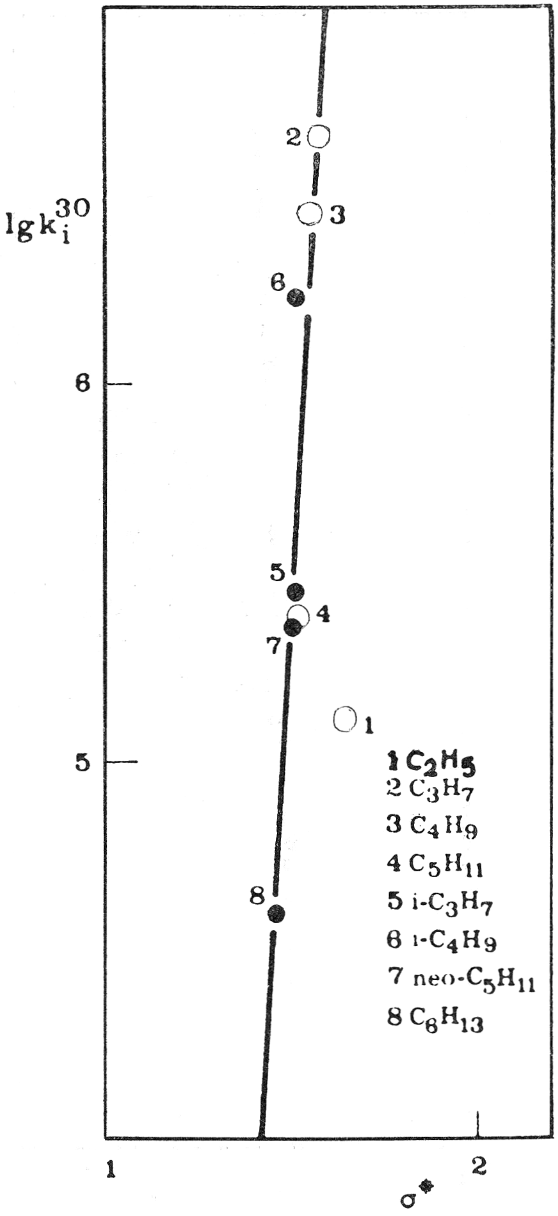

Figure 11. The correlation of inhibition rate constant of *O*-alkyl-*S*-2-dimethylaminoethyl methylphosphonothiolates with Tafts constants

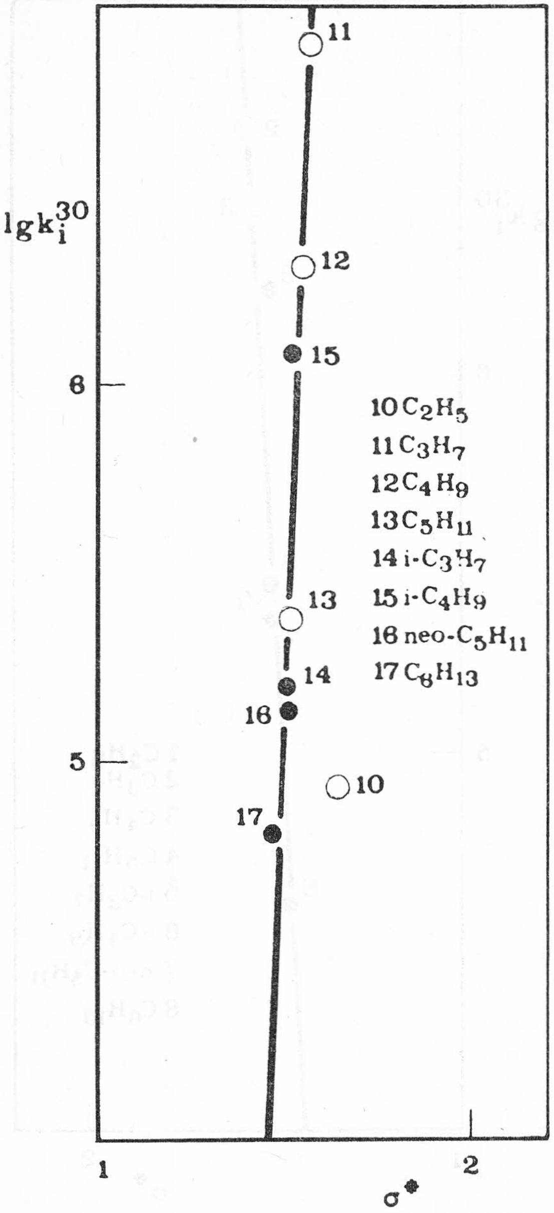

Figure 12. The correlation of inhibition rate constant of *O*-alkyl-*S*-2-trimethylammonioethyl methylphosphonothiolates methyl sulfato with Tafts constants.

positive ϱ constant values are noticed. This fact is showing the high polar transition state. Besides this fact, the positive constant values confirm that both reactions alkaline hydrolysis and inhibition BuChE with examined esters take place according to the $S_N2(P)$ mechanism.

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SAŽETAK

Neki aspekti izokinetičkog zakona i kompenzacijskih efekata u organofosfornim spojevima. Dio II. Korelacijska analiza *O*-alkil-*S*-2-dimetilaminoetil metan-tiofosfonata i njihovih tetraalkilamonijum derivata

D. Minić

Izvršena je korelacijska analiza reakcija alkalne hidrolize i inhibicije BuChE sa *O*-alkil-*S*-2-dimetilaminoetilmetan-tiofosfonatima i njihovim tetraalkilamonijum-derivatima.

Funkcionalna zavisnost logaritma konstante brzina na dvema temperaturama potvrdila je da reakcije ispitivanih estera metan-tiofosfonske kiseline sa OH^--jonom i BuChE pokazuju izokinetičku zavisnost, tj. ovi esteri obrazuju izokinetički niz. Korelacijska analiza sa različitim Hammett-ovim konstantama potvrdila je da alkoksi-radikali, koji su vezani za fosfor$^{(IV)}$ u ispitivanim jedinjenjima pokazuju nešto veći rezonantni efekt ($\alpha = 1{,}21$) u poređenju sa induktivnim efektom u reakciji alkalne hidrolize.

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