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Hydrolysis of Some Organophosphorus Compounds. Part I. Reactions in Alkaline Solution

D. Minić and D. Rakin

Military Technical Institute, 11000 Beograd, Serbia, Yugoslavia

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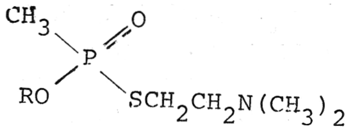
The alkaline hydrolysis series of compounds derived from *O*-alkyl-*S*-2-dimethylaminoethyl methylphosphonothiolate, *O*-alkyl-*S*-2-trimethylammonioethyl methylphosphonothiolate methyl sulfato, and *O,O*-diethyl-*S*-2-dimethylaminoethyl phosphorothiolate are studied in order to show substituent effects in these reactions.

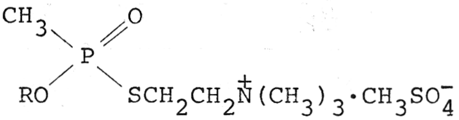
The influence of structural change of alkyl radical in RO group as well as electrophilic characteristic of phosphorus atom and charge effects on nitrogen atom on the hydrolysis rate are discussed.

Tetrahedral organic phosphorus compounds undergo nucleophilic substitution[1-3]. Reactions in which the hydroxylic ion takes the part of nucleophil are the most interesting, since they are relatively simple and quick[4]. In this work we examined the alkaline hydrolysis series of compounds derived from *O*-alkyl-*S*-2-dimethylaminoethyl methylphosphonothiolates (a), *O*-alkyl-*S*-2-trimethylammonioethyl methylphosphonothiolates methyl sulfato (b) and *O,O*-diethyl-*S*-2-dimethylaminoethyl phosphorothiolate (IX) (see Table I), in order to show effects of alkyl in RO group as well as the effects of positive nitrogen in thioalkyl radical in these reactions.

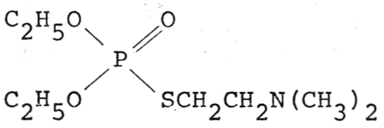
The general structural formulas of these compounds are shown below.



(a)



(b)



(IX)

EXPERIMENTAL AND RESULTS

Materials. — The preparation of the *O*-alkyl-*S*-2-dimethylaminoethyl methylphosphonothiolates and their methyl sulfato derivatives has been described[5]. *O,O*-diethyl-*S*-2-dimethylaminoethyl phosphorothiolate has been prepared by published methods[6,7]. All compounds were purified by multiple (2—3 times) vacuum distillation and their purity was determined by volumetric method[8]. *O*-alkyl-*S*-2-trimethylammonioethyl methylphosphonothiolates methyl sulfato were purified by recristalyzation to constant melting point.

Kinetics. — Hydrolysis of the *O*-alkyl-*S*-2-dimethylaminoethyl methylphosphonothiolates, *O*-alkyl-*S*-2-trimethylammonioethyl methylphosphonatiolates methyl sulfato and *O,O*-diethyl-*S*-2-dimethylaminoethyl phosphorothiolate was followed by po-

TABLE I

Second-Order Rate Constants of Alkaline Hydrolysis k_2 *(in* $dm^3/mol\ min$*)*
$CH_3(RO)P(O)SCH_2CH_2N(CH_3)_2$

No	R	Compound No	30 °C		40 °C		50 °C	
			k_2	k_2'	k_2	k_2'	k_2	k_2'
1.	C_2H_5	I			2.246		5.433	
2.	n-C_4H_9	II	0.748	0.768	1.754	1.761	3.300	3.425
3.	n-C_5H_{11}	III	0.905		1.665			
4.	i-C_3H_7	IV	0.342	0.348	0.791	0.764	1.568	1.597
5.	i-C_4H_9	V	0.510	0.511	1.018	1.016	1.933	1.936
6.	neo-C_5H_{11}	VI	0.511	0.546	1.061	1.081	2.011	2.051
7.	C_6H_{13} (pinacolyl)	VII	0.0628	0.0615	0.118	0.122	0.243	0.234
8.	C_6H_{11} (cyclohexyl)	VIII	0.183	0.185	0.412	0.402	0.820	0.831
9.	C_2H_5*	IX	1.726	1.712	3.538	3.594	7.268	7.208

* CH_3 is substituted with C_2H_5O
k_2 — experimental values of rate constant
k_2' — estimated values of rate constant

TABLE II

Second-Order Rate Constants of Alkaline Hydrolysis k_2 *(in* $dm^3/mol\ min$*)*
$CH_3(RO)P(O)SCH_2CH_2\overset{+}{N}(CH_3)_3 \cdot CH_3SO_4^-$

No	R	Compound No	20 °C		30 °C		40 °C	
			k_2	k_2'	k_2	k_2'	k_2	k_2'
1.	C_2H_5	X	8.091*		16.201			
2.	n-C_3H_7	XI	3.805		7.706			
3.	n-C_4H_9	XII	6.183		11.757			
4.	n-C_5H_{11}	XIII	3.891		8.095			
5.	i-C_3H_7	XIV	2.791					
6.	i-C_4H_9	XV	3.765		6.608			
7.	neo-C_5H_{11}	XVI	1.555	1.566	3.297	3.246	6.372	6.422
8.	C_6H_{13} (pinacolyl)	XVII	0.409	0.424	1.070	0.990	2.100	2.187
9.	C_6H_{11} (cyclohexyl)	XVIII	0.711	0.730	1.662	1.570	3.121	3.214

tentiometric titration using the »Radiometer« Titrator TTT1 with glass electrode G 202B, and calomel electrode K 100.

The reaction mixture was prepared with 100 ml 0.01 mol/dm^3 organophosphorus compounds and 100 ml of 0.025 mol/dm^3 KOH. For titration 5 ml of this mixture was taken and the excess of alkali was titrated with 0.04 mol/dm^3 hydrochloric acid.

Results. — The second-order rate constants for the hydrolysis of *O*-alkil-*S*-2-dimethylaminoethyl methylphosphonothiolates, *O*-alkyl-*S*-2-trimethylammonioethyl methylphosphonothiolates methyl sulfato and *O,O*-diethyl-*S*-2-dimethylaminoethyl phosphorothiolate in alkaline solution are given in Tables I and II.

Figures 1 and 2 show linear function lgb-x/a-x with time and confirm that the reactions are second order.

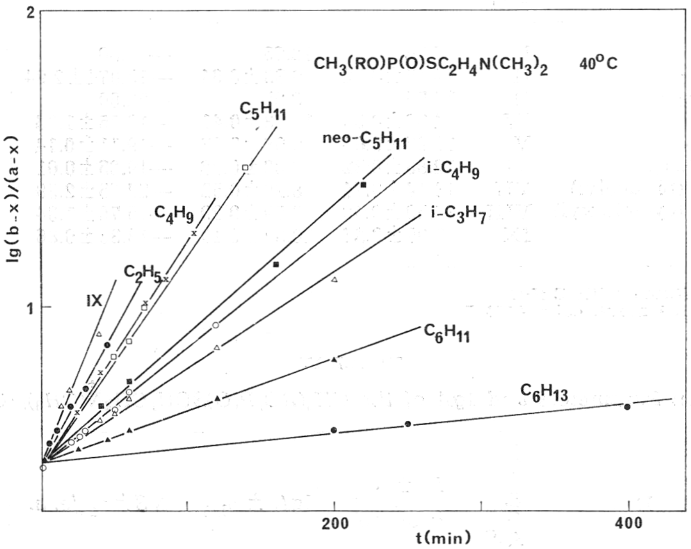


Figure 1. The change of concentration *O*-alkyl-*S*-2-dimethylaminoethyl methyl-phosphonothiolates with time.

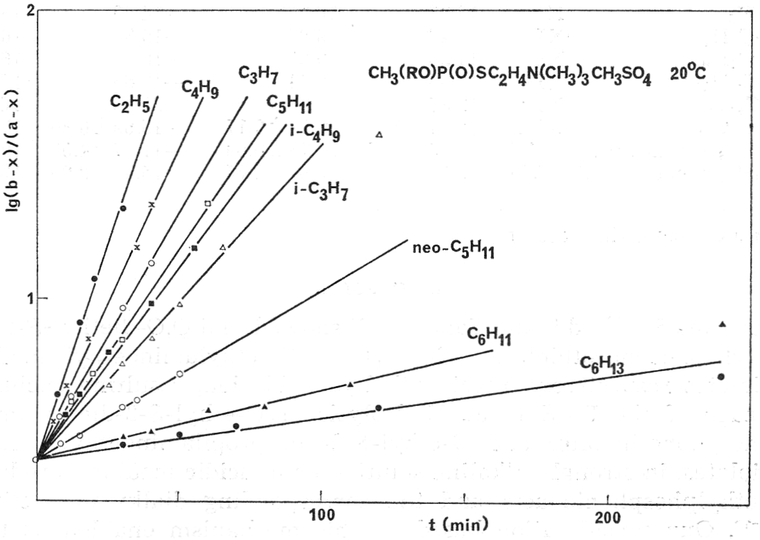


Figure 2. The change of concentration *O*-alkyl-*S*-2-trimethylamonioethyl methyl-phosphonothiolates methyl sulfato with time.

Energy of activation, lg A, entropy of activation and energy activation (with standard error) are given in Tables III and IV.

TABLE III

Activation Parameters and 1gA of the $CH_3(RO)P(O)SCH_2CH_2N(CH_3)_2$

No	R	Compound No	$E_a \pm \sigma_{E_a}$ kcal/mol	$\lg A \pm \sigma_{\lg A}$	$\Delta S \pm \sigma_{\Delta S}$/e. u.	$\Delta G \pm \sigma_{\Delta G}$ kcal/mol
1.	C_2H_5	I	17.76	12.75	— 2.30	17.85
2.	n-C_4H_9	II	14.55 ± 0.92	10.38 ± 0.64	—13.074 ± 2.94	19.44 ± 0.89
3.	n-C_5H_{11}	III	14.55	8.25	—22.80	**17.81**
4.	i-C_3H_7	IV	14.82 ± 0.58	10.23 ± 0.41	—13.75 ± 1.86	19.35 ± 0.56
5.	i-C_4H_9	V	12.97 ± 0.04	9.06 ± 0.03	—19.11 ± 0.14	18.23 ± 0.04
6.	*neo*-C_5H_{11}	VI	12.88 ± 0.32	9.03 ± 0.22	—19.25 ± 0.01	17.59 ± 0.31
7.	C_6H_{13} (pinacolyl)	VII	13.14 ± 0.74	8.26 ± 0.52	—22.75 ± 2.38	18.20 ± 0.72
8.	C_6H_{11} (cyclohexyl)	VIII	14.59 ± 0.42	9.79 ± 0.29	—15.76 ± 1.34	19.46 ± 0.41
9.	C_2H_5*	IX	13.99 ± 0.27	10.32 ± 0.19	—13.33 ± 0.86	16.98 ± 0.26

* CH_3 is substituted with C_2H_5O
e.u. = 4.184 JK^{-1} mol^{-1}, cal = 4.184 J

TABLE IV

Activation Parameters and 1gA of the $CH_3(RO)P(O)SCH_2CH_2\overset{+}{N}(CH_3)_3 \cdot CH_3SO_4^-$

	R	Compound No	$E_a \pm \sigma_{E_a}$ kcal/mol	$\lg A \pm \sigma_{\lg A}$	$\Delta S \pm \sigma_{\Delta S}$/e. u.	$\Delta G \pm \sigma_{\Delta G}$ kcal/mol
1.	C_2H_5	X	12.26	10.05	—14.49	16.54
2.	n-C_3H_7	XI	12.46	9.87	—15.31	16.37
3.	n-C_4H_9	XII	11.35	9.25	—18.15	16.08
4.	n-C_5H_{11}	XIII	12.94	10.24	—13.65	16.35
5.	i-C_4H_9	XIV	12.87	7.98	—23.96	16.37
6.	*neo* C_5H_{11}	XVI	12.87 ± 0.24	9.79 ± 0.17	—15.69 ± 0.80	17.20 ± 0.23
7.	C_6H_{13} (pinacolyl)	XVII	14.95 ± 1.23	10.78 ± 0.89	—11.17 ± 4.07	19.69 ± 1.19
8.	C_6H_{11} (cyclohexyl)	XVIII	13.51 ± 0.90	9.94 ± 0.65	—15.01 ± 2.96	18.82 ± 0.87

e.u. = 4.184 JK^{-1} mol^{-1}, cal = 4.184 J

DISCUSSION

Fukuto and Stafford[10], and Tammelin[11] showed that *O,O*-diethyl-*S*-2-diethylaminoethyl phosphorothiolates, *O*-ethyl-*S*-2-dimethylaminoethyl methylphosphonothiolates respectively, react with hydroxide ion, resulting exclusively in the cleveage of the P—S bond. Hydrolysis of *O*-ethyl-*S*-2-diethylaminoethyl methylphosphonothiolates and *O*-ethyl-*S*-2-diisopropilaminoethyl methylphosphonothiolates, in strongly alkaline solution or in acidic medium, produces only ethyl methylphosphonic acid and the corresponding dialkylaminoethyl mercaptan[10–12]. Our consideration based on this mechanism enabled us to follow all correlations as a result of the biomolecular reactions of nucleophilic substitution. The second-order rate constant change of alkaline hydrolysis with temperature is in well agreement with Van't Hoffs and Arhenius laws. The temperature coefficient according to empirical Van't Hoff law for both series of compounds correspond to the most known reactions of nucleophilic substitution (1.8—2.1). At the same time the change of the second-order constants of alkaline hydrolysis gives linear correlation with temperature as shown in Figures 3 and 4.

Equations parameters are given in Tables V and VI.

TABLE V

Parameters of Linear Equation ($lgk_2 = B + A \cdot 10^3/T$) $CH_3(RO)P(O)SCH_2CH_2N(CH_3)_2$

No	R	Compound No	B	A
1.	*n*-C_4H_9	II	10.3792	—3.1814
2.	*i*-C_3H_7	IV	10.2291.	—3.2400
3.	*i*-C_4H_9	V	9.0594	—2.8349
4.	*neo*-C_5H_{11}	VI	9.0267	—2.8162
5.	C_6H_{13}	VII	8.2624	—2.8719
6.	C_6H_{11}	VIII	9.7911	—3.1901
7.	C_2H_5*	IX	10.3216	—3. 0583

* CH_3 is substituted with C_2H_5O

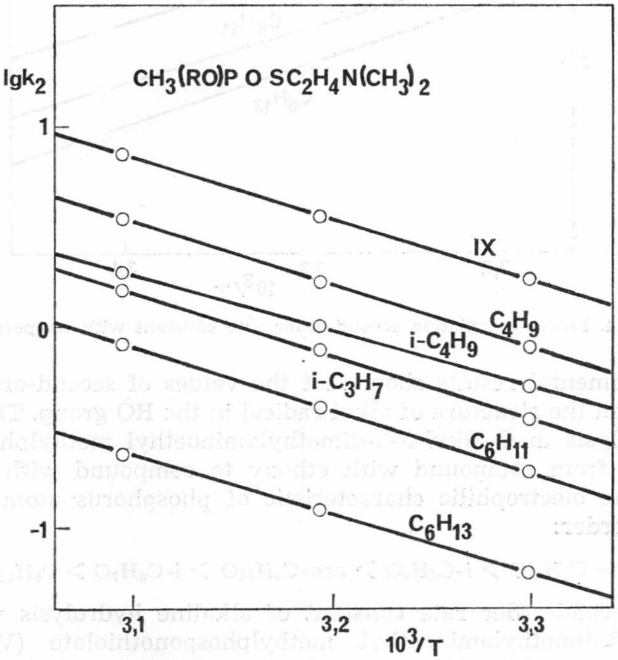


Figure 3. Linear correlation second-order rate constant with temperature.

TABLE VI

Parameters of Linear Equation ($1gk_2 = B + A \cdot 10^3/T$)

$CH_3(RO)P(O)SCH_2CH_2\overset{+}{N}(CH_3)_3 \cdot CH_3SO_4^-$

No	R	Compound No	B	A
1.	*neo*-C_5H_{11}	XVI	9.7902	—2.8129
2.	C_6H_{13}	XVII	10.7784	—3.2689
3.	C_6H_{11}	XVIII	9.9396	—2.9539

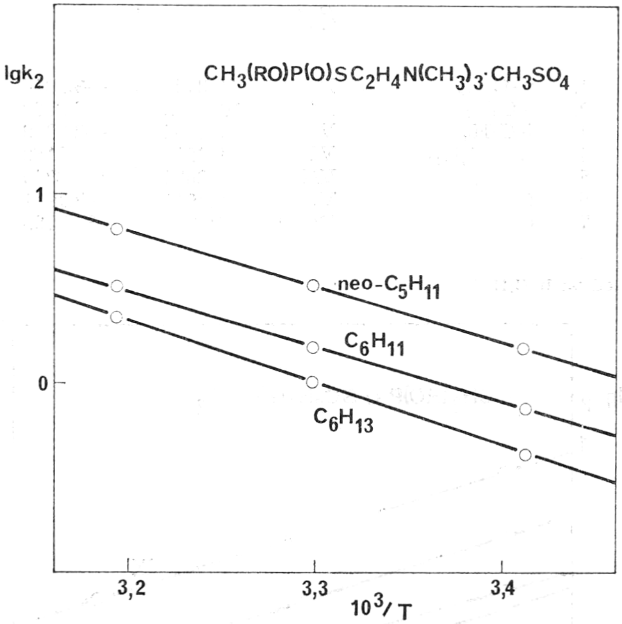


Figure 4. Linear correlation second-order rate constant with temperature.

Our experimental results show that the values of second-order rate constants depend on the structure of alkyl radical in the RO group. The constant of alkaline hydrolysis in *O*-alkyl-*S*-2-dimethylaminoethyl methylphosphonothiolates decreases from compound with ethoxy to compound with pinacolyloxy radical, i. e. the electrophilic characteristic of phosphorus atom decreases in the following order:

$C_2H_5O > C_4H_9O \sim C_5H_{11}O > i\text{-}C_4H_9O > neo\text{-}C_5H_{11}O > i\text{-}C_3H_7O > C_6H_{11}O > C_6H_{13}O$.

The slowest second-order rate constant of alkaline hydrolysis was found in *O*-pinacolyl-*S*-2-dimethylaminoethyl methylphosponothiolate (VII) ($k_2^{40\,^0C} = = 0.12$ l/mol.min), and the highest one in *O*-ethyl-*S*-2-dimethylaminoethyl methylphosphonothiolate (I) ($k_2^{40\,^{\circ}\mathrm{C}} = 2.25$ l/mol.min) (Table I) of phosphonothiolates series.

As can be seen from Table I, *O,O*-diethyl-*S*-2-dimethylaminoethyl phosphorothiolate (IX) shows a higher rate of alkaline hydrolysis than phosphonothiolates.

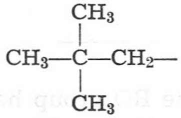
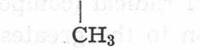
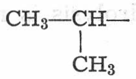
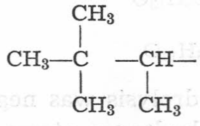
O-alkyl-*S*-2-trimethylammonioethyl methylphosphonothiolates methyl sulfato has the same trend of reactivity (Table II).

$$C_2H_5O > C_4H_9O > C_5H_{11}O \sim C_3H_7O > i\text{-}C_4H_9O > i\text{-}C_3H_7O > neo\text{-}C_5H_{11}O > C_6H_{11}O > C_6H_{13}O$$

In both series of compounds the second-order rate constant of alkaline hydrolysis is changed gradually with the structural change of alkyl radical in the RO group. The relative rate constant (Table VII) confirms that the influence of the alkyl group on chemical reactivity is the most typical in the pinacolyloxy group. The rate constant of alkaline hydrolysis is about twenty times lower in *O*-pinacolyl-*S*-2-dimethylaminoethyl methylphosphonothiolate (VII) than in *O*-ethyl-*S*-2-dimethylaminoethyl methylphosphonothiolate (I). The rate differences observed on changing the substituent R with normal chain are very small. The same relative reactivity correlation is noticed in the tetraalkylammonio derivatives of methylphosphonothiolates. In this series of compounds the

TABLE VII

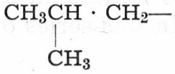
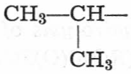
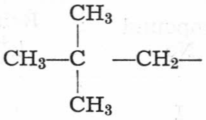
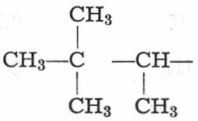
Relative Second-Order Rate Constant of Alkaline Hydrolysis of O-alkyl-S-2--dimethylaminoethyl Methylphosphonothiolates $CH_3(RO)P(O)SCH_2CH_2N(CH_3)_2$

No	R	Compound No	Relative $k_2^{40\,^{\circ}\mathrm{C}}$
1.	CH_3CH_2-	I	1
2.	$CH_3CH_2CH_2CH_2-$	II	0.78
3.	$CH_3CH_2CH_2CH_2CH_2-$	III	0.74
4.	 $CH_3-\overset{CH_3}{\underset{CH_3}{C}}-CH_2-$	VI	0.47
5.	 $CH_3-\underset{CH_3}{CH}-CH_2-$	V	0.45
6.	 $CH_3-\underset{CH_3}{CH}-$	IV	0.35
7.	 $CH_3-\overset{CH_3}{\underset{CH_3}{C}}-\underset{CH_3}{CH}-$	VII	0.05

phosphorus atom in *O*-pinacolyl-*S*-2-trimethylammonioethyl methylphosphonathiolate methyl sulfato (XVII) was also of about twenty times lower electrophilic characteristics, in comparison with *O*-ethyl-*S*-2-trimethylammonioethyl methylphosphonothiolates methyl sulfato (X) (Table VIII).

TABLE VIII

Relative Second-Order Rate Constant of O-alkyl-S-2-trimethylammonioethyl Methylphosphonothiolates Methyl Sulfato $CH_3(RO)P(O)SCH_2CH_2\overset{+}{N}(CH_3)_3\cdot CH_3SO_4^-$

No	R	Compound No	Relative $k_2^{20\,^0C}$
1.	CH_3CH_2-	X	1
2.	$CH_3CH_2CH_2CH_2-$	XII	0.76
3.	$CH_3CH_2CH_2CH_2CH_2-$	XIII	0.48
4.	$CH_3CH_2CH_2-$	XI	0.47
5.	 $CH_3\underset{\underset{CH_3}{\vert}}{CH}\cdot CH_2-$	XV	0.46
6.	 $CH_3-\underset{\underset{CH_3}{\vert}}{CH}-$	XIV	0.34
7.	 $CH_3-\overset{\overset{CH_3}{\vert}}{\underset{\underset{CH_3}{\vert}}{C}}-CH_2-$	XVI	0.19
	 $CH_3-\overset{\overset{CH_3}{\vert}}{\underset{\underset{CH_3}{\vert}}{C}}-\underset{\underset{CH_3}{\vert}}{CH}-$	XVII	0.05

Our results suggest that α-substitution in the RO group has greater effect on the rate of alkaline hydrolysis than β-substitution. Thus, the isopropyl radical (compound IV), and especially pinacolyl radical (compound VII) in the RO group mostly decreases the rate of reaction to the greatest extent.

The second-order rate constant of alkaline hydrolysis is more drastically changed in series of substituents

$$C_2H_5O > i\text{-}C_3H_7O > C_6H_{13}O$$

than in series:

$$C_2H_5O > C_4H_9O > C_5H_{11}O$$

The second-order rate constant of alkaline hydrolysis was negligibly changed when the carbon in α-position contained two hydrogen atoms.

Since the pinacolyl radical in the RO group has the greatest influence on the alkaline hydrolysis of the examined organophosphorus compounds of both series, one can say that steric effects are more likely to be responsible for the reactivity of the phosphorus atom[13]. Such, assumption can be confirmed by relatively change of lgA and entropy of activation (Table III). However, a more detailed analysis of the activation parameters (Tables III and IV) shows that the influence of the alkoxy group in nucleophilic substitution on the tetrahedral phosphorus atom is very complicated. Qualitative evaluation of the effect of structural changes of the alkyl radicals in the RO group in the examined esters of methylphosphonothiolic acid must be taken with certain reserve, especially because space effects (among other things) can influence also the change of energy activation. It is even more complicated when one tries to explain the electrophilic characteristics of the phosphorus atom by hyper conjugation and other electronic effects of alkoxy groups.

Positive Charge Effects of Nitrogen Atom on the Reactivity of Tetrahedral Phosphorus Atom

The presence of a cationic group in molecules of *O*-alkyl-*S*-2-trimethylammonioethyl methylphosphonothiolates methyl sulfato gives to these compounds specific characteristics. The electron attracting properties of this group increase the partial positive charge on the phosphorus atom, and consequently $p_\pi - d_\pi$ conjunction of the phosphoryl group is increased in a ground state. In this way, the increase in the electrophilic characteristics of the phosphorus atom can be explained in *O*-alkyl-*S*-2-trimethylammonioethyl methylphosphonothiolates methyl sulfato in comparison with *O*-alkyl-*S*-2-dimethylaminoethyl methylphosphonothiolates. Our experimental results suggest that the cationic group assists the rate of alkaline hydrolysis and confirms this hypothesis (Table IX).

TABLE IX

Relative Second-Order Rate Constant of Alkaline Hidrolysis in Effects of Positive Charge of Nitrogen Atom in $CH_3(RO)P(O)SCH_2CH_2\overset{+}{X}$

No	R	Relative k_2^{30}*
1.	n-C_4H_9	15.40
2.	n-C_5H_{11}	8.96
3.	i-C_4H_9	12.92
4.	neo-C_4H_{11}	7.69
5.	C_6H_{13}	15.96
6.	C_6H_{11}	8.49

* Relative $K_2 = (k_2\ [X = \overset{+}{N}\ (CH_3)_3]\ \ (k_2\ [X = N\ (CH_3)_2])$

Namely, the greater electrophilic characteristics of the phosphorus atom (10 to 15 times) in organophosphorus compounds with a cationic group in the thioalkyl radical seem to be due to the inductive effects of this radical only, since energy activation and free energy activation differ in comparison with these two series by about 1—3 kcal/mol.

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SAŽETAK

Hidroliza nekih organofosfornih jedinjenja. Deo I. Reakcije u alkalnom rastvoru

D. Minić i D. Rakin

Izučavana je alkalna hidroliza *O*-alkil-*S*-2-dimetilaminoetil-metantiofosfonata i njihovih tetraalkilamonijum-derivata, kao i *O,O*-dietil-*S*-2-dimetilaminoetil tiofosfata. Pokazano je na osnovu eksperimentalnih rezultata da α-substitucija u alkil radikalu u RO grupi ima veći uticaj na brzinu alkalne hidrolize od β-substitucije. Istovremeno, pozitivno naelektrisan atom azota u tioalkil-radikalu najverovatnije svojim induktivnim efektom u prelaznom stanju utiče na brzinu ove reakcije.

VOJNOTEHNIČKI INSTITUT
11000 BEOGRAD
JUGOSLAVIJA

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