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Kinetics of the Hydrolysis of Phosphate Esters

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The available information about the kinetics of the hydrolysis of phosphate esters in neutral, alkaline, and acidic media is considered and the mechanisms of the hydrolysis of various reactive forms of mono-, di-, and tri-esters are discussed. A systematic account is given of the rate constants, taking into account the type of ester and its reactive form.
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I. INTRODUCTION

Quantitative data on the reactivities of the labile P-O-C ester linkages, which are frequently encountered in various organophosphorus compounds, are of intersst for a number of scientific disciplines. The hydrolytic reactions of phosphate esters have been the subject of vigorous kinetic studies in view of their extensive practical applications in engineering, agriculture, and medicine, and the growing interest of investigators in the mechanisms of biochemical processes in which individual phosphate esters play an important role.

The reactivity of ester linkages involving the phosphorus atom can vary within very wide limits (by a factor greater than 10^{10}) and it is therefore often necessary to estimate it *a priori*. Theoretical methods for the estimation of the reaction rate constants have not has yet been adequately developed and one therefore usually employs empirical correlations based on the principle of linear relations between the free energies of various chemical processes. It is important to arrange systematically the results accumulated and to express them in a form convenient for analytical research.

II. FUNDAMENTAL DATA ON THE MECHANISMS OF THE HYDROLYSIS OF P-O-C ESTER LINKAGES

The mechanisms of reactions involving nucleophilic substitution at the phosphorus atom, including the hydrolysis of ester linkages, have been frequently discussed[1-8]. Under certain conditions, there is a possibility of monomolecular heterolytic cleavage of the bond between phosphorus and the group to be eliminated (S_N1P mechanism) and of bimolecular substitution with attack by the nucleophile on phosphorus in the rate-determining stage of the reaction (S_N2P mechanism). Nucleophilic substitution reactions involving phosphorus acid esters can also take place at the carbon atom of the ester linkage.

The anionic forms of phosphate monoesters[9-11] and monoacyl phosphates[12,13] are hydrolysed via the S_N1P mechanism. The metaphosphate ion, formed in the hydrolysis of such compounds, is unstable owing to its coordination unsaturation and is rapidly hydrated. The S_N2P mechanism is more common. Studies of the hydrolysis of certain cyclic esters of phosphorus acids have shown that it proceeds as described by Westheimer[6]. The formation of a bond between phosphorus and the attacking nucleophile leads to five-coordinated phosphorus in the transition state, the structure of which may be represented by a trigonal bipyramid with the axial disposition of the eliminated and introduced groups. This geometry is supported by data for the molecular structures of five-coordinated phosphorus compounds, in which the axial bonds are longer and weaker than the equatorial bonds[14,15].

Westheimer[6,16] discussed the possibility of the existence of a relatively unstable intermediate compound with five-coordinated phosphorus in the hydrolysis of cyclic phosphates. Rapid exchange of ligands between the axial and equatorial positions in the intermediate via the pseudorotation of the bipyramid could ensure the simultaneous cleavage of the endo- and exo-cyclic ester linkages, which has been observed experimentally.

Bimolecular substitution of the S_N2P type is also characteristic of the alkaline hydrolysis of many phosphorus acid esters. In neutral and acidic media, the POAlk linkages are frequently hydrolysed with the cleavage of the C-O bond (via the S_N2 or S_N1 mechanism) at the carbon atom of the alkoxy-group[7,8,17-19].

The hydrolysis of partly esterified phosphoric acid may be complicated by the involvement in the mechanism of various ionic forms of the substrate. At different pH, the monoesters exist in the form of the dianions $ROPO_3^{2-}$, the monoanions $ROPO_3H^-$, the neutral molecules $ROP(O).(OH)_2$, and the protonated form $ROP(OH)_3^+$. The considerable differences between the successive dissociation constants of these species are responsible for the preferential existence of only one or two of them at a fixed pH of the medium. Because of this, only some of the many possible reaction pathways actually occur under specific conditions. The displacement of the ionisation equilibria as the pH is altered changes the reactive species and frequently the reaction mechanism.

III. KINETICS OF THE HYDROLYSIS OF PHOSPHATE ESTERS

The kinetics and mechanisms of the hydrolysis of phosphate esters, higher polyphosphates, and mixed anhydrides, such as acetyl phosphate, have been examined in a review[7] devoted mainly to the hydrolysis of polyphosphates; earlier results are described in other communications[5,8]. The existence of three series of phosphate esters—the monoesters $ROPO_3H_2$, the diesters $(RO)_2PO_2H$, and triesters $(RO)_3PO$—as well as their

different ionic species differing in the degree of protonation necessitated a systematic arrangement in groups of the available kinetic data in terms of the type of ester and its reactive form. Each group may include data for esters reccting via different mechanisms. In some cases, the observed rate constant may be a compound quantity reflecting the overall rate of reaction proceeding via two or more parallel mechanisms.

1. Hydrolysis of Phosphate Monoesters

Phosphate monoesters are dibasic acids with pK_{a1} = 1 to 2 and pK_{a2} = 6–7.[3,9] As mentioned above, the monoesters can exist in four forms differing in the charge and degree of protonation. For each of them, it is possible to postulate hydrolytic mechanisms involving nucleophilic attack by a water molecule on the phosphorus atom or the carbon of the ester linkage and monomolecular heterolysis with the cleavage of the bond at the phosphorus or carbon atom. The site of cleavage of the bond during the reaction can be reliably determined by an isotope method and a conclusion may be reached concerning the mechanism on the basis of kinetic data. The variation of the observed rate constant with the acidity of the medium is due to the influence of the latter on the relative contents of the different monoester species; for this reason, the involvement of the individual species in the reaction mechanisms is elucidated by analysing the dependence of the effective rate constant on pH. According to the data in Ingold's book[20], studies on the influence of the pH of the medium on the rate of hydrolysis of monoalkyl phosphates began at the end of the past century.

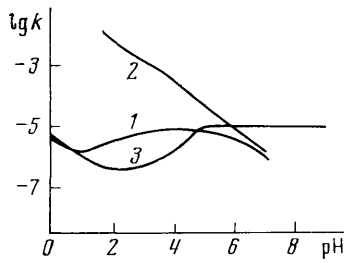


Figure 1. Dependence of lg k on the pH of the medium in the hydrolysis of monoesters: 1) $C_2H_5OP(O)(OH)_2$ at 100°C [21]; 2) t-$C_4H_9OP(O)(OH)_2$ at 74°C [29]; 3) 2,4-$(NO_2)_2$. .$C_6H_3OP(O)(OH)_2$ at 25°C.[10]

The type of dependence of the rate constant for the hydrolysis of monoesters on pH encountered most frequently is described by curve *1* in Fig. 1. The rate of reaction dc/dt depends only on the concentration of the monoanions over a wide range of pH:

$$\frac{dc}{dt} = k[ROPO_3H^-] = kc\frac{K_1[H^+]}{[H^+]^2 + K_1[H^+] + K_1K_2},$$

where c is the overall concentration of the monoester in solution:

$$c = [ROPO_3^{2-}] + [ROPO_3H^-] + [ROP(O)(OH)_2];$$

K_1 and K_2 are the first and second ionisation constants of the monoester. The rate constant passes through a maximum at pH = $(pK_1 + pK_2)/2$, where the relative content of the monoanion is a maximum, which indicates a much higher reactivity of the monoanion compared with the dianion and the neutral molecule. Plots of the rate of hydrolysis against pH have been investigated for a series of monoalkyl and monoaryl phosphates[9,10,21-27,31-36]. The rate maximum in the pH range 3–5 has been observed for many monoesters, but such behaviour is not general. On the other hand, when the neutral molecule is more reactive than the monoanion, the rate constant increases monotonically with decrease of pH (curve *2*). Relations of this kind are characteristic of the monoesters which hydrolyse with the cleavage of the C–O bond via the S_N1 mechanism with formation of a carbonium ion[28-30], and also of certain monoacyl phosphates[12,13]. The dependence of the rate of hydrolysis of highly reactive monoaryl and acyl phosphates on pH is described by curve *3* in Fig. 1. A higher reactivity of the dianion compared with that of the monoanion corresponds to this type of dependence. For all three types of relation, the rate constants increase on passing to highly acidic media as a result of acid hydrolysis. The protonated form of the monoester is involved in the latter.

Detailed information is now available about the site of the dissociation of the bond in the hydrolysis of phosphate monoesters with participation of different reactive species. The cleavage of the bonds at the phosphorus atom has been demonstrated on many examples for monoaryl phosphates reacting as the monoanions[25], the dianions[11,39,40], the neutral molecules[25], and the protonated forms[25]. The bond at the phosphorus atom is also dissociated in the monoanions of alkyl phosphates[23,29,32,34,41], except for the t-butyl ester in which the C–O bond is partly cleaved[28].

The hydrolysis of neutral monoalkyl phosphate molecules proceeds with the rupture of the C–O bond, as shown for methyl phosphate[23] and t-butyl phosphate[28]. In the acid hydrolysis of monomethyl and monoethyl phosphates, simultaneous cleavage of the bonds at the phosphorus and carbon atoms takes place[23,32], while in the hydrolysis of the isopropyl and t-butyl esters, the C–O bonds are ruptured exclusively[28,32].

The rate of hydrolysis of many phosphate monoesters is very low at the usual temperatures and in many studies the kinetics have been investigated at 100°C. We adjusted some of the constants in Table 1 to these conditions on the basis of the temperature relations. The rate constants for the monoanions of many monoalkyl phosphates increase after the introduction of electron-accepting substituents in the alkyl group. A similar effect has been observed also for the monoanions of monoaryl phosphates. An exception is provided by the data quoted in the paper of Mhala et al.[38] The rate constants for the hydrolysis of the monoanions of aryl and acyl phosphates are higher by 1.5–2 orders of magnitude than the corresponding values for the monoanions of alkyl phosphates. This is probably due to the favourable role of the resonance interaction of the ester oxygen with the benzene ring or the carbonyl group, which may compete with the effect of the $p\pi - d\pi$ conjugation between oxygen and phosphorus, which weakens the P–O bond ruptured in the reaction.

The inductive effect of the electron-accepting groups and the resonance delocalisation of the lone electron pairs of the ester oxygen atom must have an unfavourable influence on the proton transfer to the group being eliminated, which is believed[5,9,11] to facilitate the rupture of the P–O bond in the monoanions. Since the rate constants actually increase as the basic properties of the ester oxygen are reduced, the variation of another factor, which more than compensates for the decrease of the basicity of the oxygen,

is probably responsible for the increase of the reactivity. This factor may be the decrease of the energy of the ruptured bond. Owing to the opposed effects of these factors, whose influences on the reactivity are not comparable in magnitude, the dependence of the rate constants on the nature of the groups eliminated is weakened, which is confirmed when the slopes of the lg k–pK_a relations are compared for the monoanions and dianions[9,11]. In the dianions, there is no proton transfer to the eliminated group and the reactivity is determined solely by the bond energy. For the monoanions of aryl and alkyl phosphates, the dependence of lg k on the pK_a of the eliminated group is characterised by a slope several times smaller than the slopes of the corresponding relation for the dianions of aryl and acyl phosphates[11].

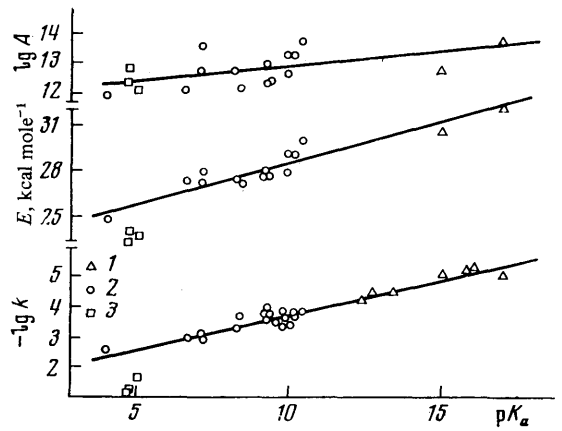


Figure 2. Dependence of the parameters lg k, E, and lg A for the hydrolysis of the monoester monoanions at 100°C on the pK_a of the eliminated group. The pK_a values were taken from Refs. 9 and 11, the sources indicated therein, and from Refs. 46–49: 1) alkyl phosphates; 2) aryl phosphates; 3) acyl phosphates.

Fig. 2 illustrates the variation of lg k with pK_a for monoanions, expressed by the equation†

$$\lg k = -0.23pK_a - 1.38 \quad (n = 25;\ r = 0.97;\ s = 0.2),$$

which differs only slightly from that quoted by Kirby and Varvoglis[11]. With decrease of the pK_a of the eliminated group, the rate constant for the hydrolysis of monoanions increases and the activation energy E and the pre-exponential factor diminish (Fig. 2). Hence it follows that the reactivity increases owing to the decrease of E. The very low values of E and lg A quoted by Mhala et al.[38] for the monoanions of 4-bromophenyl and 2-methoxyphenyl phosphates do not fit on the plots of E and lg A against pK_a in Fig. 2, in contrast to the remaining data. The markedly higher reactivity of the monoanions of acyl phosphates is due to the additional decrease of E compared with the value expected from the plot of E against pK_a.

†Here and henceforth n is the number of compounds, r the correlation coefficient, and s the standard deviation.

The higher reactivity of the monoanions of acyl phosphates is probably associated with the unusual mechanism of their hydrolysis. A proton may be transferred to the oxygen of the carbonyl group and not to the anhydride oxygen[12]. The mechanism established for the monoanions of certain carbamoyl phosphates, which are hydrolysed with the cleavage of the C–O bonds, is more significantly different[50].

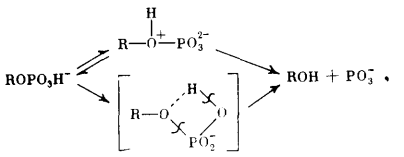
Table 1. The rate constants for the hydrolysis of phosphate monoester monoanions $ROPO_3H^-$ at 100°C and the parameters of the equation $k = A\exp(-E/RT)$.

R	10^6k, s^{-1}	E, kcal mole^{-1}	lg$A$ (s^{-1})	References
CH_3	8.23	30.6	12.81	23
C_2H_5	6.0	—	—	22
C_3H_7	5.1[a]	—	—	31
iso-C_3H_7	9.7	32.1	13.80[a]	32
n-C_4H_9	6.0	31	12.94	24
n-C_5H_{11}	4.8[a]	—	—	31
iso-C_5H_{11}	5.9	29.6	12.12[a]	30
$(CH_3)_3CCH_2$	1.06	—	—	33
n-C_6H_{13}	4.2[a]	—	—	31
$(CH_3)_3CCH_2CH_2$	0.92	—	—	43
$CH_2{=}C(CH_3)CH_2CH_2$	7.1	35.7	15.75[a]	30
$(CH_3)_2C(OH)CH_2CH_2$	6.4	—	—	30
$HOCH_2CH(OH)CH_2$	13.5	29.9	12.63	34
$(HOCH_2)_2CH$	27.7	30.3	13.18	34
$H_3N^+CH_2CH_2$	31	29.6	12.83	34
$(C_2H_5)N^+H_2CH_2CH_2$	28[a]	—	—	35
$(C_2H_5)_3N^+HCH_2CH_2$	28[a]	—	—	35
$(CH_3)_3N^+CH_2CH_2$	18	24.3	9.49	44
$H_3N^+CH_2CH_2CH_2$	12[a]	—	—	31
$H_3N^+(CH_2)_4$	6.2[a]	—	—	31
$H_3N^+(CH_2)_5$	7.7[a]	—	—	31
$H_3N^+(CH_2)_6$	4.2[a]	—	—	31
3-$(C_5H_4N^+H)CH_2$	27[a]	29.3	12.61	36
2-$(C_5H_4N^+H)CH_2$	69[a]	28.2	12.35	36
$CH_3C(O)NHCH_2CH_2$	15[a]	—	—	31
$HOC(O)CH_2CH_2$	11[a]	—	—	31
$HOC(O)CH_2$	39[a]	—	—	31
$NCCH_2CH_2$	11[a]	—	—	31
$NCCH_2$	39[a]	—	—	31
$HC{\equiv}CCH_2$	26	—	—	27
F_3CCH_2	57	—	—	11
FCH_2CH_2	13[a]	—	—	45
$(FCH_2)_2CH_2$	28[a]	—	—	45
$F_2CHF_2CCH_2$	39[a]	—	—	45
Glucose-1-	11	30	12.70	29
Glucose-6-	20	30.5	13.20[a]	37
C_6H_5	289	29.0	13.32	25
4-$CH_3C_6H_4$	230	29.0	13.26	25
2-(t-C_4H_9)C_6H_4	40	—	—	9
4-(t-C_4H_9)C_6H_4	178	—	—	9
2,6-$(CH_3)_2C_6H_3$	161	30	13.77[a]	9
2,6-(t-C_4H_9)$_2$4-$CH_3C_6H_2$	33.5	—	—	9
2-ClC_6H_4	230	27	12.17[a]	9
4-ClC_6H_4	180[a,b]	27.5	12.36	38
4-Cl-3-$CH_3C_6H_3$	186[a]	27.5	12.38	38
4-BrC_6H_4	110[a]	21.7	8.75	38
2-$CH_3OC_6H_4$	470[a]	21.4	9.21	38
4-$CH_3OC_6H_4$	420[a]	22.9	10.04	38
4-$C_2H_5OC_6H_4$	120[a]	19.4	7.45	38
3-$(CO_2^-)C_6H_4$	270[a]	27.7[a]	12.66[a]	26
4-$(CO_2^-)C_6H_4$	350[a]	28.0[a]	12.94[a]	26
3-$(COOH)C_6H_4$	380[a]	27.9[a]	12.92[a]	26
4-$(COOH)C_6H_4$	720[a]	28.3[a]	13.44[a]	26
α-Naphthyl	150[a]	30.6[a]	14.10[a]	26
β-Naphthyl	360[a]	29.8[a]	14.02[a]	26
3-$NO_2C_6H_4$	573	27.3[a]	12.76[a]	9
4-$NO_2C_6H_4$	1050[a]	27.2	12.82[a]	9
2-$NO_2C_6H_4$	1450[a]	28	13.56[a]	9
3,5-$(NO_2)_2C_6H_3$	1 310	27.3[a]	12.11[a]	11
2,4-$(NO_2)_2C_6H_3$	3 080	24.8	12.02[a]	11
$CH_3C(O)$	65 000	23.1	12.33	12
$(CH_3)_2CHCH_2C(O)$	60 000	24.0	12.84	13
$(CH_3)_3CC(O)$	24 000	23.5	12.17	13

[a]These values were calculated by the author of the review from data in the studies quoted.
[b]According to Bunton et al.[9], $k = 302 \times 10^6$ s^{-1} at 100°C.

High activation energies are characteristic of almost all the monoanions investigated. Estimates of the activation entropies from the pre-exponential factors listed in Table 1 yield in most cases $\Delta S^{\neq} \simeq 0 \pm 5$ cal mole^{-1} k^{-1},

in agreement with the monomolecular S_N1P mechanism of the rate-limiting stage of the hydrolytic reaction. A proton may be transferred to the eliminated group either in the rapid pre-equilibrium process or synchronously with the dissociation of the bond at the phosphorus atom[11]:



Nor can one exclude the possibility of the involvement of a water molecule in the proton transfer[41]. The six-membered ring formed in the reaction with participation of water may be less strained than the four-membered ring without water.

The small kinetic isotope effect in the hydrolysis of the monoanion of methyl phosphate ($k_{H_2O}/k_{D_2O} = 0.87$)[23] shows that in alkyl esters the proton transfer occurs in the pre-equilibrium stage and not in the rate-limiting stage. However, for highly reactive monoanions, the situation may change in favour of the mechanism with the synchronous proton transfer. In particular, this is indicated by the much greater isotope effect in the hydrolysis of the monoanion of 2,4-dinitrophenyl phosphate ($k_{H_2O}/k_{D_2O} = 1.45$).[11]

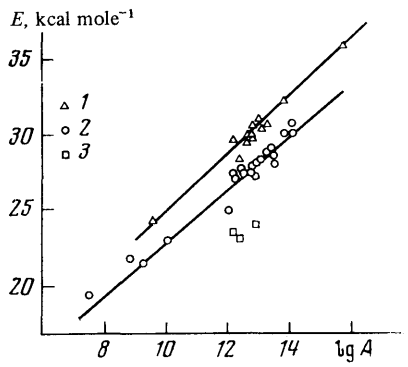
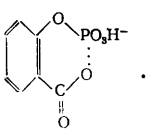


Figure 3. Relation between E and lg A for the hydrolysis of monoester monoanions: 1) alkyl phosphates; 2) aryl phosphates; 3) acyl phosphates.

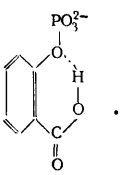
The parameters of the Arrhenius equation E and lg A for the monoanions of alkyl phosphates tend to cancel out, which has also been noted for aryl phosphates (Fig. 3). There is no general relation between E and lg A for alkyl and aryl phosphates, although they fit on a single straight line in the plot of lg k against pK_a. Possibly a unique line is obtained only approximately owing to the similarity of the influence of the conjugation effect on the ionisation of phenols and the reaction under consideration.

The metaphosphate ion formed on cleavage of the bond in the monoanions is rapidly hydrated, which hinders the demonstration of its formation. At low water concentrations in the reaction medium, the hydration is accompanied by the polymerisation of the metaphosphate ions; the formation of trimetaphosphate has been demonstrated in the hydrolysis of a concentrated solution of potassium monophenyl phosphate[51]. Attempts have been made at an indirect confirmation of the formation of the metaphosphate ion by studying the composition of the solvolysis products of monoesters in aqueous alcoholic media[5,8]. It was assumed that the metaphosphate ion reacts non-selectively with water and alcohol, giving a product ratio corresponding to the composition of the aqueous alcoholic medium. However, the metaphosphate ion formed on hydrolysis in many cases reacted preferentially with alcohol, which may be due to the selective solvation by one of the components of the solvent of the substrate and of the metaphosphate ions formed[5,11].

In the hydrolysis of certain monoanions, intramolecular catalysis was observed in some cases. The monoanions of *o*-carboxyphenyl and *o*-carboxynaphthyl phosphates are particularly reactive[26,52]. For example, $E = 24.1$ and lg $A = 12.97$ for the monoanion of salicyl phosphate[52], so that the rate constant at 100°C is 7.1×10^{-2} s^{-1}. This value is approximately 200 times greater than the *m*- and *p*-carboxyphenyl phosphates and higher than all the constants quoted in Table 1. To explain the exceptionally high rate of hydrolysis of the monoanions of salicyl phosphate and similar esters, the authors suggested[26,52] intramolecular nucleophilic catalysis by the carboxylate group with the possible formation of an acyl phosphate as an intermediate:



Bender and Lawlor later showed[53] that the acyl phosphate cannot be an intermediate owing to the relatively low rate of hydrolysis and pointed out the possibility of intramolecular acid catalysis in the hydrolysis of salicyl phosphate and similar esters:



The intramolecular catalysis by the hydroxy-group, demonstrated for the monoanions of 8-hydroxy-1-naphthyl phosphate[53] and 3-hydroxy-2-pyridylmethyl phosphate[54], involves a similar mechanism. Catalysis by the N^+–H group has been demonstrated for 2-pyridylmethyl and 2-pyridylethyl phosphates[55].

At high pH values, phosphate monoesters exist as doubly charged anions. The reactivity of the dianions of monoalkyl phosphates is extremely low and for this reason there are virtually no kinetic data for such species. The dianions of aryl phosphates are more reactive than their alkyl analogues. As for the monoanions, the rate of reaction increases in the presence of electron-accepting substituents in the eliminated group. Comparison of the data in Tables 1 and 2 shows that the activation energy as well as the pre-exponential factor for the hydrolysis of the dianions are as a rule higher than for the monoanions.

The estimation of the values of $\Delta S^{\neq}$ from the data presented in Table 2 shows that they are positive in all cases. In this connection, a monomolecular mechanism has been proposed[10-12] for the rate-limiting stage of the hydrolysis of the dianions:

$$ROPO_3^{2-} \rightarrow PO_3^- + RO^- .$$

The alternative hypothesis, according to which the mechanism can be regarded as involving a bimolecular reaction between the hydroxide ion and the monoanion of the monoester, was disproved[10,11], because it would necessitate the assumption of an unrealistically high rate constant for the latter process. The rate-limiting stage does not include proton transfer from the solvent, as shown by the absence of a kinetic isotope effect in the hydrolysis of the dianion of 2,4-dinitrophenyl phosphate[11]. The high slope of the relation between lg k and the pK_a for the eliminated group is consistent with an S_N1P reaction mechanism[9,11]. According to the data in Table 2, this relation (at 100°C) is described by the following equation for the dianions of aryl phosphates:

$$\lg k = -1.01\ pK_a + 3.15 \quad (n = 10,\ r = 0.991,\ s = 0.3)$$

Table 2. Kinetic parameters of the hydrolysis of phosphate monoester dianions $ROPO_3^{2-}$ in aqueous solutions.

R	10^4k, s^{-1} (100°C)	E, kcal mole^{-1}	lg$A$ (s^{-1})	References
C_2H_5	<0.0001[b]	—	—	27
t-C_4H_9	<0.002[b]	—	—	42
$H_2N(CH_2)_4$	0.0006[b]	—	—	31
$(CO_2^-)CH_2CH_2$	0.48[a,b]	—	—	31
$HC{\equiv}CCH_2$	0.069[b]	—	—	27
Glucose-6-	1.02	33	15.3	37
3-NCC_6H_4	0.064[a,b]	—	—	35
4-NCC_6H_4	0.096[a,b]	—	—	35
3-$(CO_2^-)C_6H_4$	0.0024[a,b]	—	—	35
4-$(CO_2^-)C_6H_4$	0.0039[a,b]	—	—	35
2-$(CO_2^-)C_6H_4$	1.5[a,b]	—	—	35
3-$NO_2C_6H_4$	0.023	—	—	9
4-$NO_2C_6H_4$	0.65	31.2	14.09	40
2-$NO_2C_6H_4$	1.16	—	—	9
2,5-$(NO_2)_2C_6H_3$	63[a]	28	14.20[a]	10
2,4-$(NO_2)_2C_6H_3$	1500[a]	26	14.41[a]	10
2,6-$(NO_2)_2C_6H_3$	3300[a]	26	14.74[a]	10
$CH_3C(O)$	650[a]	26.0	14.04[a]	13
$(CH_3)_3CC(O)$	49[a]	28.3	14.27[a]	13

[a] See footnote to Table 1.
[b] The rate constants in 1 N NaOH solution are quoted.

A similar slope (−1.23) has been found (at 39°C) for the dianions of aryl and acyl phosphates[11]. Comparison with the analogous relation for the monoanions shows that, for pK_a < 5.8, the dianions are more reactive than the monoanions, as mentioned previously[11].

The dianion of salicyl phosphate 2-$(CO_2^-)C_6H_4OPO_3^{2-}$ hydrolyses approximately 500 times faster than the dianions of m- and p-carboxyphenyl phosphates[35]. This is probably due to the intramolecular nucleophilic catalysis by the carboxylate anion, postulated initially for the hydrolysis of the monoanion of salicyl phosphate[26,52]. Intramolecular catalysis by the hydroxyl has been observed in the hydrolysis of the dianion of 3-hydroxy-2-pyridylmethyl phosphate[54]. The hydrolysis of the dianion of glucose-6-phosphate[37] can apparently also be accelerated as a result of the intramolecular catalysis by the OH group.

At pH < 1, the ionisation of the acid groups of the monoesters is suppressed and they exist predominantly in the neutral form $ROP(O)(OH)_2$, which is usually unreactive. For monoalkyl phosphates, which are incapable of undergoing the cleavage of the C–O bond via the formation of a carbonium or a hydroxycarbonium ion, the dependence of the reaction rate constant on pH has a minimum in the pH range 0–1.[22-24] Owing to the low reactivity of the neutral form compared with the monoanion and the protonated form, the hydrolysis in this region is frequently represented by the sum of the reactions involving the monoanions and the neutral and protonated forms, which complicates the estimation of the reactivity of the neutral monoester molecules. The simplest example is provided by the hydrolysis of phenyl and p-cresyl phosphates, for which the absence of acid catalysts has been suggested because of the insignificant change in the reaction rate constant in $HClO_4$ solutions. The rate constant was attributed (after subtracting the contribution due to the monoanion) to the reaction proceeding via the neutral form[25]. For many substituted aryl phosphates, acid catalysts begins to be manifested in the region where the monoanion makes a large contribution to the overall reaction and a reliable estimate of the reactivity of the neutral molecules becomes impossible[9,10].

Table 3. Kinetic parameters of the hydrolysis of the neutral forms of phosphate monoesters $ROP(O)(OH)_2$.

R	10^6k, s^{-1} (100°C)	E, kcal mole^{-1}	lg$A$ (s^{-1})	References
CH_3	0.5	—	—	23
C_2H_5	0.7	—	—	32
n-C_3H_9	0.89	16	3.32[a]	24
iso-C_3H_7	0.3	—	—	32
$(CH_3)_2C{=}CHCH_2$	240 000	22.6	12.62[a]	30
Glucose-1-	29 000[a]	31.0	16.63	29
t-C_4H_9	150 000[a]	33.3	18.58[a]	28
C_6H_5	30.5	—	—	25
4-$CH_3C_6H_4$	24	—	—	25
4-ClC_6H_4	72[a]	28.5	12.55	38
2-$CH_3OC_6H_4$	160[a]	19.4	7.56	38
4-$C_2H_5OC_6H_4$	23[a]	20.2	7.20	38

[a] See footnote to Table 1.

Table 3 lists the rate constants for the hydrolysis of the neutral molecules of certain monoesters. It is noteworthy that the neutral molecules of monoalkyl and monoaryl phosphates react via different mechanisms. Alkyl phosphates are involved in reactions of the S_N2 and S_N1 type at the carbon atom[5,23,28-30,32], while in aryl phosphates substitution at the phosphorus atom takes place[25].

By considering jointly data for the hydrolysis of the dianions, monoanions, and neutral molecules of monoesters, one may note a definite similarity of the mechanisms of the reactions involving the dianions and monoanions and the clear difficulty of a similar mechanism for the neutral molecule. The S_N1P mechanism is manifested in the purest form in the hydrolysis of the dianions. The latter shows that the capacity for the elimination of the metaphosphate ions depends strongly on the pK_a of the eliminated group and diminishes as the pK_a increases. In the series of monoanions, the elimination of the metaphosphate ion is complicated by the proton transfer to the eliminated group. The role of the proton transfer should probably be small in the case of aryl phosphates with readily removed groups and the sequence of rate constants observed for such compounds (dianion > monoanion) reflects the reactivity in the processes proceeding via an S_N1P mechanism. The significant role of the additional factor (proton transfer) in the hydrolysis of monoanions in which the pK_a values of the eliminated groups are high leads to an alteration of this sequence (the monoanion

becomes more reactive). The reactivity via an S_N1P mechanism decreases further on passing to the neutral molecule. The absence of the cleavage of the C–O bond in the hydrolysis of the neutral molecules of monoalkyl phosphates is consistent with this observation. The hydrolysis of the neutral molecules of monoaryl phosphates probably proceeds via an S_N2P mechanism[9].

The acid catalysed hydrolysis of phosphate monoesters has been studied in a number of investigations[9,10,25,28,29,32,33,38,56]. The acid hydrolysis of the phenyl and alkyl esters proceeds via different mechanisms. Two parallel reactions, leading to the dissociation of the P–O and C–O bonds at comparable rates, have been demonstrated for the alkyl esters[23,32], but in the esters eliminating a carbonium ion there is exclusive dissociation of the C–O bond[28,29,32]. The dependence of the rate constant on the stoichiometric acid concentration over a wide range of compositions and at a constant ionic strength has been found for the acid hydrolysis of methyl and ethyl phosphates[23,32]. On this basis, a bimolecular mechanism was proposed for each of the parallel processes. It is suggested that the rate-limiting stage involves nucleophilic attack by an H_2O molecule on the phosphorus or carbon atom in the ester linkage of the protonated form of the ester[23]. In the acid hydrolysis of the t-butyl and isopropyl esters, only the C–O bond is cleaved. The linear dependence (with a slope of unity) of lg k on the acidity function H_0 indicates the unimolecular cleavage of the protonated form. The assessment of the reaction mechanism with the aid of Bunnett's criterion also confirms the unimolecularity of the rate-limiting stage[32]. Fig. 4 shows that the hydrolysis of isopropyl phosphate, which proceeds via unimolecular heterolysis (curve *2*), is most sensitive to changes in the acidity of the medium. The behaviour of acyl phosphates in acid hydrolysis shows a definite analogy with that of methyl and ethyl phosphates, although the dissociation of the C–O bond is preferred for acyl phosphates[56]. An increase of the hydrolysis rate constant in proportion to the stoichiometric acidity of the solution at a constant ionic strength has been established for certain acyl phosphates (Table 4) and a bimolecular reaction mechanism is therefore proposed[56].

phenyl phosphates with electron-donating groups in the benzene ring has been postulated[9,10,25] in view of the insignificant change in the rate constant in concentrated solutions of strong acids. In this connection, one should note that the involvement of the protonated form of the ester is probable in acid hydrolysis. If the rate constant for the reaction proceeding via the protonated form (k_{SH^+}) is greater than the rate constant for the reaction involving the neutral molecule (k_S), then the observed rate constant $k = k_S + k_{SH^+}$ should increase on conversion of the ester into the protonated form. On the other hand, when $k_S > k_{SH^+}$, the observed rate constant should decrease with increase of the acid concentration. One may assume, with some approximation, that the invariance of the rate constant as the acid concentration is altered over a fairly wide range indicates the similarity of the rate constants k_S and k_{SH^+}.

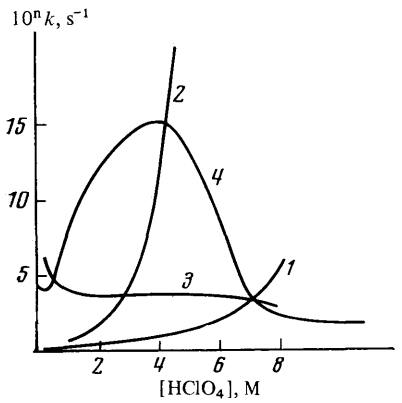


Figure 4. Dependence of the rate constants for the hydrolysis of monoesters on the acid concentration: 1) $C_2H_5OP(O)(OH)_2$, $n = 6$, 100°C [32]; 2) iso-$C_3H_7OP(O).(OH)_2$, $n = 5$, 100°C [32]; 3) $C_6H_5OP(O)(OH)_2$, $n = 5$, 100°C [25]; 4) 4-$NO_2C_6H_4OP(O)(OH)_2$, $n = 5$, 73°C.

Table 4. Kinetic parameters of the hydrolysis of the protonated forms of phosphate monoesters $ROP(OH)_3^+$ in aqueous acid media.

R	Composition of medium	10^4k, s^{-1} (100°C)	E, kcal mole^{-1}	lg$A$ (s^{-1})	References
CH_3	4*M* $HClO_4$	0.15	25 2	9.94[a]	32
C_2H_5	4*M* $HClO_4$	0.099	29.3	12.16[a]	32
iso-C_3H_7	4*M* $HClO_4$	10.5	31.0	15.18[a]	32
Glucose-6-	4,6*M* $HClO_4$	0.58	24	9.8	37
C_6H_5	3,8*M* $HClO_4$	0.366	—	—	25
3-$NO_2C_6H_5$	4*M* $HClO_4$	3.0[a]	20	8.22[a]	10
4-$CH_3C(O)C_6H_4$	4*M* $HClO_4$	4.1[a]	22.7[a]	9.91[a]	25
4-$NO_2C_6H_4$	4*M* H_2SO_4	15.0[a]	18.7	8.06	25
2-$NO_2C_6H_4$	4*M* $HClO_4$	20[a]	20	9.03	10
2,4-$(NO_2)_2C_6H_3$	6*M* $HClO_4$	290[a]	18	9.0	10
$CH_3C(O)$	2.87*M* HCl	50 000[a]	21.8	13.47[a]	56
$(CH_3)_3CC(O)$	2.87*M* HCl	7 200[a]	21.8	12.63[a]	56
$(CH_3)_3CCH_2C(O)$	2.87*M* HCl	155 000[a]	23.8	15.13[a]	56

[a]See footnote to Table 1.

Acid hydrolysis of monoaryl phosphates includes a reaction at the phosphorus atom[25]. The absence of an acid-catalysed reaction of phenyl phosphate and substituted

The slope of the plot of lg k against pK_a for acid hydrolysis, amounting to −0.5,[9,10] is smaller than for the reactions of dianions, but larger than for monoanions. Judging from the data in Table 4, the activation entropies for the acid hydrolysis of aryl phosphates are significantly lower than for reactions of mono- and di-anions, which suggests a bimolecular mechanism of the acid hydrolysis of monoaryl phosphates.

In a rigorous consideration of acid hydrolysis, account must be taken of the effects due to changes in the ionic strength and the activity of water with increase of the concentration of acid. It has been shown[10,25] that the rate of the acid-catalysed hydrolysis of aryl phosphates passes through a maximum in concentrated solutions of acids. However, the maximum disappears if the rate of reaction is measured in solutions at a constant ionic strength. Since the influence of salts and acids on the activity of water is similar, the maintenance of a constant ionic strength in solution smooths out the changes in the activity of water. Hence it follows that the maximum on the curves relating the rate constant to the concentration of acid may be attributed to a change in the activity of water. The rate

of hydrolysis of 2-methoxy-, 4-methoxy-, and 4-ethoxyphenyl phosphates in perchloric acid solutions at a constant ionic strength was independent of the acidity of the medium[38]. It was noted above that such behaviour probably indicates similar values of the rate constants for the reactions involving the neutral and protonated forms.

2. Hydrolysis of Phosphate Diesters

Phosphate diesters contain a single acid group at the phosphorus atom with $pK_a = 1-2$ (Kirby and Warren[3]) and can participate in reactions as anionic, neutral, and protonated species. The reactivity of the diester anions is very low, the anions of five-membered cyclic esters being an exception. The difficulty of the unimolecular heterolysis of the P=O bond in the diester anions also shows that the relatively high reactivity of the monoester monoanions is due to the special role of the P–O–H fragment in the reaction mechanism. Proton transfer to the eliminated group in the hydrolysis of monoester monoanions constitutes in essence a variety of the intramolecular catalysis by the acidic hydroxyl. In bimolecular nucleophilic substitution reactons, conditions for nucleophilic attack on the diester anion are unfavourable for two reasons. The first is the displacement of electron density from the oxygen atom to phosphorus, which makes the latter less electrophilic. The second factor, which is important in reactions with negatively charged nucleophiles, is the electrostatic repulsion of the two anionic species involved in the reaction.

The reactivity of neutral diester molecules is much higher than that of the anions. Analysis of the dependence of the rate constants for the hydrolysis of diesters on pH [25,57-64] reveals an increase of reactivity in the sequence

$$(RO)_2PO_2^- < (RO)_2P(O)OH < (RO)_2P(O)(OH)_2^+.$$

Typical relations between the rate constants and pH are illustrated in Fig. 5.

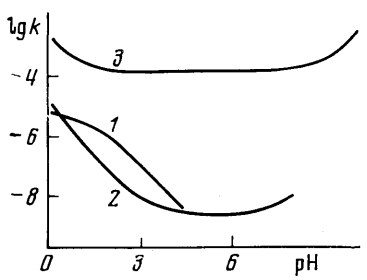


Figure 5. Dependence of lg k on pH for the hydrolysis of diesters at 100°C: 1) $(CH_3O)_2P(O)OH$ [57]; 2) $(C_6H_5O)_2$. $P(O)OH$ [25]; 3) $[2,4-(NO_2)_2C_6H_3O]_2P(O)OH$.[58]

The kinetics and mechanism of the hydrolysis of dimethyl phosphate have been investigated in detail[57]; a similar behaviour should probably be expected also for many other dialkyl phosphates which do not show a tendency towards the elimination of alkyl groups in the form of carbonium ions. In the pH range 0–5, the dependence of the rate constant for the hydrolysis of dimethyl phosphate on pH differs sharply from the corresponding dependence for monomethyl phosphate, the hydrolysis rate constant of which has a maximum at pH 4.[23] Dimethyl phosphate hydrolyses extremely slowly at pH > 4 even at high temperatures, which precludes the determination of the rate constant for the reaction of its anion with water; when the pH is reduced, there is a monotonic increase of the reaction rate, which continues also in strongly acidic media. In the pH range 1–4, the increase of the rate constant is proportional to the relative content of neutral dimethyl phosphate molecules in equilibrium with the anions[57].

Experiments with $H_2^{18}O$ have shown that hydrolysis of the neutral dimethyl phosphate molecule proceeds via two parallel mechanisms with the cleavage of the P–O and C–O bonds. In the acid and alkaline hydrolysis, the dissociation of these bonds also takes place at comparable rates[57,65]. A bimolecular nucleophilic substitution mechanism has been adopted for reactions involving the neutral molecule and dimethyl phosphate species protonated at both reaction centres[57], in agreement with the mechanisms of the analogous processes for monomethyl and trimethyl phosphates. Data for the reactivity of various forms of dimethyl phosphate are presented in Table 5. Near pH ~ 1, mainly the neutral forms of dialkyl phosphates are present and the contribution of acid hydrolysis to the overall rate is insignificant judging from the data for dimethyl phosphate. Comparison of the rate constants at pH 1.25 [57,61] therefore yields the correct idea about the variation of the reactivities of neutral dialkyl phosphate molecules in the following sequence [the values of 10^6k (s^{-1}) at 100°C and pH 1.24 are quoted]:

$$\underset{4,56}{(\text{iso-}C_3H_7O)_2P(O)OH} > \underset{3,13}{(CH_3O)_2P(O)OH} > \underset{0,8}{(p\text{-}C_3H_7O)_2P(O)OH}.$$

Table 5. The rate constants for the hydrolysis of various reactive forms of dimethyl phosphate[57] at 100°C in aqueous solutions.

Ruptured bond	$10k$, s^{-1}		10^6k, litre $mole^{-1}$ s^{-1}
	$(CH_3O)_2PO_2^-$	$(CH_3O)_2P(O)OH$	$(CH_3O)_2P(OH)_2^+$
P–O	$<10^{-3}$	0.9	0.11
C–O	$<10^{-3}$	3.3	0.91

The high reactivity of the di-isopropyl ester can be due to the S_N1 mechanism of the reaction with elimination of a carbonium ion, as in the case of tri-isopropyl phosphate[66].

The dimethyl phosphate anion is extremely stable and the kinetics of its alkaline hydrolysis have been investigated at 115° and 125°C.[67] Extrapolation of these data to 25°C yields the approximate rate constant listed in Table 6. Under the conditions of alkaline hydrolysis, dimethyl phosphate reacts mainly via the carbon atom, which results in the cleavage of the C–O bond to the extent of 90%.[65]

In neutral, acidic, and alkaline media, aromatic diesters hydrolyse with the dissociation of the P–O bond[25,58,59]. Some contribution by the dissociation of the C–O bond was noted only for bis-(2,4-dinitrophenyl) phosphate[62], the benzene ring of which is activated (in relation to aromatic nucleophilic substitution) by two strong electron-accepting groups. Diaryl phosphates have low pK_a values, the determination of which is difficult. Probably owing to the lack of pK_a values, the dependence of the rates of hydrolysis of diaryl phosphates on pH in

order to estimate the rate constants for the hydrolysis of the neutral molecules was not analysed[58] and only the rate constants for the hydrolysis of the anions were obtained. The anions of diaryl phosphates are much more reactive than those of dialkyl phosphates and certain kinetic data for their interaction with water (spontaneous hydrolysis) and hydroxide ions are available (Tables 6 and 7). The low activation entropy for the spontaneous hydrolysis of the anion of bis-(2,4-dinitrophenyl) phosphate ($\Delta S^{\neq}$ = −26 cal mole^{-1} K^{-1}) indicates a bimolecular mechanism of their reaction with water[58,59]. The kinetic isotope effect k_{H_2O}/k_{D_2O} = 1.5 observed for this reaction suggests the occurrence of general base catalysis by a second water molecule[58]. The bimolecular S_N2P mechanism was also adopted for the alkaline hydrolysis of the diester anions[59]. The negative charge on the oxygen atom, capable of being delocalised to the reaction centre via a p_π–d_π interaction, inhibits significantly the nucleophilic attack by the hydroxide ion. This increases the activation energy, which is higher by several kcal mole^{-1} for the diester anions than for the full esters of phosphoric acid.

Table 6. The rate constants for the spontaneous hydrolysis of diaryl phosphate anions $(RO)_2PO_2^-$ in water.

R	10^7k, s^{-1} (100°C)	References
C_6H_5	0.03	25
3-$NO_2C_6H_4$	0.0503	58
2-$NO_2C_6H_4$	0.562	58
4-$NO_2C_6H_4$	0.630	58
4-Cl-2-$NO_2C_6H_3$	4.08	58
4-$CH_3C(O)$-2-$NO_2C_6H_3$	122	58
2,4-$(NO_2)_2C_6H_3$*	1550	58

*According to Kirby and Younas[58], E = 19.6 kcal mole^{-1} and lg A = 7.77. The value of lg A (s^{-1}) was estimated by the present author.

The influence of the structure of diaryl phosphate anions on the rate of their reaction with water has been investigated[58]. The dependence of lg k on the pK_a for the phenols formed in the reaction at 100°C is expressed by the equation[58]

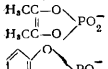
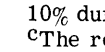
$$\lg k = -0.97pK_a - 0.20.$$

The authors[58] noted that the sensitivity of the reaction to the nature of the eliminated group in diarl phosphate anions is much greater than in the monoester monoanions. However, one must bear in mind that, in the reaction series under consideration, the coefficient of pK_a reflects not only the influence of the eliminated group but also of the remaining group and the latter is not constant either. If it is assumed that both groups have the same effect on the rate of reaction, the slope of the relation between lg k and pK_a calculated per eliminated group is lower by a factor of 2 (0.5). An analogous relation between lg k and the pK_a of the eliminated group (or the remaining group, since both are varied) exists in the alkaline hydrolysis of phosphate diester anions (Fig. 6). For the hydrolysis at 25°C, it corresponds to the equation

$$\lg k = -0{,}80\,pK_a + 0.76 \quad (n = 4,\ r = 0.996,\ s = 0{,}27)\ .$$

The rate constant for the alkaline hydrolysis of dimethyl phosphate as well as the rate constants for the hydrolysis of diaryl phosphates are described by this equation when account is taken of the reaction of dissociated P–O bonds in the reaction (10%).

Table 7. Kinetic parameters of the alkaline hydrolysis of phosphate diester anions in aqueous solutions.

Anion	10^5k, litre mole^{-1} s^{-1} (25°C)	E, kcal mole^{-1}	lg A[e]	References
$(CH_3O)_2PO_2^-$[b]	$3\cdot10^{-6}$	28.2	10.20[a]	67
$(C_6H_5O)_2PO_2^-$	0.015[a]	15.9[a]	4.83[a]	69
$(4\text{-}NO_2C_6H_4O)_2PO_2^-$[c]	0.58	18.3	8.23	71
$[2,4\text{-}(NO_2)_2C_6H_3O]_2PO_2^-$	301	16.6	9.65[a]	59
	36.5	—	—	67
	630[a]	15.8	9.38[a]	75
	440	17.1	10.18	70
	40 500	—	—	69
	15 600	10.5	6.89	74
	550	14.2	8.15	74
	210	13.7	7.36	74
	0.19; 0.003[d]	16.2; 22.2[d]	6.15; 8.76[d]	74
	1 860	17.5	11.10[a]	63

[a]See footnote to Table 1.
[b]The P–O bond is cleaved to an extent of approximately 10% during the reaction.
[c]The reaction was investigated in 20% aqueous ethanol solution.
[d]Parameters for the elimination of epoxypropane.
[e]A in litre mole^{-1} s^{-1}.

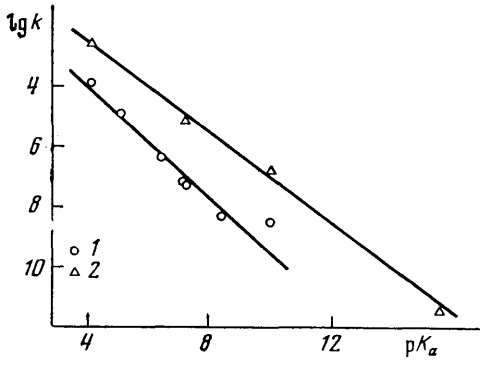


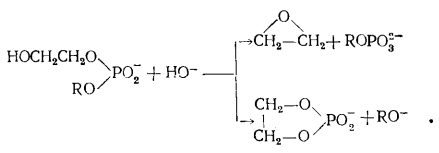
Figure 6. Dependence of lg k on the pK_a of the eliminated group for the spontaneous [k (s^{-1}) at 100°C (line *1*)] and alkaline [k (litre mole^{-1} s^{-1}) at 25°C (line *2*)] hydrolysis of phosphate diester anions.

Five-membered cyclic phosphate esters exhibit an unusually high reactivity, the rate of their hydrolysis being higher by a factor of 10^7–10^8 than that of acyclic diesters[57,68-70]. According to Westheimer[6], the much

higher reactivity of five-membered cyclic phosphates is partly due to the steric strain in the five-membered rings. Neutral and alkaline hydrolysis of the ethylene phosphate anion includes the cleavage of the P–O bond[65]. In the acid-catalysed hydrolysis, there is oxygen exchange between the phosphoryl group of ethylene phosphate and $H_2^{18}O$, the rate of which is comparable to the rate of cleavage of the ester bond. Since the oxygen exchange does not require the opening of the ring, it was assumed that the ring strain is reduced on formation of the intermediate containing the five-coordinated phosphorus atom[65]. The enthalpy of hydrolysis of the ethylene phosphate anion quoted by Westheimer and coworkers[68] is higher by 4.5 kcal mole^{-1} than for the diethyl phosphate anion, which confirms the strain in the cyclic ester.

Penta-alkoxyphosphoranes with five-membered rings are known to be formed more readily than the acyclic analogues[72] and this confirms indirectly the possibility of the involvement of such structures in the mechanism of the hydrolysis. The favourable effect of the stereochemistry of the transition state on the reaction is indicated by the activation entropy $\Delta S^{\neq} = -15$ cal mole^{-1} K^{-1} found for the alkaline hydrolysis of the dimethylvinylene phosphate anion[70]. The mechanism of the hydrolysis of cyclic phosphates has been discussed in detail in a review[6].

The acceleration of the hydrolysis of certain phosphate diesters owing to intramolecular catalysis has been observed. Intramolecular catalysis in the hydrolysis of β-hydroxyalkyl phosphate anions is important for the understanding of the mechanisms of certain biochemical reactions[73,74]. It has been established that the alkaline hydrolysis of anions containing the β-hydroxyalkyl group proceeds via two competing mechanisms, one of which involves the formation of an oxiran ring on elimination of the β-hydroxyalkyl group and the other is associated with the intermediate formation of a five-membered cyclic phosphate:



The oxiran ring and the five-membered cyclic phosphate are then rapidly converted into a glycol and a glycol phosphate. The ratio of these products depends on the second alcoholic moiety of the ester if the latter is an alkoxyalkyl group. However, the exclusive elimination of phenoxides in the reaction was observed for aryl β-hydroxyalkyl phosphates. The rate of reaction depended on the pK_a of the eliminated phenols or alcohols if the fraction of the observed rate constant referring to hydrolysis via a five-membered cyclic phosphate was considered for the latter[73].

Another example of intramolecular catalysis in the hydrolysis of phosphate diesters is the nucleophilic catalysis by the carboxylate group in the *o*-position relative to the ester linkage in aryl 2-carboxyphenyl phosphates[63]. The alkaline hydrolysis of the anions of these esters is 10^7–10^8 faster than that of the analogous compounds without a CO_2^- group in the *o*-position. The intermediate formation of a cyclic acyl phosphate during this reaction was demonstrated[63].

3. Hydrolysis of Phosphate Triesters

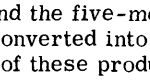
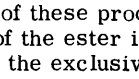
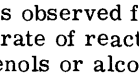
The hydrolysis of triesters is a potentially multistage process whose final product is phosphoric acid. The first stage, involving a change in the structure of the substrate, is considered in this section. Owing to the tribasic nature of phosphoric acid, there is a considerable scope for the alteration of the structures of triesters by the synthesis of mixed compounds with different alcoholic groups. The study of the kinetics of the hydrolysis of trialkyl phosphates began in the past century[76,77]; nevertheless, the number of triesters investigated hitherto is small (Table 8–10).

Table 8. Kinetic parameters of the spontaneous hydrolysis of phosphate triesters in water.

Compound	10^6k, s^{-1} (100°C)	E, kcal mole^{-1}	lg$A$ (s^{-1})	References
$(CH_3O)_3PO$	36.5	22.7	8.86[a]	79
$(CH_3O)_2P(O)OC_2H_5$	39.5[b]	—	—	84
$CH_3OP(O)(OC_2H_5)_2$	18.6[b]	—	—	84
$CH_3OP(O)(OCH_2CH(O)CH_3)_2$	29[a]	19.2	6.71	91
$(CH_3O)_2P(O)OCH{=}CCl_2$	660[a]	23.3[a]	10.47[a]	85
$(C_2H_4O)_3PO$	9.1[a]	24.4	9.25	90
$4\text{-}NO_2C_6H_4OP(O)(OC_2H_5)_2$	98[a]	22.5[a]	9.17[a]	85
$4\text{-}CH_3SO_2C_6H_4OP(O)(OC_2H_5)_2$	98[a]	22.5[a]	9.17[a]	85
$(C_6H_5O)_3PO$	0.06[c]	—	—	79
$(iso\text{-}C_3H_7O)_3PO$	4.5 (at 90°C)	—	—	66
$(t\text{-}C_4H_9O)_3PO$	30[d] (at 60°C)	—	—	66

[a]See footnote to Table 1.
[b]The values at 101–102°C and pH 4.7–4.9 are quoted.
[c]In water–dioxan (66 vol.%).
[d]In water–ethanol (50 vol.%).

Table 9. Kinetic parameters of the spontaneous hydrolysis of cyclic phosphate esters at 25°C.

Compound	10^5k, s^{-1} (25°C)	E, kcal mole^{-1}	lg$A$ (s^{-1})	References
	2.3	—	—	86
	830	8.4	4.12	92
	940	10.8	5.89	92
	660	9.8	4.97	92
	470	8.3	3.79	92
	0.26	15.5[a]	5.77[a]	80

[a]See footnote to Table 1.

In reactions involving neutral triester molecules, the attack by the nucleophile may be directed to the phosphorus or carbon atom of the ester linkage. Water and the hydroxide ion react with trialkyl phosphates in conformity with Pearson's concept of the interaction of hard and soft acids and bases. In alkaline hydrolysis, the reaction centre is the phosphorus atom, while in the reaction with water or in spontaneous hydrolysis the reaction centre is the α-carbon atom of the alkoxy group of the ester. Using $H_2^{18}O$, it was possible to establish that the dissociation of the P–O bond occurs in the alkaline hydrolysis of alkyl[78,79] and aromatic[79,80] esters, but in the reaction with water these two types of ester linkages, POAr and POAlk, are cleaved via different mechanisms. Aromatic nucleophilic substitution is known to proceed readily only when the benzene ring contains strongly electron-accepting groups[20],

Table 10. Kinetic parameters of the alkaline hydrolysis of phosphate triesters in aqueous solutions.

Compound	10^3k, litre mole^{-1} s^{-1}(25°C)	E, kcal mole^{-1}	lg$A$ (litre mole^{-1} s^{-1})	Refs.
$(CH_3O)_3PO$	0.146	15.9	7.82	79
$(C_2H_5O)_3PO$	0.0132	15 3[a]	6.32[a]	71
$CH_3OP(O)(OCH_2CH{-}CH_2)_2$ (O)	2.2	15.1	8.41	91
$(C_2H_5O)_2P(O)OCH{=}CH_2$	2.0	—	—	94
$(C_2H_5O)_2P(O)OCH_2CH_2N^+(CH_3)_3$	30	—	—	93
$(C_2H_5O)_2P(O)OP(O)(OC_2H_5)_2$	2630	—	—	93
$(CH_3O)_2P(O)OCH(CH_3)C(O)CH_3$	387 000	—	—	95
	9000[b]	—	—	95
$(C_2H_5O)_2P(O)OCH(CH_3)C(O)CH_3$	64 000	—	—	95
$(iso\text{-}C_3H_7O)_2P(O)OCH(CH_3)C(O)CH_3$	2200	—	—	95
$(C_6H_5O)_2P(O)OCH(CH_3)C(O)CH_3$	820 000	—	—	95
$CH_2{-}O$ | $CH_2{-}O$ $P(O)OCH_3$	64 000	—	—	86
O O $P(O)OC_2H_5$	0.57[a]	13.8	6.87	97
$(C_6H_5O)_3PO$	14.0	9.2	4.91	96
$4\text{-}NO_2C_6H_4OP(O)(OC_6H_5)_2$	490	—	—	100
$4\text{-}NO_2C_6H_4OP(O)(OCH_3)_2$	39	12.2	7.55[a]	98
$4\text{-}NO_2C_6H_4OP(O)(OC_2H_5)_2$	11	13.5	7.95[a]	98
$4\text{-}NO_2C_6H_4OP(O)(OC_3H_7)_2$	7.45	13.0	7.43[a]	98
$4\text{-}NO_2C_6H_4OP(O)(OC_3H_7\text{-}iso)_2$	1.00	14.5	7.64[a]	98
$4\text{-}NO_2C_6H_4OP(O)(OC_4H_9\text{-}n)_2$	7.2	13.2	7.55[a]	98
$4\text{-}NO_2C_6H_4OP(O)(OC_4H_9\text{-}iso)_2$	6.2	13.2	7.52[a]	98
$4\text{-}NO_2C_6H_4OP(O)(OC_4H_9\text{-}s)_2$	0.48	14.3	7.20[a]	98
$4\text{-}NO_2C_6H_4OP(O)(OC_6H_{13}\text{-}n)_2$	7.5	—	—	100
$4\text{-}H_2NC_6H_4OP(O)(OC_2H_5)_2$	0.243	—	—	49
$4\text{-}(CH_3)_2NC_6H_4OP(O)(OC_2H_5)_2$	0.278	—	—	49
$4\text{-}CH_3OC_6H_4OP(O)(OC_2H_5)_2$	0.280	—	—	49
$4\text{-}C_2H_5C_6H_4OP(O)(OC_2H_5)_2$	0.325	—	—	49
$4\text{-}(iso\text{-}C_3H_7)C_6H_4OP(O)(OC_2H_5)_2$	0.337	—	—	49
$4\text{-}CH_3C_6H_4OP(O)(OC_2H_5)_2$	0.353	—	—	49
$C_6H_5OP(O)(OC_2H_5)_2$	0.463	—	—	49
$3\text{-}CH_3OC_6H_4OP(O)(OC_2H_5)_2$	0.622	—	—	49
$4\text{-}CH_3SC_6H_4OP(O)(OC_2H_5)_2$	0.742	—	—	49
$4\text{-}(CO_2^-)C_6H_4OP(O)(OC_2H_5)_2$	0.920	—	—	49
$4\text{-}ClC_6H_4OP(O)(OC_2H_5)_2$	1.15	—	—	49
$4\text{-}BrC_6H_4OP(O)(OC_2H_5)_2$	1.26	—	—	49
$4\text{-}IC_6H_4OP(O)(OC_2H_5)_2$	1.29	—	—	49
$3\text{-}ClC_6H_4OP(O)(OC_2H_5)_2$	1.56	—	—	49
$3\text{-}BrC_6H_4OP(O)(OC_2H_5)_2$	1.65	—	—	49
$4\text{-}CH_3C(O)C_6H_4OP(O)(OC_2H_5)_2$	3.23	—	—	49
$4\text{-}NCC_6H_4OP(O)(OC_2H_5)_2$	6.37	—	—	49
$3\text{-}NO_2C_6H_4OP(O)(OC_2H_5)_2$	6.38	—	—	49
$2\text{-}(CH_3)_2NC_6H_4OP(O)(OC_2H_5)_2$	0.148	—	—	49
$2\text{-}(iso\text{-}C_3H_7)C_6H_4OP(O)(OC_2H_5)_2$	0.172	—	—	49
$2\text{-}C_2H_5C_6H_4OP(O)(OC_2H_5)_2$	0.192	—	—	49
$2\text{-}CH_3OC_6H_4OP(O)(OC_2H_5)_2$	0.367	—	—	49
$2\text{-}IC_6H_4OP(O)(OC_2H_5)_2$	1.92	—	—	49
$2\text{-}BrC_6H_4OP(O)(OC_2H_5)_2$	2.38	—	—	49
$2\text{-}ClC_6H_4OP(O)(OC_2H_5)_2$	2.60	—	—	49
$2\text{-}NO_2C_6H_4OP(O)(OC_2H_5)_2$	22.2	—	—	49

[a] See footnote to Table 1.
[b] The rate constant for the cleavage of the P–OCH_3 bond.

so that the spontaneous hydrolysis of aromatic esters, like the alkaline hydrolysis, usually takes place at the phosphorus atom [79,80]; the same type of cleavage of P–OAr bonds is characteristic of the acid hydrolysis [80]. The spontaneous and acid hydrolysis of alkyl esters takes place with rupture of the C–O bond [66,79,81,82]. As a rule the POAr ester linkages are less resistant to hydrolysis than the POAlk linkages and in the alkaline hydrolysis of mixed compounds the P–OAr bonds are cleaved preferentially. It has been shown for dibenzyl *p*-nitrobenzoyl phosphate that the anhydride linkage is the most reactive [83], being hydrolysed at the carbonyl carbon atom. Fig. 7 shows that plots of the hydrolysis rate constants for certain triesters against pH have a plateau in the region of weakly acid pH values. The extent of the plateau on the side of high pH values is determined by the ratio of the rate constants for the alkaline and spontaneous hydrolysis and on the side of low pH values by the ratio of the rate constants for the acid and spontaneous hydrolysis and the pK_a for the protonated form of the ester. In the region of the plateau, the reaction between the neutral trialkyl phosphate molecule and water may proceed via an S_N2 or S_N1 mechanism at the carbon atom of the ester linkage. A mechanism of the S_N1 type, involving the cleavage of a carbonium ion, has been demonstrated for esters of secondary and tertiary alcohols [66].

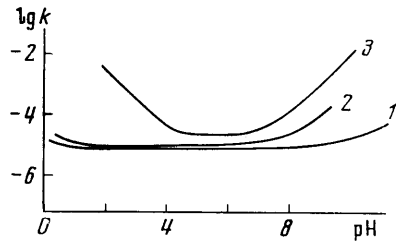


Figure 7. Dependence of the rate constants for the hydrolysis of triesters on the pH of the medium: 1) $(C_2H_5O)_3PO$ at 101°C [84]; 2) $4\text{-}NO_2C_6H_4OP(O)(OC_2H_5)_2$ at 70°C [85]; 3) ethylene methyl phosphate at 25°C. [86]

The kinetic isotope effect for trimethyl and triethyl phosphates (k_{H_2O}/k_{D_2O} = 1.25) agrees with the hypothesis of an S_N2 mechanism of the spontaneous hydrolysis of these esters [81,87]. The low values of $\Delta S^{\neq}$ for the esters (−18 and −20 cal mole^{-1} K^{-1} respectively) are consistent with a bimolecular rate-limiting stage. A significantly greater isotope effect for the solvent ($k_{H_2O}/k_{D_2O} \simeq 2$) was noted in the cleavage of the P–OAr bond in the spontaneous hydrolysis of 2-aryloxy-2-oxo-1,3,2-dioxaphosphorinanes, which enabled the authors [80] to postulate the occurrence of general base catalysis by a second water molecule in the reaction via an S_N2P mechanism involving the phosphorus atom.

Unsubstituted trialkyl phosphates are insensitive to acid catalysis. In the hydrolysis of trimethyl phosphate, the replacement of water by a 3 M $HClO_4$ solution increases the rate of reaction by [only] 20%. [79] Appreciable catalysis by 0.5 M H_2SO_4 of the hydrolysis of triethyl phosphate was not observed either [81]. The appearance of an acid-catalytic effect is promoted by carrying out the reaction in aqueous organic media, where the rate of spontaneous hydrolysis is sharply reduced owing to the decrease of the activity of water [81,87]. The low sensitivity of trialkyl phosphates to acid catalysis may be attributed to the long distance between the site of addition of the proton (the phosphoryl group) and the reaction centre. The high negative activation entropy for the acid hydrolysis of triethyl phosphate and the low isotope effect (k_{H_2O}/k_{D_2O} = 0.6 in 0.56 M $HClO_4$) served as a basis for the adoption of a bimolecular reaction mechanism, including proton transfer in the equilibrium stage [81].

An isokinetic relation of the compensation type and covering the $\Delta S^{\neq}$ range from 0 to −50 kcal mole^{-1} K^{-1} has been established between the activation parameters in the acid hydrolysis of triesters [88]. It probably due to the gradual transition from an S_N2 to an S_N1 mechanism as the structure of the trialkyl phosphate is altered.

In contrast to trimethyl and triethyl phosphates, the rate constants for the hydrolysis of which increase monotonically with increase of the concentration of acid in aqueous organic media (Fig. 8), the rate constants for the acid hydrolysis of aromatic esters passes through a

maximum, whose position depends on the nature of the ester and the acid employed, as for mono- and di-aryl phosphates[25,80].

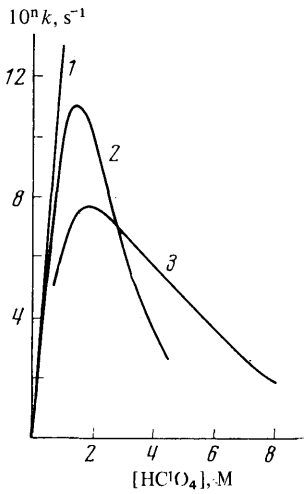


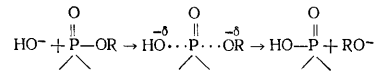
Figure 8. Dependence of the rate constants for the hydrolysis of triesters on the $HClO_4$ concentrations: 1) $(C_2H_5O)_3PO$, $n = 6$, in water–dioxan (35%) at 101°C [81]; 2) $(C_6H_5O)_3PO$, $n = 5$, in water–dioxan (60%) at 100°C [25]; 3) $4\text{-}NO_2C_6H_4OP(O)(OC_6H_5)_2$, $n = 4$, in water–dioxan (5%) at 100°C. [89]

The acid hydrolysis of *p*-nitrophenyl diphenyl has been studied in detail[89]. In this case, the maximum is due to the strong negative salt effect in concentrated solutions of inorganic acids. At a constant ionic strength, the hydrolysis rate cojstant therefore increases in proportion to the stoichiometric acidity and has no maximum. The use of Bunnett's improved method makes it possible to characterise the reaction mechanism in terms of the slope of the relation

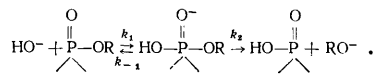
$$\lg k + H_0 = f(\lg c_{H^+} + H_0),$$

where H_0 is the acidity function and c_{H^+} the stoichiometric concentration of H_3O^+. In H_2OS_4, HCl, and $HClO_4$ solutions, these relations had slopes of 1.5, 1.1, and 1.25 respectively, which is characteristic of reactions with a slow proton transfer in the rate-limiting stage. Similar slopes (1–1.4) were obtained for the corresponding relations in the acid hydrolysis of monoaryl phosphates[89]. In HCl solution, the maximum corresponds to an acid concentration of 6 M; the parameters of the Arrhenius equation under these conditions are $E = 14.8$ kcal mole^{-1} and $\lg A = 5.4$, whence $\Delta S^{\neq} = -39$ cal mole^{-1} K^{-1}.[89] The value $\Delta S^{\neq}$ obtained indicates the vigorous solvation of the transition state, in the formation of which the activity of water plays an important role. In conformity with these findings, the rate of acid hydrolysis is reduced by a factor of approximately 2 when the reaction is carried out in a 60% aqueous solution of dioxan. According to Bunton[5], the attack by a water molecule on the phosphorus atoms in the acid hydrolysis of the P–O–Ar linkages may proceed in unison with proton transfer to the ester molecule, complete proton transfer not being obligatory for the attainment of the transition state.

The alkaline hydrolysis of phosphate triesters, which is as a rule described by a kinetic equation for second-order reactions and has an S_N2P mechanism, has been investigated in greatert detail[1–8]. Two types of S_N2P mechanisms are possible for the alkaline hydrolysis. In one of them, the synchronous formation and cleavage of bonds in the transition state is postulated:



In the other version, the successive addition of the nucleophile and removal of the eliminated group with participation of a metastable intermediate compound in the reaction is postulated:



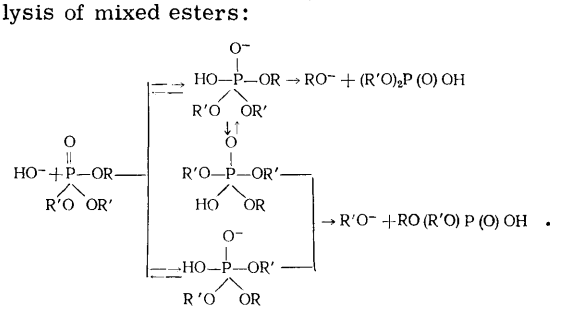
According to the method of steady-state concentrations, the observed rate constant is a compound quantity. The rate of this reaction dc/dt is expressed by the equation

$$\frac{dc}{dt} = k_1 k_2 c\,[HO^-]/(k_{-1} + k_2),$$

where c and $[HO^-]$ are the concentrations of the ester and the hydroxide ions respectively. It follows from the last equation that, for comparable values of k_{-1} and k_2, oxygen should be exchanged during the reaction between the phosphoryl group of the ester and water. It has been shown for triphenyl phosphate that in reality there is no exchange between $H_2^{18}O$ and phosphate triesters during alkaline hydrolysis[79]. This is probably due to the low stability of the negatively charged phosphorans[97]. In the absence of oxygen exchange, one may assume that $k_2 \gg k_{-1}$ and the expression for the reaction rate simplifies to

$$dc/dt = k_1 c\,[HO^-].$$

In the alkaline hydrolysis of diethyl *p*-nitrophenyl phosphate and *p*-nitrophenyl diphenyl phosphate, $k_{H_2O}/k_{D_2O} \simeq 1$ (more precisely 0.87 and 1.10 respectively), which agrees with the hypothesis of the nucleophilic attack by the hydroxide ion on the phosphorus atom in the rate-limiting stage[100]. The activation entropies $\Delta S^{\neq} < -20$ cal mole^{-1} K^{-1}, which can be found from the data in Table 10, are also consistent with this hypothesis. The increase in the complexity of the S_N2P mechanism may be due to the rapid ligand exchange between non-equivalent positions in the intermediate compound[99], for which a bipyramidal structure is postulated. According to Westheimer[6], as a result of the pseudorotation of the bipyramid the hydrolysis of cyclic phosphates may involve the formation of various reaction products. The hypothesis of pseudorotation in the intermediate is difficult to prove, as can be seen from the general scheme for the possible pathways in the alkaline hydrolysis of mixed esters:



When the influence of the structure on the rate of spontaneous, acid, and alkaline hydrolysis of triesters is considered, one may note a definite analogy in the influence of the nature of the alcoholic ester moieties on the rate of hydrolysis of phosphate mono-, di-, and tri-esters. Electron-accepting substituents in alkyl and aryl groups usually favour the dissociation of ester linkages, which is confirmed for triesters by the data in Tables 8–10.

The esters of secondary and tertiary alcohols exhibit a higher reactivity during spontaneous hydrolysis than those of primary alcohols owing to the ease of the cleavage of the C–O bonds via an S_N1 mechanism[66], which is analogous to the behaviour of the corresponding phosphate mono- and di-esters. An unusually high reactivity has been observed for five-membered cyclic esters, which hydrolyse in neutral, acid, and alkaline media 10^6–10^8 faster than their six- or seven-membered cyclic analogues and cyclic esters[86,97]. Among five-membered cyclic phosphates, derivatives of vinylene phosphate are particularly unstable[92].

The influence of the structure of triesters on the rate of spontaneous and acid hydrolysis cannot be considered in greater detail owing to the scarcity of the available data. It has been shown for the alkaline hydrolysis[101] that the dependence of lg k on the pK_a of the eliminated group is close to linearity when the nature of the eliminated group is altered in the sequence OAlk, OAr, $OP(O)R_2$, F. However, using detailed data for the kinetics of the alkaline hydrolysis of substituted aryl diethyl phosphates[98], one may note that a more rigorous linear relation between lg K and the pK_a of the eliminated groups is observed when the nature of such groups is altered only slightly. For example, Fig. 9 shows that the relation between lg k and the pK_a of the eliminated group of aryl diethyl phosphates is described (at 25°C) by the equation

$$\lg k = -0.57\mathrm{p}K_a + 2.48 \quad (n = 27,\ r = 0.976,\ s = 0.1),$$

which differs from the general relation

$$\lg k = -0.42\mathrm{p}K_a + 0.86 \quad (n = 29,\ r = 0.974,\ s = 0.2),$$

where the rate constants for the hydrolysis of triethyl phosphate and tetraethyl pyrophosphate are included. One should note, however, that the relation (at 39°C)

$$\lg k = -0.41\mathrm{p}K_a + 2.79,$$

whose slope is close to that of the general relation, has been obtained for the alkaline hydrolysis of 2-aryloxy-2-oxo-1,3,2-dioxaphosphorinanes[80], whose structures are very similar to those of aryl diethyl phosphates.

The intramolecular catalysis of the hydrolysis of phosphate triesters has been investigated in a number of studies[95,102–106]. In the hydrolysis of aryl 2-carboxyphenyl phosphates intramolecular nucleophilic catalysis by the ionised carboxy-group led to the preferential cleavage of the P–OAr bond[63], which was explained by the inhibition of pseudorotation in the five-coordinated intermediate compounds containing two negatively charged oxygen atoms in the equatorial positions of the bipyramidal structure. In triesters of similar structure [but without a carboxylate group], there is only one negatively charged ligand in the equatorial position and pseudorotation is not hindered. The ready transfer of the salicylate oxygen to the axial position of the bipyramid ensures the possibility of the formation of two reaction products. Salicylic acid is the main product (96%) of the hydrolysis of 2-carboxyphenyl diphenyl phosphate in alkaline media, but in the region of acid pH the elimination of phenol predominates (90%).[104] The intermediate formation of an acyl phosphate in an alkaline medium has been established for the reaction with hydroxylamine; it was shown that the rate of formation of the acyl phosphate is close to the rate of hydrolysis of the substrate. The ratio of the two reaction products (salicylic acid and phenol) depended on the pK_a of the phenol when the latter contained substituents, a decrease of pK_a favouring the elimination of the phenol[104].

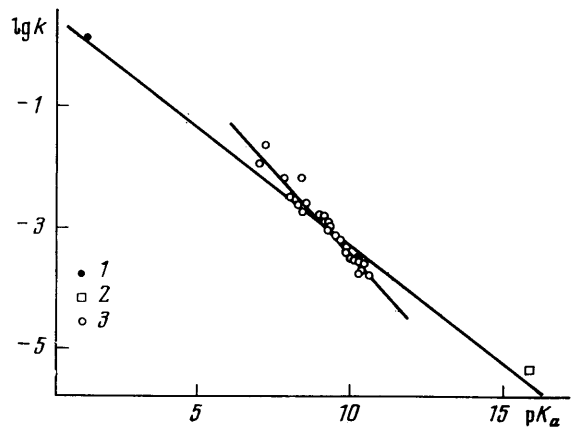


Figure 9. Dependence of lg k on the pK_a of the eliminated group in the alkaline hydrolysis of triesters at 25°C: 1) tetraethyl pyrophosphate (lg k – lg 2); 2) triethyl phosphate (lg k – lg 3); 3) aryl diethyl phosphates.

In the hydrolysis of dialkyl 2-carboxyphenyl phosphates, intramolecular catalysis, accelerating the hydrolysis of such esters by a factor of approximately 10^7 relative to the corresponding compounds without a carboxy-group, was also observed[103]. Other examples of intramolecular catalysis in the hydrolysis of phosphate triesters have been described[102,105,106].

In conclusion, we may note that the data presented in this review characterise the kinetics of the hydrolysis of an extremely small proportion (approximately 140 compounds) of the many thousands of phosphate mono-, di-, and tri-esters available at the present time. The need for further studies of the kinetics of the hydrolysis of phosphate esters is therefore evident. The author believes that the data, a systematic account of which has been given in this review, will be useful in the consideration of various problems concerning the determination of the relation between the structure and reactivity of phosphates.

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