273. *The Reactivity of Esters of Quinquevalent Phosphorus towards Anions.*

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The rate of reaction of trimethyl phosphate, dimethyl ethylphosphonate, and dibenzyl methylphosphonate with a series of anions follows the redox potentials of the ions fairly closely. This is considered to be characteristic of a bimolecular displacement reaction at the saturated carbon atom. The high reactivity of the hydroxide ion is attributed to alternative reaction at the phosphorus atom.

Previously,[1] the effect of substitution on the rate of alkaline hydrolysis of phosphonate esters was discussed in terms of a displacement reaction at the phosphorus atom. Although the evidence in favour of this reaction is highly suggestive, the possibility of alternative substitution at the saturated carbon atom of the ester group cannot be definitely excluded in view of the high yields of ethers obtained on trans-esterification.[1b] The possibility of differentiating between these alternative reactions by kinetic measurements has been considered in the following way. It is well known that certain anions, in particular highly polarisable ions, *e.g.*, I^- and $S_2O_3^{2-}$, are very reactive towards the saturated carbon atom. Rate measurements indicate a common order of reactivity [2] in the bimolecular displacement reactions of alkyl halides, sulphonates, epoxides, and β-lactones. Moreover, the reactivities of a series of ions towards any two of these alkylating agents can be represented fairly closely [2] by the relation

$$\log k_2 = \text{const.} \times \log k_2^1 + \text{const.}$$

where k_2 and k_2^1 are rate constants for the reactions of a particular ion with these two reactants. This linear relation suggests that the reactivity of a particular ion can be represented by a parameter characteristic of the ion but independent of the substrate. When, however, the nature of the transition state changes considerably, *e.g.*, to an ionisation process, the common order of anion reactivity no longer prevails.

As a result of detailed measurements of the rates of substitution of several chalcogens with anionic reagents, Foss [3] noted a close relation between the reactivity and the redox potential of the ion. A similar relation is found to hold approximately for the bimolecular substitution reactions of the alkylating agents so far examined.[4]

If attention is confined to S_N2 displacements only, the rate constant k_2 can be related to the redox potential E_r as follows,

$$\log k_2 = \alpha E_r + \log k^\circ_2 \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (1)$$

where α is a constant characteristic of the substrate, and k°_2 is the rate constant of a reference reaction, *e.g.*, solvolysis.

The proportionality between the free energy of the substitution reaction and the oxidation–reduction potential shows that the energy changes in the two processes are determined by similar factors:

$$(a)\ N^- + R{-}X \rightleftharpoons N^{\delta-} \cdots R \cdots X^{\delta-}$$

$$(b)\ N^- \rightleftharpoons \tfrac{1}{2}N_2 + e$$

In both processes the energy of electron transfer from the ion N^-, and the resultant change in solvation energy are more significant than the energy of the bond formed. This is also

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[1] (*a*) Hudson and Keay, *J.*, 1956, 2463; (*b*) Toy, *J. Amer. Chem. Soc.*, 1944, **66**, 499; Rueggeberg and Chernak, *ibid.*, 1948, **70**, 1802.

[2] Scott and Swain, *ibid.*, 1953, **75**, 141.

[3] Foss, *Acta Chem. Scand.*, 1947, **1**, 8, 307; 1949, **3**, 1385.

[4] Edwards, *J. Amer. Chem. Soc.*, 1954, **76**. 1540.

shown by semi-empirical calculations of the activation energies of substitution reactions.[5] For the present purpose a detailed interpretation of equation (1) is not required.

A similar energy balance is not to be expected in reactions with widely varying transition states, and Edwards[4] has demonstrated the necessity of a four-parameter equation in relating the rate to the properties of the ion. Thus he found that the rate of a wide range of reactions could be represented as a linear function of the oxidation–reduction potential and the pK_a of the conjugate acid of the nucleophil. An examination of the limited data on the rate of substitution at the phosphoryl centre shows that anions which are the most reactive towards the saturated carbon atom are amongst the least reactive nucleophils towards phosphorochloridates, as shown by the rate sequence given by Dostrovsky and Halmann:[6]

$$OH^- > F^- > OMe^- > OPh^- > EtOH > PhS^-,\ AcO^-$$

The reactivity of a particular ion is highly dependent on the basicity (towards protons) relative to that of the displaced group.[7] Thus, although fluoride and phenoxide ions readily react with phosphorochloridates, they are unreactive towards esters in protolytic solvents. In general, it may be assumed that an ion does not displace a more basic group from a phosphoryl group at a measurable rate in a solvolytic medium, and consequently the number of anions which can displace alkoxy-groups from esters is very limited. For example, the hydroperoxide ion is highly reactive towards acyl halides, anhydrides, and aromatic esters but is inert towards aliphatic esters.[7]

These considerations suggest strongly that only the most basic anions can remove the alkoxy-groups from phosphorus esters at an appreciable rate by attack at the phosphorus atom. Anions of strong acids will react preferentially at the carbon atom as shown, for example, by the ready reaction of lithium chloride with benzyl phosphates.[8]

TABLE 1.

	k_1 (min.$^{-1}$)	$\log\frac{k_2}{k_{H_2O}}$	k_1 (min.$^{-1}$)	$\log\frac{k_2}{k_{H_2O}}$	k_1 (min.$^{-1}$)	$\log\frac{k_2}{k_{H_2O}}$
Nucleophilic reagent	$PO(OMe)_3$ *		$Et{\cdot}PO(OMe_2)_2$ *		$Me{\cdot}PO(O{\cdot}CH_2Ph)_2$ †	
Water	$2{\cdot}02 \times 10^{-2}$	0	$1{\cdot}5 \times 10^{-3}$	0	$6{\cdot}4 \times 10^{-2}$	0
Chloride	$0{\cdot}49 \times 10^{-2}$	1·83	$0{\cdot}3 \times 10^{-3}$	1·74	$8{\cdot}3 \times 10^{-2}$	2·46
Bromide	$2{\cdot}40 \times 10^{-2}$	2·52	$1{\cdot}8 \times 10^{-3}$	2·52	$11{\cdot}9 \times 10^{-2}$	2·61
Thiocyanate	$8{\cdot}71 \times 10^{-2}$	3·07	$3{\cdot}04 \times 10^{-3}$	3·75	$72{\cdot}4 \times 10^{-2}$	3·38
Iodide	$4{\cdot}65 \times 10^{-2}$	2·81	$7{\cdot}02 \times 10^{-3}$	3·10	$4{\cdot}7 \times 10^{-2}$	3·41
Thiosulphate	4·51	4·79	0·21	4·58	3·47	4·07
Hydroxide	1·67	6·09	4·70	7·40	59·0	5·31
‡ Hydroxide (estimated)	—	2·75	—	2·60	—	2·60

* With 0·2N-anion in water at 80°. † With 0·2N-anion in 25% acetone + 75% water at 100°.
‡ Estimated from equation (1).

k_1 is the first-order constant for the reaction with a particular anion of concentration [X], see equation (2): $k_2 = k_1/[X]$.

It is proposed, therefore, to relate the rate constants for the reaction of a series of anions with a particular ester to the redox potential E_r, according to equation (1). Abnormally high reactivities of highly basic ions may then be attributed to the reaction at the phosphoryl group. This principle can be illustrated by the well-known alkylation of β-lactones. Isotope analysis shows that the neutral hydrolysis proceeds with alkyl–oxygen fission,[9] and the rate of reaction with a series of anions[10] is given closely by equation (1). The hydroxide ion is, however, *ca.* 10^3 times more reactive than predicted by this equation, indicating preferential reaction at the carbonyl group. This has been confirmed[9] by ^{18}O tracer work.

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[5] Baughan and Polanyi, *Trans. Faraday Soc.*, 1941, **37**, 648.

[6] Dostrovsky and Halmann, *J.*, 1953, 502.

[7] Wiberg, *J. Amer. Chem. Soc.*, 1955, **77**, 2521.

[8] Clark and Todd, *J.*, 1950, 2030.

[9] Long and Purchase, *J. Amer. Chem. Soc.*, 1950, **72**, 3267; Olsen and Miller, *ibid.*, 1938, **60**, 2687.

[10] Bartlett and Small, *ibid.*, 1950, **72**, 4867.

In the present investigation several esters of quinquevalent phosphorus have been found to behave in a similar manner. First, trimethyl phosphate was studied, since the positions of bond fission on acid, alkaline, and neutral hydrolysis are established in this case.[11] The data given in Table 1 show the hydroxide ion to be *ca.* 10^3 times more reactive than predicted by equation (1), and considerably more reactive than the other anions. With the exception of the hydroxide ion, the rate constant is observed to increase regularly with E_r (Table 1), suggesting strongly that the reaction proceeds at the saturated carbon atom. The abnormal reactivity of the hydroxide ion is then attributed to the preferential reaction at the phosphonyl group, which has been established by ^{18}O analysis.

Similar data are given in Table 1 for methyl ethylphosphonate and benzyl methylphosphonate. No direct investigations of the position of bond fission in the alkaline hydrolysis of phosphonate esters have been made, although various observations [1, 12] point to a mechanism similar to that of phosphate esters. The greatly enhanced reactivity of the esters towards the hydroxide ion compared with the other nucleophiles (Table 1) strongly supports this conclusion. It is noted that an increase in temperature reduces the difference between the reactivity towards the hydroxide and the other ions. This is no doubt due to the low energy of activation for the reaction of the hydroxide ion at the phosphonyl group [1] [14 kcal./mole (compared with the activation energy for S_N2 reactions at the saturated carbon atom (20—23 kcal./mole)].

These investigations were extended by the preparation of methyl diethylphosphinate and measurement of its rate of alkaline hydrolysis (Table 3). The rate of reaction with most of the other ions was too small to be measured satisfactorily owing to the incursion of simultaneous side reactions. An approximate value of the rate of reaction with sodium thiosulphate was obtained, and found to be almost one half of the rate of reaction with dimethyl ethylphosphonate (Table 2). In this case also the rate of alkaline hydrolysis is *ca.* 10^4 times greater than predicted from equation (1), suggesting strongly that hydroxide ions attack the phosphorus atom preferentially.

TABLE 2. *Relative reactivity of phosphorus esters towards thiosulphate and hydroxide ions in water.**

	$PO(OMe)_3$	$Et\cdot PO(OMe)_2$	$Et_2PO(OMe)$
$k_{S_2O_3}$	15·7	1·1	1
k_{OH}	1	4·2	5·9
pK_a of acid	1·29	2·00	3·40

* The rate constants are divided by the number of alkoxy-groups in the ester.

The effect of progressive substitution of alkoxy-groups on the rates of alkylation and phosphonylation is shown in Table 2. Although the reactivities of the mono- and di-alkyl phosphonates are very similar, the rate of reaction of the three esters with sodium thiosulphate decreases with the pK_a of the acid released. This is in agreement with the generalisation that esters of strong acids tend to be strong alkylating agents,[13] although there is no quantitative correlation between the rate of reaction and pK_a of the acid, even in the series of closely related esters investigated here.

Substitution produces small changes in the rate of the alkaline reaction, trimethyl phosphate being significantly less reactive than the phosphonates.

EXPERIMENTAL

Materials.—Commercial trimethyl phosphate (Albright and Wilson Ltd.) was purified by fractional distillation under reduced pressure, then having b. p. 97—98°/36—38 mm. (lit., b. p. 97°/36 mm.), n_D^{18} 1·3941.

Dimethyl ethylphosphonate was prepared by refluxing ethyl iodide with 1 equiv. of trimethyl

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[11] Blumenthal and Herbert, *Trans. Faraday Soc.*, 1945, **41**, 611; Barnard, Bunton, Llewellyn, Oldham, Silver, and Vernon, *Chem. and Ind.*, 1955, 761.

[12] Gerrard, Green, and Nutkins, *J.*, 1952, 4076.

[13] Anbar, Dostrovsky, Samuel, and Joffe, *ibid.*, 1954, 3604.

phosphite (Arbusov reaction), itself prepared[14] by the action of phosphorus trichloride (1 mol.) on methanol (3 mol.) and diethylaniline (3 mol.) in light petroleum (b. p. 40—60°); b. p. was 70—71°/11 mm. (lit., b. p. 70°/12 mm.).

Methyl diethylphosphinate was prepared by the action of diazomethane on diethylphosphinic acid, itself prepared by reaction between thiophosphoryl chloride and ethylmagnesium iodide, followed by oxidation of the intermediate bisdiethylphosphine disulphide. Thiophosphoryl chloride (64·5 g.) was added slowly with stirring to ethylmagnesium iodide (1·5 moles) at −10°. The mixture was stored at room temp. for 12 hr. and then decomposed in 750 ml. of 10% sulphuric acid. The ether layer was separated, and the remainder extracted twice with ether. The ether was removed, leaving a pale yellow solid which, recrystallised from ether, had m. p. 74·5° (yield 65%) (Found: C, 39·4; H, 8·26. $C_8H_{20}P_2S_2$ requires C, 39·8; H, 8·27%). Hydrogen peroxide was added slowly (76·5 ml. of 100-vol.), with stirring to this *bisdiethylphosphine disulphide* (17 g.) in acetic acid (200 ml.). The mixture was filtered, water and acetic acid were removed by the water pump, and the residual oil was distilled (11 g., 62%; b. p. 138—142°/0·7 mm.; lit., b. p. 132°/1·5 mm.) (Found: C, 38·9; H, 9·0. Calc. for $C_4H_{11}O_2P$: C, 39·3; H, 9·0%). A solution of diazomethane (5 g.) in sodium-dried ether was added slowly to this diethylphosphinic acid (10 g.) in ice-cooled ether. The ether was removed, and the residual oil distilled, yielding 7 g. (63%) of *methyl diethylphosphinate*, b. p. 84—86°/9 mm., 90—94°/15 mm. (Found: C, 44·1; H, 9·6; P, 21·7. $C_5H_{13}O_2P$ requires C, 44·2; H, 9·55; P, 22·8%).

Dibenzyl methylphosphonate was prepared as follows: methylphosphonyl dichloride (44·3 g.) in dry ether (300 ml.) was added slowly and with stirring to a mixture of freshly distilled diethylaniline (100 g.) and benzyl alcohol (72 g.) in dry ether (200 ml.) at 0°. The mixture was stored overnight, and the diethylaniline hydrochloride (103 g., 95%) filtered off. The filtrate was refluxed gently for 24 hr., the ether removed, and the oil distilled (yield 85%), having b. p. 163—164°/0·05 mm., n_D^{19} 1·5479 (Found: C, 65·0; H, 6·1; P, 9·9. $C_{15}H_{17}O_3P$ requires C, 65·2; H, 6·2; P, 11·2%).

Diethyl vinyl phosphate was prepared by the action of carefully dried monochloroacetaldehyde on triethyl phosphite [yield, 50%; b. p. 70—72°/4 mm., n_D^{35} 1·4100; lit., b. p. 79°/6 mm.].

Kinetic Measurements.—The rate of reaction was followed by the conventional manner described previously,[1] the method of analysis depending on the particular reaction.

In the alkaline hydrolyses, aliquot parts were titrated against standard acid, bromocresol-purple being used as indicator. Since only one group is removed during hydrolysis, the rate coefficient was calculated from the general equation for a second-order process.

Reaction with Halide Ions.—The rate of neutral hydrolysis, which is accelerated by reaction with halide ions, was determined by titration of the acid released with sodium hydroxide solution, methyl-orange being used as indicator. Free iodine was liberated in the reaction with iodide ions, and the acid titration was affected as the reaction proceeded, as illustrated by the following data for the reaction of dimethyl ethylphosphonate (0·02N) at 80° with 0·2N-potassium iodide:

Time (hr.)	0	10	31	54	95	117	141
Titration (ml.) ...	0·0	0·74	1·92	2·79	3·59	3·08	1·95

In the course of the decomposition, the phosphonate or hemi-ester is probably reduced as follows: $\mathrm{Et{\cdot}PO(OR){\cdot}O^- + 2H^+ + 2I^- \longrightarrow Et{\cdot}P(OR){\cdot}O^- + H_2O + I_2}$. The rate constants for the reaction of iodide ions with the esters were therefore determined from the initial part of the reaction. The second-order rate constant for the reaction with anion X^- was calculated from the observed first-order rate constant for the production of acid, k, by the equation

$$k = k_{\mathrm{H}} + k_1 = k_{\mathrm{H}} + k_2[\mathrm{X}^-] \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (2)$$

where k_1 is the pseudo-unimolecular rate constant for the reaction with the nucleophile X^-, and k_{H} the rate constant for the hydrolysis of the ester alone.

This equation assumes that the rate of hydrolysis of the intermediate alkyl halide is greater than that of the initial reaction, *i.e.*,

$$\mathrm{R'{\cdot}PO(OR)_2 + X^- \xrightarrow{\text{Slow}} R'{\cdot}PO(OR){\cdot}O^- + RX}$$

$$\mathrm{RX + H_2O \longrightarrow ROH + H^+ + X^-}$$

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[14] Ford-Moore and Williams, *J.*, **1947**, 1465; McCombie, Saunders, and Stacey, *J.*, **1945**, 380.

The rate constant for the hydrolysis of methyl iodide at 100° was found to be 0·71 hr.$^{-1}$, compared with the value of $4{\cdot}2 \times 10^{-3}$ hr.$^{-1}$ at 80° for the reaction between potassium iodide (0·2M) and dimethyl ethylphosphonate. The relative rates of hydrolysis of methyl chloride, bromide, and iodide confirm that the rate of the first step is considerably slower than the subsequent hydrolysis in these reactions.

Reaction with Sulphur Anions.—Acid titration could not be used to follow the reactions with thiosulphate and thiocyanate ions, and in these cases the rate was determined by following the rate of disappearance of the nucleophile. For the thiosulphate reaction, iodometric titration was used, and the reaction with thiocyanate was followed by titration with mercuric nitrate, ferric alum being used as indicator. In these cases the bimolecular rate constant is given simply by $k_2 = k_1/[X^-]$.

The stability of sodium methyl thiosulphate under the conditions of the experiment was investigated. A sample of this hemi-ester, prepared by Walden's method,[15] was recrystallised twice from water. Solutions of this salt were heated at 100° for 3 days but no iodine titrations were obtained.

The rates of alkaline hydrolysis of the esters were measured at various temperatures with the results shown in Table 3.

TABLE 3. *Hydrolysis of* 0·025N-*ester with* 0·05N-NaOH *in water.*

$Et{\cdot}PO(OMe)_2$		$Et_2PO(OMe)$		$Me{\cdot}PO(O{\cdot}CH_2Ph)_2$*		$PO(OMe)_3$				$PO(OEt)_2{\cdot}O{\cdot}CH{:}CH_2$	
Temp.	k_2	Temp.	k_2	Temp.	k_2	Temp.	k_2	Temp.	k_2	Temp.	k_2
80°	94·0	80°	66·0	62°	51·84	79·9°	0·556	63·8°	0·192	25°	7·20
25	0·105	25	2·16	25	9·38	72·2	0·325	60·1	0·143		

* 0·01N-Ester used. k_2 is given in l. mole^{-1} hr.$^{-1}$ units in all cases.

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[*Received, September 27th,* 1957.]

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[15] Walden, *Ber.*, 1907, **40**, 3214.