738. *The Effects of Substituents on the Rates of Hydrolysis of Some Organophosphorus Compounds. Part I. Rates in Alkaline Solution.*

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The rates of hydrolysis, in alkaline solution, of compounds of the types RR'P(O)X and RR'P(S)X, where R and R' are alkoxy- or alkylamino-groups and X is an acidic group, are summarized, and more results are given. The mechanism is of type S_N2. The electromeric and inductive effects of substituents are usually very similar to those found in carbon chemistry for reactions of this type. However, ethyl *NN*-dimethylphosphoramidocyanidate and compounds containing P–S–C bonding are hydrolysed exceptionally rapidly, perhaps because the cyanide group and the sulphur atom are very readily polarized relatively to the other substituents considered. In the phosphorodiamidic fluoride series, those compounds containing four alkyl substituents are hydrolyzed markedly more slowly than those containing only three, owing to a steric effect. For the same reason di*iso*propyl phosphorofluoridate is hydrolyzed more slowly than would be expected from its structure.

ORGANOPHOSPHORUS compounds of the types RR'P(O)X and RR'P(S)X, where R and R' are alkoxy- or alkylamino-groups and X is an acidic group, are hydrolysed in neutral and alkaline aqueous solutions. Several authors [1,2,3] have discussed the inductive and steric effects of substituents on the rates of hydrolysis of small groups of these compounds. My present purpose is to present more results, and to apply the electronic theory of organic

[1] Topley, *Chem. and Ind.*, 1950, 859.
[2] Ketelaar, Gersmann, and Koopmans, *Rec. Trav. chim.*, 1952, **71**, 1253.
[3] Dostrovsky and Halmann, *J.*, 1953, 503.

chemistry systematically to most of the available data. Rates for reactions catalyzed by hydroxyl ions are discussed in Part I, and rates under conditions where this catalysis can be neglected in Part II.

It is sometimes difficult to assess the reliability of the published constants. The compounds have been studied almost exclusively as biochemical agents, so that accurate constants have not been required. Generally the most recent values have been taken. The effects of substituents are considerable, so that the results are adequate for a semi-quantitative treatment.

Experimental

Materials.—Where rates are taken from other papers no methods for preparation or properties are given.

NN'-Di*iso*propylphosphorodiamidic fluoride was prepared by Mr. D. W. J. Lane, of these laboratories. The other compounds were prepared by Mr. D. W. Pound and Mr. J. Hulme of these laboratories. I am indebted to all three for the experimental details and properties given in this section.

Fluorine Derivatives.—Ethyl phosphoromorpholidofluoridate was prepared by allowing phosphoromorpholidic dichloride (1 mol.) to react with sodium ethoxide (1 mol.) in toluene. The product was separated by distillation, and let react with 50% aqueous potassium fluoride at room temperature. The product, extracted with chloroform and fractionated, had b. p. 128°/8 mm. The hydroxyl ion consumed on hydrolysis agreed with the formula.

NN'-Di*iso*propylphosphorodiamidic fluoride was prepared from [^{32}P]phosphorus oxychloride of specific activity 1 mc/g. *iso*Propylamine (42·9 g.) in chloroform (50 ml.) was run into phosphorus oxychloride (28·6 g.) in chloroform (100 ml.) with stirring at −10°. The temperature was allowed to rise to 0°, and aqueous potassium fluoride (29 g. of fluoride, 0·5 g. of potassium carbonate, 29 ml. of water) run in with stirring. The temperature was raised to 40° and held there for 30 min. The chloroform layer was separated and evaporated *in vacuo* until the product began to crystallize. Light petroleum (300 ml.; b. p. 40—60°) was added, and the mixture refluxed. On cooling, 19 g. of product, m. p. 65°, were obtained. Owing to its high specific activity it was not analyzed. Its m. p. agrees with that of samples containing the theoretical amount of nitrogen.

The following were prepared by the method of B.P. 700,322 (analyses by estimation of amine liberated by acid hydrolysis gave theoretical values): *NNN'*-Trimethyl-, b. p. 110°/3 mm., *N'*-ethyl-*NN*-dimethyl-, b. p. 138°/18 mm., *N'*-*n*-butyl-*NN*-dimethyl-, b. p. 101°/1 mm., *NN*-dimethyl-*N'*-*iso*propyl-, b. p. 129°/11 mm., *NN*-diethyl-*N'N'*-dimethyl-, b. p. 102°/10 mm., *NNN'N'*-tetraethyl-, b. p. 128°/22 mm., and *NN*-diethyl-*N'*-methyl-phosphorodiamidic fluoride, b. p. 104—106°/1 mm.; *N'N'*-dimethyl-, b. p. 137°/8 mm., and *N'N'*-diethyl-phosphoramidomorpholidic fluoride, b. p. 153°/8 mm.

Azides.—Tetramethyl- and *NN*-dimethyl-*N'*-*iso*propyl-phosphorodiamidic azide were prepared by the method of B.P. 698,093. The compounds cannot be distilled, and were used in the crude state. Determination of the azide liberated by hydrolysis showed purities of 97—98%.

NN'N''N'''-Tetra*iso*propylpyrophosphoramide, m. p. 148—149°, was prepared by the method of B.P. 688,766.

Rates of Reaction.—(*a*) All rates of reaction in neutral solution and several of the slower ones in alkaline solution were determined on compounds labelled with ^{32}P. This is the most accurate of the methods used. The hydrolysing medium and the labelled compound were let reach temperature equilibrium (thermostat) and mixed. The hydrolysis products are ions, and not extractable by chloroform. Aliquot parts were extracted from time to time and shaken with an equal volume of chloroform. The layers were separated quickly and counted in a liquid-counting tube. It was sometimes found that 1—2% of the radioactive material remained extractable by chloroform, however long the run. This represents compounds $R_nR'_{3-n}PO$, which are very stable and are often difficult to separate completely from compounds RR'PO·X by fractionation or crystallization. This fraction was therefore subtracted from counts of the chloroform layers.

If the unchanged compound has a partition coefficient K for chloroform–water, the fraction unhydrolyzed at time A/A_0 is given by:

$$A/A_0 = (1 + 1/K)x \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (a)$$

where x is the fraction of the total active material extracted by chloroform.

Two cases must be considered: (i) When the concentration of the compound is negligible compared with that of the hydrolytic agent, the reaction followed first-order kinetics, $A = A_0e^{-kt}$, whence

$$\ln x = -kt - \ln (1 + 1/K) \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (b)$$

If ln x is plotted against t, k can be found by the method of least squares.

(ii) When the molar concentration of the compound is an appreciable fraction, say 0·05—0·15, of the concentration of the hydrolytic agent (*e.g.*, if the specific activity of the compound is low), the rate constant can be calculated from the second-order equation:

$$kt(B_0 - 2A_0) = \ln (BA_0/B_0A) \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (c)$$

where B_0 and B are the hydroxyl-ion concentrations at times 0 and t. There does not however appear to be a method for determining the standard error of constants obtained for this equation, so that it is better to set up an equivalent first-order equation as follows: Rewriting eqn. (*c*) we have:

$$t = \frac{1}{k(B_0 - 2A_0)} \cdot \left(\ln \frac{A_0}{A} - \ln \frac{B_0}{B} \right) \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (d)$$

The corresponding first order equation is:

$$t' = \frac{1}{kB_0} \ln \frac{A_0}{A} \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (e)$$

Whence

$$(t - t')/t = \left(\frac{2A_0}{B_0} \ln \frac{A_0}{A} - \ln \frac{B_0}{B} \right) \Big/ \left(\ln \frac{A_0}{A} - \ln \frac{B_0}{B} \right) \quad . \quad . \quad . \quad . \quad . \quad . \quad (f)$$

Thus, to find k, ln x is plotted against t to afford ln $(1 + 1/K)$ from eqn. (*b*), whence A can be found, and hence t and t'. ln (A/A_0) is plotted against t', and k found by eqn. (*e*), the method of least squares being used. The standard error is found in the usual way.

This method is convenient in that A_0 need only be known to an accuracy of $\pm 2\%$, which is readily achieved by counting the hydrolyzing solution. There is no need to weigh the organophosphorus compound to determine its concentration in solution by chemical methods, or to find $(B_0 - 2A_0)$ by titration at the end of the reaction.

(*b*) Some rates were determined by estimating consumption of hydroxyl ions by back-titration with standard acid to thymolphthalein. The constants were calculated from eqn. (*c*).

(*c*) The faster rates in alkaline solution (those of some of the fluorides) were determined by a modification of Walker's conductivity method.[4] The cell consisted of two arms at right angles, one containing platinized-platinum electrodes. Standard sodium hydroxide was placed in one arm, and an equal volume of an aqueous solution of the phosphorus compound in the other. The cell was immersed in a thermostat, and, when temperature equilibrium had been reached, partially rotated several times to mix the solutions. The mixture was then drained into the arm containing the electrodes, and the conductivity determined at set times on an a.c. bridge. The conductivity could be read to about $\pm 0{\cdot}1\%$. (The bridge, from Doran Instrument Co. Ltd., Stroud, Gloucestershire, presented no novel features.)

Let C_0, C_t, and C_∞ be the conductivities at times 0, t, and infinity, and let the molar concentration of hydroxyl ions be initially $2a$ times the molar concentration of the phosphorus compounds. Then

$$kt(B_0 - 2A_0) = \ln [C_t + (a - 1)C_0 - aC_\infty] - \ln a(C_t - C_\infty) \quad . \quad . \quad . \quad (g)$$

$(B_0 - 2A_0)$ was found by titrating the excess of hydroxyl ion after reaction for a few minutes in the same proportions as in the run, but at much higher concentrations. C_0 was found by the application of eqn. (*f*) to the first few points. C_∞ was found from the values of C_t when more than 90% of the compound had been hydrolyzed by using an approximate hydrolysis constant in eqn. (*g*).

The method was accurate only to about $\pm 3\%$. The mobility of the fluoride ion and other products is such that when $B_0 = 4A_0$ the conductivity is only reduced by about 25% during a run. Also, when the runs lasted more than about 50 min., C_∞ tended to drift slowly to lower values and could not be obtained accurately enough. No cause was found for this. In consequence, however, runs had to be performed rapidly, with some loss of accuracy.

[4] Walker, *Proc. Roy. Soc.*, 1906, *A*, **78**, 157.

Order of Reactions.—The rate of disappearance of the organophosphorus compounds followed first-order kinetics within experimental error in all the runs where a large excess of sodium hydroxide was used. Whenever the concentrations of hydroxyl ion and organophosphorus compound were similar, the rate followed second-order kinetics. The rate constants calculated from the second-order equation (*c*) for the hydrolysis of *NN'*-di*iso*propylphosphorodiamidic fluoride are given in Table 1, and are the same throughout the run. The same characteristics are shown by the results already published; the kinetics are of first order with respect to the concentration of both organophosphorus compound and hydroxyl ion.

Rates of Hydrolysis in Alkaline Solution.—In Table 2 are given the hydrolysis constants for a series of phosphorodiamidic fluorides, and in Table 3 for a number of other compounds.

Discussion

The general approach adopted is that reviewed in detail by Hinshelwood, Laidler, and Timms,[5] Hammett,[6] Watson,[7] and Dewar.[8]

Each rate is proportional to the concentrations of hydroxyl ion and organophosphorus compound. The mechanism is thus analogous to the $-S_{O}2$ hydrolysis of many organic esters. Rates should thus be controlled by the ease with which the hydroxyl ion can approach the central phosphorus atom, and by the ease with which the acidic group can be displaced.

As in the hydrolysis of organic esters, the approach of hydroxyl ion depends on the charge on the central atom, on the degree to which the transition state is stabilized by the overlapping of π-electrons in double bonds in the complex with p-electrons in the hydroxyl ion and on steric hindrance by groups surrounding the central atom. The charge on the phosphorus atom in the system AlkO·P:O is affected by the overlap of p-electrons on the AlkO-oxygen atom and the electrons in the P:O bond. The effect is to donate electrons to the phosphorus, so increasing its negative charge, *i.e.*, it is a $-E$ effect. The alkyl group donates electrons by an inductive effect ($-I$). In addition, as phosphorus can accommodate more than eight valency electrons,[9,10] both oxygen atoms may be back-co-ordinated to the phosphorus atom, further increasing the net negative charge. Although this is not an electromeric effect in the usual sense, it is likely to depend in a similar way on the relative electronegativities of the central and the attached atoms, so that for the purposes of this paper it will be included as a $-E$ effect. The negative charge on a phosphorus atom is likely to be greater than on a carbon atom with similar substituents, which may lead to greater stability to hydrolysis, and may explain why hexamethylphosphoramide, $(Me_2N)_3PO$, is extremely stable to alkali compared with tetramethylurea, $(Me_2N)_2CO$. The stabilizing influence of electromeric effects on the transition state cannot be allowed for, as nothing is known of the stereochemistry of the transition state. It can only be assumed that the effect is constant. Steric effects may be important, as phosphorus is surrounded by five groups in the transition state.

The ease with which the acidic radical, X, is replaced depends on the strength of the P–X bond in the transition state, and on the readiness with which X accepts a negative charge to separate as an anion, *i.e.*, on the acid strength of XH. There is no need in the compounds under consideration to postulate differences in P–X bond strength, although they are important in the hydrolysis of phosphorus compounds of a different type.[11] Rates of hydrolysis are correlated with the acid strength of XH, but, as the $(E + I)$ effects become more positive the stronger the acid, the tendency of X to accept a negative charge in the transition state cannot usually be distinguished from electromeric effects.

Hydrolysis of Some Fluorophosphorus Compounds.—The constants for these compounds are given in Table 2. The compounds all contain the group :PO·F, so that we are only concerned with the electronic and steric effects of the alkoxy- and alkylamino-groups.

The $-I$ effect increases up the series, H, Me, Et, Bu^n, Pr^i. Also, the $-E$ effects of

[5] Hinshelwood, Laidler, and Timms, *J.*, 1938, 848.
[6] Hammett, *J. Amer. Chem. Soc.*, 1937, **59**, 96.
[7] Watson, "Modern Theories of Organic Chemistry," Oxford, 1941.
[8] Dewar, "The Electronic Theory of Organic Chemistry," Oxford, 1949.
[9] Phillips, Hunter, and Sutton, *J.*, 1945, 146.
[10] Rothstein, *J.*, 1953, 3991.
[11] Chanley and Feargeson, *J. Amer. Chem. Soc.*, 1955, **77**, 4002.

alkylamino-groups are greater than those of alkoxy-groups, so that we should expect on the electronic theory alone that the rates at any fixed temperature, with some omissions explained later, would decrease and the activation energies increase in the following order (:PO·F is omitted; the numerals refer to the serial numbers in the Table): $(Pr^iO)_2$ (2), $(Pr^i{\cdot}NH)_2$ (3), $(Me{\cdot}NH)(Me_2N)$ (4), $(Et{\cdot}NH)(Me_2N)$ (5), $(Bu^n{\cdot}NH)(Me_2N)$ (6), $(Pr^i{\cdot}NH)(Me_2N)$ (7), $(Me_2N)_2$ (10), $(Et_2N)(Me_2N)$ (12), $(Et_2N)_2$ (13). This is the order in which the rates

TABLE 1. *Second-order constants determined by the conductivity method for the hydrolysis of* NN′-*di*iso*propylphosphorodiamidic fluoride in aqueous sodium hydroxide at* 25·08°.* $B_0 = 0{\cdot}00104_2$M, $2A_0 = 0{\cdot}000538$M.

Time (min.)	Conductivity (arbitrary units)	k (mole min.$^{-1}$)	Time (min.)	Conductivity (arbitrary units)	k (mole min.$^{-1}$)	Time (min.)	Conductivity (arbitrary units)	k (mole min.$^{-1}$)
0	2530 * †	—	9	2240	48·22	18	2070	48·85
1	2484	48·81	10	2214	48·90	19	2056	48·81
2	2446	49·27	11	2192	49·04	20	2044	48·54
3	2410	48·95	12	2172	48·95	22	2016	48·95
4	2377	48·90	13	2152	49·09	24	1995	48·63
5	2344	49·82	14	2135	48·81	26	1973	48·90
6	2313	49·63	15	2119	48·54	30	1937	48·45
7	2287	48·95	16	2100	48·90	37	1885	48·45
8	2258	49·82	17	2084	48·95	∞	1672 †	—

* For brevity only alternate values obtained are given in this table. † Calc.

TABLE 2. *Constants for the hydrolysis in alkaline solution of compounds* RR′PO·F.

No.	R	R′	Temp.	k (OH^-) (min.$^{-1}$)	E * (kcal. mole^{-1})	Ref.†
1	$CH_2{:}CH{\cdot}CH_2{\cdot}NH$	$CH_2{:}CH{\cdot}CH_2{\cdot}NH$	16°	~1000	—	*b*
2	Pr^iO	Pr^iO	25·00	50	—	*d*
3	$Pr^i{\cdot}NH$	$Pr^i{\cdot}NH$	10·4	18·4	11·2 ± 0·5	*c*
			25·09	48·9		
4	$Me{\cdot}NH$	Me_2N	25·08	17·6	11·2 ± 0·5	*c*
			39·55	42·4		
5	$Et{\cdot}NH$	Me_2N	25·0	12·3	11·4 ± 0·3	*c*
			38·9	29·5		
			42·15	35·3		
			42·2	35·1		
6	$Bu^n{\cdot}NH$	Me_2N	25·0	11·1	11·4 ± 0·5	*c*
			25·08	10·6		
			39·55	26·1		
			42·1	31·1		
7	$Pr^i{\cdot}NH$	Me_2N	25·0	8·43	11·9 ± 0·5	*c*
			25·05	8·05		
			38·9	20·0		
8	$Me{\cdot}NH$	Et_2N	25·00	1·69	—	*c*
9	$O{<}[CH_2{\cdot}CH_2]_2{>}N$	Me_2N	25·00	$9{\cdot}0 \pm 0{\cdot}2 \times 10^{-3}$	—	*ai*
10	Me_2N	Me_2N	28·9	$4{\cdot}70 \times 10^{-2}$	14·7 ± 0·5	*e*
			42·3	$1{\cdot}32 \times 10^{-2}$		
11	$O{<}[CH_2{\cdot}CH_2]_2{>}N$	Et_2N	25·0	$1{\cdot}0 \pm 0{\cdot}05 \times 10^{-3}$	—	*ai*
12	Et_2N	Me_2N	25·00	$2{\cdot}878 \pm 0{\cdot}017 \times 10^{-4}$	16·58 ± 0·02	*aii*
			50·00	$2{\cdot}497 \pm 0{\cdot}021 \times 10^{-3}$		
			70·55	$1{\cdot}171 \pm 0{\cdot}005 \times 10^{-2}$		
13	Et_2N	Et_2N	25·2	$2{\cdot}5 \pm 0{\cdot}2 \times 10^{-5}$	17·1 ± 1·0	*ai*
			49·2	$2{\cdot}2 \pm 0{\cdot}1 \times 10^{-4}$		

* E was often calculated from rates at two temperatures only. Bell ("Acid–Base Catalysis," Oxford, 1941) has given the arguments against this. When, however, more than two temperatures have been used, in this and other work, the Arrhenius plots are satisfactory for this type of compound.

† *ai*, *aii*, *b*, and *c* refer to the methods already described. *d*, Kilpatrick and Kilpatrick, *J. Phys. Colloid Chem.*, 1949, **53**, 1371. *e*, Heath and Casapieri, *Trans. Faraday Soc.*, 1951, **47**, 1093.

fall, and, within the considerable experimental error, the order in which the activation energies increase.

That a second effect also operates may be seen most clearly from the effect on the rate and activation energy of successive substitutions of dimethylamino- for *iso*propylamino-groups. Thus substituting one dimethylamino-group for *iso*propylamino in *NN′*-di-*iso*propylphosphorodiamidic fluoride [converting compound (3) into compound (7)] reduces

the rate 6-fold at 25°, and increases the energy of activation by about 0·7 kcal./mole. The second substitution [converting compound (7) into compound (10)] reduces the rate by a factor of 2400 and raises E by 2·8 kcal./mole. From the general rate equation $k = PZ \cdot e^{-E/RT}$, where Z is the collision number and P is the probability factor, it follows that

TABLE 3. *Constants * for the hydrolysis in alkaline solution of compounds* RR'PO·X, *etc.*

No.	Compound	k (OH^-) (min.$^{-1}$)	Temp.	E (kcal. mole^{-1})	Ref.†
14	$(EtO)_4P_2O_3$	158	25°	—	*d*
15	$(Pr^i{\cdot}NH)_4P_2O_3$	$1{\cdot}31 \times 10^{-1}$	25	—	*ai*
16	$(Me_2N)_3(Me{\cdot}NH)P_2O_3$	$3{\cdot}10 \times 10^{-2}$	25	—	*e*
17	$(Me_2N)_4P_2O_3$	$4{\cdot}7 \times 10^{-3}$	100	—	*ai*
18	$(Me_2N)_5P_3O_5$	$4{\cdot}8 \times 10^{-3}$	25	—	*b*
19	$(MeO)_2PS{\cdot}O{\cdot}C_6H_4{\cdot}NO_2$-*p*	$2{\cdot}3 \times 10^{-1}$	25	15·45	1, *f*
20	$(EtO)_2PS{\cdot}O{\cdot}C_6H_4{\cdot}NO_2$-*p*	$5{\cdot}7 \times 10^{-2}$	25	16·6	1, *f*, *g*
		1·3 $\times 10^{-2}$	25	*19·2*	
21	$(Pr^iO)_2PS{\cdot}O{\cdot}C_6H_4{\cdot}NO_2$-*p*	$3{\cdot}3 \times 10^{-3}$	25	—	1
22	$(MeO)PO(O{\cdot}C_6H_4{\cdot}NO_2$-*p*$)_2$	*34*	25	*13·4*	
23	$(EtO)PO(OC_6H_4{\cdot}NO_2$-*p*$)_2$	4·3	25	—	1
		31	25	*14·3*	
24	$(MeO)PS(O{\cdot}C_6H_4{\cdot}NO_2$-*p*$)_2$	*1·35*	25	*13·9*	
25	$(EtO)PS(O{\cdot}C_6H_4{\cdot}NO_2$-*p*$)_2$	4×10^{-1}	25	—	1
		9·7 $\times 10^{-1}$	25	*12·1*	
26	$(EtO)_2PO{\cdot}O{\cdot}C_6H_4{\cdot}NO_2$-*p*	$5{\cdot}2 \times 10^{-1}$	25	—	*g*
		4·0 $\times 10^{-1}$	25	*12·4*	
27	$(EtO)(EtS)PO{\cdot}O{\cdot}C_6H_4{\cdot}NO_2$-*p*	800	37	—	*h*
28	$(EtO)_2PO{\cdot}S{\cdot}C_6H_4{\cdot}NO_2$-*p*	150	37	—	*h*
29	$PO(O{\cdot}C_6H_4{\cdot}NO_2$-*p*$)_3$	*2060*	25	*4·1*	
30	$PS(O{\cdot}C_6H_4{\cdot}NO_2$-*p*$)_3$	$3{\cdot}3 \times 10^{-2}$	25	—	1
		12·4	25	*5·7*	
31	$(EtO)_2PO{\cdot}S{\cdot}C_2H_4{\cdot}SO{\cdot}Et$	3·33	25	—	*e*
32	$(EtO)_2PO{\cdot}S{\cdot}C_2H_4{\cdot}SEt$	$8{\cdot}1 \times 10^{-1}$	25	—	*i*
33	$(EtO)_2PS{\cdot}O{\cdot}C_2H_4{\cdot}SEt$	$9{\cdot}2 \times 10^{-3}$	25	—	*i*
34	$Me_2N{\cdot}PO(CN){\cdot}OEt$	$6{\cdot}3 \times 10^{6}$	25	—	*j*
35	$(Me_2N)_2PO{\cdot}N_3$	$9{\cdot}5 \times 10^{-4}$	25	—	*b*
36	$(EtO)_3PO$	$4{\cdot}86 \times 10^{-4}$	25	16·1	*k*

* Values in italics were determined for aqueous acetone solutions by Ketelaar *et al.*[3], and are not therefore strictly comparable with the rest. However, the effect of substituents on the rates is not likely to be very different within this group.

The constants given by Cavalier [k] are heavily weighted by values obtained very near the beginnings and ends of runs. I have taken the values 3·37 hr.$^{-1}$ at 88° and 0·0093 hr.$^{-1}$ at 13° from the middle of the runs.

† *ai* and *b* refer to the methods described in the text. *d*, Ketelaar and Bloksma, *Rec. Trav. chim.*, 1948, **67**, 665. *e*, Health, Park, and Lane, *Phil. Trans.*, 1955, *B*, **239**, 191. *f*, Ketelaar, *Rec. Trav. chim.*, 1950, **69**, 649. *g*, Williams, *Ind. Eng. Chem.*, 1951, **43**, 950. *h*, Aldridge and Davison, *Biochem. J.*, 1952, **52**, 663. *i*, Gardner and Heath, *Analyt. Chem.*, 1953, **25**, 1849. *j*, Larson, *Acta Chem. Scand.*, 1953, **7**, 306. *k*, Cavalier, *Ann. Chim. Phys.*, 1899, **18**, 449.

(as Z is nearly constant in this series), if P is constant, a graph of ln k against E should be a straight line, of slope $1/RT$. This is consistent for the separate series, (*a*) $(Pr^i{\cdot}NH)_2$, $(Me{\cdot}NH)(Me_2N)$, $(Et{\cdot}NH)(Me_2N)$, $(Bu^n{\cdot}NH)(Me_2N)$, and $(Pr^i{\cdot}NH)(Me_2N)$; and (*b*) $(Me_2N)_2$, $(Me_2N)(Et_2N)$, and $(Et_2N)_2$; but the second series requires a value of P less by a factor of about 11 than the first. Thus increasing the number of N–C bonds from 3 to 4 both increases the activation energy more than would be expected from the inductive effects of the additional alkyl substituent, and decreases the probability factor. Such a combination of effects suggests that the approach of the hydroxyl ion to the phosphorus is hindered by a steric factor in the second series. Models of the molecules made with Hartley–Conmar Robinson [12] atomic models tend to confirm this. Those of the tetra-alkyl compounds are very compact and rigid; those of the trialkyl compounds are much looser, and the alkylamino-groups can be rotated freely.

The bulk of the alkyl groups increases as the hydrolysis rate decreases in both series. Following Taft [13] and Reeve *et al.*[14] we must consider the possibility that the difference in rate within each series is also partly due to steric effects. A steric effect should influence

[12] Hartley and Conmar Robinson, *Trans. Faraday Soc.*, 1952, **48**, 847.
[13] Taft, *J. Amer. Chem. Soc.*, 1952, **74**, 3120.
[14] Reeve, McCoffery, and Kaiser, *ibid.*, 1954, **76**, 2280.

both P and E, but the effect on P may well be small and E is not known accurately enough to prove P constant. The steric effect of a given group, however, should depend markedly on the size of the surrounding groups. It is shown in Table 4 that the substitution of a

TABLE 4. *Effect of substituting dimethylamino for ethylamino on the rate constants at 25° for three phosphorodiamidic fluorides* $(Et_2N)(R)PO{\cdot}F$.

R	Me·NH	Me_2N	Et_2N
k_{Me}/k_{Et}	10·4	11·9	11·5

dimethylamino- for a diethylamino-group alters the rate by a constant factor in pairs of compounds in which the other alkylamino-groups are very different in size. It is therefore most probable that the changes in rate within each series are due primarily to inductive effects, and that steric effects are of little importance.

The inductive effects are not, however, strictly additive. Thus, substituting one methyl for one ethyl group increases the rate by a factor of about 1·4 [pair (4) and (5)], whereas substituting two methyl for two ethyl groups on the same nitrogen atom increases the rate about 11-fold (Table 4) and not by $1{\cdot}4^2$. Audrieth and Toy [15] have pointed out the powerful hydrogen-bonding properties of the dialkylphosphoramido-group, and it is thus possible that the substituent effects of primary and secondary amino-groups are influenced by interaction with the aqueous solvent.

The rates of reaction of the four fluorides not so far considered fit in well with the rest. Substitution of dimethylamino by morpholino [pairs (9) and (10), and (11) and (12)] increases the rate by a factor of 4—5. The morpholino-group is likely to exert the same steric forces as other dialkylamino-groups, but to be more negative owing to the presence of the oxygen atom in the ring. Consequently hydrolysis should be faster than for the corresponding dimethylamino-compounds. The diallylamino-compound (1) is hydrolysed very rapidly owing to the negativity of the allyl group in the transition state. Similarly Cavalier [16] observed that diallyl hydrogen phosphate is hydrolysed in water about 13 times as rapidly as diethyl hydrogen phosphate. The rate of hydrolysis of di*iso*propyl phosphorofluoridate (2) is unexpectedly slow; an alkoxy-group is expected to exert a much smaller $-E$ effect than an alkylamino-group. It is shown in the following paper that several *iso*propyl esters are hydrolyzed slowly, probably owing to steric effects.

Hydrolysis of the Compounds of Table 3.—The effects on the rate constants of altering R and R′ are closely parallel to those already discussed. Substitution of ethyl for methyl decreases the rate [pairs (19) and (20), (22) and (23), and (24) and (25)], as does the substitution of *iso*propyl for ethyl [(20) and (21)]. The pyrophosphoric compounds (14)—(17) show both electronic and steric effects. If a reasonable activation energy is assumed for octamethylpyrophosphoramide the rate constant at 25° is about 2×10^{-5} (OH^-) min.$^{-1}$. In a symmetrical pyrophosphoric ester or amide the rate with respect to each phosphorus atom is half the rate with respect to the whole molecule, as both phosphorus atoms are equally readily attacked. In an unsymmetrical compound the rate may be almost entirely accounted for by the rate of attack by the hydroxyl ion on the phosphorus atom surrounded by the most electrophilic substituents. Thus, in octamethylpyrophosphoramide (17), the rate constant per phosphorus atom is about 1×10^{-5} min.$^{-1}$. In heptamethylpyrophosphoramide $(Me{\cdot}NH)(Me_2N)PO{\cdot}O{\cdot}PO(NMe_2)_2$ (16), the rate is controlled by the attack on the left-hand phosphorus atom, and the constant is $3{\cdot}1 \times 10^{-2}$ min.$^{-1}$. Thus, substituting methylamino for dimethylamino increases the rate about 3100-fold in these compounds, compared with 3740-fold in trimethyl- (4) and tetramethyl-phosphorodiamidic fluoride (10). In the latter pair this large increase was attributed mainly to a steric effect. The constant per phosphorus atom in *NN′N″N‴*-tetra*iso*propylpyrophosphoramide (15) is $6{\cdot}5 \times 10^{-2}$ min.$^{-1}$. Thus the substitution of two *iso*propylamino-groups for one methylamino- and one dimethylamino-group increases the rate relatively little, as in the fluoride series [(3)–(4)]. Tetraethyl pyrophosphate (14) is naturally hydrolysed the most rapidly, as the alkoxy-groups are more electrophilic than the alkylamino-groups and the acid produced by hydrolysis considerably stronger.

[15] Audrieth and Toy, *J. Amer. Chem. Soc.*, 1942, **64**, 1553.
[16] Cavalier, *Ann. Chim. Phys.*, 1899, **18**, 449.

The substitution of P=S for P=O reduces the rate somewhat [(20)–(26)], as might be expected from the lower electronegativity of sulphur than of oxygen.

Substitution of the ethyl group by the more negative *p*-nitrophenyl group greatly accelerates the rate, as shown by the series of compounds (36), (26), (23), (29), for the P=O compounds, and by the series (20), (25), (30) for the P=S compounds. The constants for all but triethyl phosphate were determined in aqueous acetone by Ketelaar *et al.*[2] who discussed the rates in terms of inductive and steric effects. The stated accuracy is ±10%, so that the activation energies may be seriously in error. Consequently only two points are made here. The substitution of the first ethyl group by *p*-nitrophenyl accelerates the rate more than any successive substitution, because the first introduces a more acidic, and consequently more readily replaceable, group, as well as one exerting a smaller $-E$ effect. In this instance it is possible to separate the effects of the acid strength of HX and the negativity of X. Secondly, there is a much greater disagreement in the constants given for tri-*p*-nitrophenyl phosphorothionate (30) by Ketelaar *et al.*[2] and by Topley [1] than can be accounted for by the difference in medium. This compound is very insoluble in water, and it appears possible that the result quoted by Topley was obtained on a suspension.

The general result of increasing the acidity of the replaced group, X, is to increase the rate. Thus triethyl phosphate (30) is hydrolysed much more slowly than any other diethyl phosphate given in the Table. In the series of tetramethylphosphorodiamido-compounds: $(Me_2N)_2PO{\cdot}X$, the rate increases as the pK of HX decreases. Thus the rate constants at 25° and pK's are fluoride (10), $3{\cdot}4 \times 10^{-3}$, 3·6; azide (35), $9{\cdot}5 \times 10^{-4}$, 4·7; and octamethylpyrophosphoramide (17), 1×10^{-5}, 6·7. Similarly tetraethyl pyrophosphate (14) is hydrolysed about 300 times faster than diethyl *p*-nitrophenyl phosphate (26), the pK's of *OO*-diethylphosphoric acid and *p*-nitrophenol being 1·5 and 7·1; and oxidising *OO*-diethyl *S*-ethylthioethyl phosphorothiolate (32) to the corresponding *S*-ethylsulphinylethyl compound (31) increases the rate by introducing the negative sulphinyl group.

Compounds containing the P–S–C group and ethyl *NN*-dimethylphosphoramidocyanidate are hydrolysed much more rapidly than would be expected by analogy with those already discussed. Thus *OO*-diethyl *S*-ethylthioethyl phosphorothiolate (32) is hydrolysed more rapidly than diethyl *p*-nitrophenyl phosphate (26), although *p*-nitrophenol is a stronger acid than ethylthioethanethiol; and *OO*-diethyl *S*-*p*-nitrothiophenyl phosphorothiolate (28) is hydrolysed at about the same rate per phosphorus atom as tetraethyl pyrophosphate (14), although *OO*-diethylphosphoric acid is a stronger acid than *p*-nitrothiophenol. Similarly, ethyl *NN*-dimethylphosphoramidocyanidate (34) is hydrolysed 10^7 times faster than diethyl *p*-nitrophenyl phosphate (26), although the dimethylamino-group has more $-E$ character than the ethoxy-group, and hydrogen cyanide, of pK 9·1, is a weaker acid than *p*-nitrophenol, of pK 7·1. Lastly, *OS*-diethyl *O*-*p*-nitrophenyl phosphorothiolate (27) is hydrolysed about 1600 times faster than diethyl *p*-nitrophenyl phosphate (26), and several times faster than its *S*-*p*-nitrophenyl isomer (28): the former observation could be explained by the greater $-E$ effect of oxygen than of sulphur, but it is interesting that in a comparison of the alkaline hydrolysis rates of alkyl acetates and thiolacetates Rylander and Tarbell [17] found that hydrolysis of the thiolacetates requires the greater energies of activation. The second observation cannot be explained in this way. In the *OS*-diethyl compound and its isomer, *p*-nitrothiophenol is a stronger acid than *p*-nitrophenol, and the $(E + I)$ effect of the sulphur atom must be assumed constant. Therefore the *S*-*p*-nitrophenyl compound is expected to be hydrolysed the faster.

These results may be explained by the ready polarizability of sulphur and cyanide. In molecules not containing these groups, the atoms directly bonded to the phosphorus are oxygen, nitrogen, or fluorine, which, by conjugation, increase the negative charge on the phosphorus atom and set up a permanent potential which must be overcome by the approaching hydroxyl ion before a transition complex can be produced. During the formation of the complex, steric changes take place which must affect this potential, but, as the bonds between phosphorus and these atoms may not be readily polarizable, it is likely that the changes in potential are very similar from molecule to molecule. When a

[17] Rylander and Tarbell, *J. Amer. Chem. Soc.*, 1950, **72**, 3021.

polarizable group such as the ethylthio-group is introduced, this is no longer true. The approach of the hydroxyl ion may polarize the P–S bond in the sense $\overset{\delta+}{P}—\overset{\delta-}{S}$, so facilitating the formation of the transition complex. In the *S*-*p*-nitrophenyl compound, however, this leads to some strengthening of the P–S bond, which is therefore hydrolysed more slowly than its *S*-ethyl isomer in spite of the greater strength of the displaced acid. Thus it appears necessary to postulate a time-variable effect in response to the reagent in compounds containing phosphorus–sulphur bonds which is absent or constant in the other compounds considered. Such an effect should be less the less polar the reagent. It is in fact found (following paper) that the rates of hydrolysis in water of diethyl *p*-nitrophenyl phosphate and *OS*-diethyl *p*-nitrophenyl phosphorothiolate and its *S*-*p*-nitrophenyl isomer differ much less than in alkali.

Although there are a few anomalies, the electronic theory, as developed to explain reaction rates in carbon chemistry, apparently applies to a wide range of organophosphorus compounds without major alteration. This is perhaps surprising. Most of the substituents considered are very close to the groups displaced, so that "*ortho*"-effects might be expected; and nothing is known of the configuration of the transition complexes, so that the precise nature of the electromeric effects postulated is doubtful.

The author thanks the Directors of Fisons Pest Control Limited, Cambridge, for permission to publish this and the following paper.

Fisons Pest Control Limited, Chesterford Park Research Station,
Little Chesterford, nr. Saffron Walden, Essex. [*Received, March 16th*, 1956.]