201. *The Mechanism of Hydrolysis of Phosphonochloridates and Related Compounds. Part V.* The Inductive Effect.*

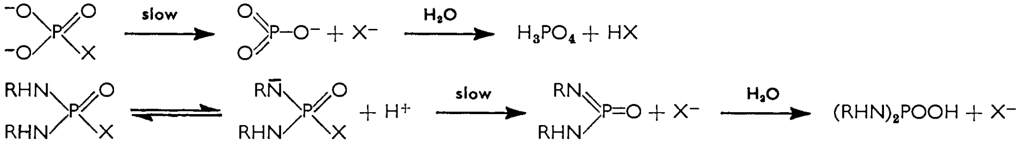
By R. F. Hudson and G. E. Moss.

The inductive effect of a chlorine atom in the α- and β-positions of phosphonates and phosphonic derivatives is discussed in terms of bimolecular displacements for solvolysis and for alkaline ester hydrolysis. The absence of slow stages in the hydrolysis of methyl- and chloromethyl-phosphonic dichlorides suggests that the second chlorine atom is removed by a unimolecular mechanism involving the anion.

In previous Papers [1,2] we have shown that substitution at the phosphonyl centre normally proceeds by bimolecular displacement, with a transition state which is probably similar to that of an S_N2 displacement on carbon.[3] The effect of substituents, which have p_π electrons available, can be interpreted by assuming weak p_π–d_π conjugation with the phosphorus atom, which leads, for example, to the following rate order for solvolysis.[2]

$(R{\cdot}CH_2)_2POX > (RO)_2POX > (RNH)_2POX$ (where X = Cl or F).

There is evidence, *e.g.*, the rate order [2] $(R_2N)_2POCl > R_2N(R'O)POCl$, to show that strongly conjugating groups promote bond breaking in the transition state,[4] and under extreme conditions S_N1 mechanisms, involving pre-ionised species, may occur,[5] *e.g.*,



The high reactivity of the intermediates (the existence of which has so far not been established), which probably assume planar p_π–$(dp)_\pi$ bonded structures is due to the relatively low energy of p_π–p_π bonds involving phosphorus compared with the energies of the corresponding σ-bonds.

Attention was drawn in Part I [1] to the lack of information on the inductive effect, and the present paper is concerned with the effect of α- and β-chlorine atoms on the reactivity of a phosphonate ester and several chloro-derivatives.

The Influence of a β-Chlorine Atom.—Electron withdrawal from the phosphonyl group

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* Part IV, *J.*, 1962, 3599.

[1] Hudson and Keay, *J.*, 1960, 1859, 1865.

[2] Crunden and Hudson, *J.*, 1962, 3591.

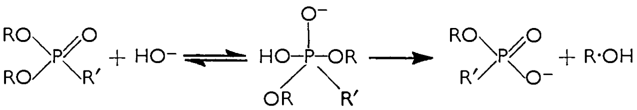
[3] Green and Hudson, *Angew. Chem.*, 1963, **75**, 47.

[4] Hall, *J. Org. Chem.*, 1956, **21**, 248.

[5] Hudson and Moss, *J.*, 1962, 3599.

brought about by a β-chlorine atom is shown by the strengths of the following phosphonic acids[6]: $MePO_3H_2$, pK_1 2·38, pK_2 7·74; $EtPO_3H_2$, pK_1 2·43, pK_2 8·05; $Cl{\cdot}CH_2{\cdot}PO_3H_2$, pK_1 1·40, pK_2 6·30, and by the infrared stretching frequencies of diethyl methyl and diethyl chloromethylphosphonates, which are 1237 and 1268 cm.$^{-1}$, respectively.[7]

The rate of alkaline hydrolysis of diethyl chloromethylphosphonate has been measured, and the Arrhenius parameters are given together with those for the corresponding alkyl phosphonates in Table 1. The electron-attracting chlorine atom produces an increase in the rate constant, and a corresponding decrease in the activation energy, showing that changes in the bond-forming energy are greater than the corresponding changes in the bond-breaking energy. The transition-state structure is probably similar to that of an addition intermediate, although the absence of ^{18}O exchange of the phosphonyl oxygen atom [8] and the complete inversion of configuration observed in similar reactions [3] show that the corresponding intermediate cannot be identified.



The influence of a β-chlorine atom on the rate of solvolysis of the corresponding chloridates (Table 2), is considerably less than on the alkaline hydrolysis (Table 1).

TABLE 1.

The alkaline hydrolysis of $RPO(OEt)_2$ in water at 59·2°.

R:	Me	Et	$Cl{\cdot}CH_2$
k_2 (l. mole^{-1} hr.$^{-1}$)	9·36	4·4 *	111
E_A (kcal. mole^{-1})	14·0	14·2	12·0
$\log_{10} PZ$	6·5	6·3	6·8

* Extrapolated.

TABLE 2.

The solvolysis of $R(EtO)POCl$ in 95% aqueous acetone at 0°.

R:	Me	Et	$Cl{\cdot}CH_2$
10^3k_1 (min.$^{-1}$)	87·6	29·7	107 *
E_A (kcal. mole^{-1})	8·5	8·9	10·9
$\log_{10} PZ$	4·0	3·9	5·9

* At 1·3°.

Moreover the activation energy is increased in this case by the chlorine atom suggesting that bond breaking (which is opposed by the electron withdrawal by the chlorine atom) is more important here than in the alkaline hydrolysis. Evans and Polanyi,[9] however, considered the rate constant to be a more significant measure of the electronic effects on the reactivity for the experimental conditions, and the significance of parallel changes of E_A and PZ have been discussed subsequently by Leffler.[10] It is not intended, therefore, to discuss this difficult question further, but to conclude that the inductive effect appears to affect the bond-breaking and bond-making energies in solvolytic transition states to a similar extent, in view of the small effect of the α-chlorine atom on the reactivity. By way of comparison, the alcoholysis of chloroacetyl chloride is *ca.* 20 times greater than that of acetyl chloride,[11] both reactions proceeding by way of a tetrahedral intermediate.[12]

[6] Crofts and Kosolapoff, *J. Amer. Chem. Soc.*, 1953, **75**, 3379, 5739.
[7] Aksnes and Gramstad, *Acta Chem. Scand.*, 1960, **14**, 1485.
[8] Dostrovsky and Halmann, *J.*, 1956, 1004; Halmann, *J.*, 1959, 305.
[9] Evans and Polanyi, *Trans. Faraday Soc.*, 1936, **32**, 1333.
[10] Leffler, *J. Org. Chem.*, 1955, **20**, 1202.
[11] Branch and Nixon, *J. Amer. Chem. Soc.*, 1936, **58**, 2499.
[12] Bender, *Chem. Rev.*, 1960, **60**, 53.

On the other hand, β-halogen atoms substituted in alkyl halides reduce the rate of reaction by a similar factor.[13] In this case the bonds ($p/2$) in the direction of the reaction co-ordinate are weaker, hence the bond-breaking energy is a more important factor in the transition state.

The small inductive effects noted here for substitution at the phosphonyl centre show that the influence of the bond-formation energy is greater (owing to the large positive charge on the phosphorus atom and possible use of $3d$ orbitals), than the influence of the bond-breaking energy.

In a further comparison, chloromethyl phosphonic dichloride was found to undergo solvolysis twice as fast as methylphosphonic dichloride (Table 8), *i.e.*, an effect similar to that observed for the chloridate. In this case measurements were made at one temperature only for practical reasons.

Some increases in reactivity produced by δ-substituents have been reported. Thus the rate constant for the alkaline hydrolysis of 2-bromoethyl methylphosphonofluoridate,[14] $k_2 = 162$ l. mole^{-1} sec.$^{-1}$ at 25°, is greater than the value of $k_2 = 54{\cdot}0$ l. mole^{-1} sec.$^{-1}$ for the n-propyl analogue.

The first-order rate constants for the solvolysis in aqueous phosphate buffer (pH 8·3; 37·5°) of ethyl *p*-nitrophenyl 3-chloropropylphosphonate [15] and of the n-butyl analogue are $7{\cdot}53 \times 10^{-4}$ and $4{\cdot}73 \times 10^{-4}$ min.$^{-1}$, respectively. These accelerations are less than those given in Tables 1 and 2, owing to the attentuation of the inductive effects along a carbon chain.

The Influence of a α-Chlorine Substituent.—The inductive effect of a α-chlorine atom substituted at the phosphonyl group should be considerably greater than that produced by a β-substituent. The reactivity is, however, only slightly modified as shown by the relative rates of solvolysis (*ca.* 3 : 1) of phosphoryl chloride and methylphosphonic dichloride (Table 8). A similar effect is produced by the replacement of the methyl group of a phosphonochloridate by a chlorine atom as shown by the data of Table 3.

TABLE 3.

Hydrolysis of R(OEt)POCl in aqueous acetone.†

	Cl			Me
Solvent (% water)	2·0	10·0	5·0	5·0
Temperature	0·3	0·6	0·0	0·0
10^3k_1 (min.$^{-1}$)	70·3	73·5	350 *	87·6

* Estimated from 2 and 10% values. † Data obtained by Dr. B. Saville.

This small effect suggests that the inductive effect is opposed by conjugation between the chlorine atom and the phosphonyl group as discussed in a previous communication. Similar rate changes are observed for carbonyl compounds, *e.g.*, the relative rate of solvolysis of chloracetyl and acetyl chlorides [11] (~20 : 1 in ether–alcohol mixtures), is similar to the relative rate of hydrolysis of carbonyl chloride and acetyl chloride in aqueous dioxan.[16] A similar explanation of opposing electronic effects can be advanced, but here both σ- and π-bond energy changes are considerably greater.

Other examples, where the inductive effect of an α-substituent is somewhat greater than the opposed conjugation, are known and it has been suggested [1] that the greater electronegativity of the sp^2 orbitals of carbon (as in the phenyl group) is responsible for the small rate increases produced by phenyl groups.

In further experiments, dimethylphosphinic chloride was found to be very reactive, and the rate of hydrolysis could not be followed in the stopped-flow apparatus. The

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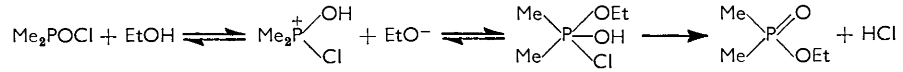
[13] Hine and Langford, *J. Amer. Chem. Soc.*, 1956, **78**, 5002.

[14] Larsson, *Acta Chem. Scand.*, 1957, **11**, 1138.

[15] Fukuto and Metcalf, *J. Amer. Chem. Soc.*, 1959, **81**, 372.

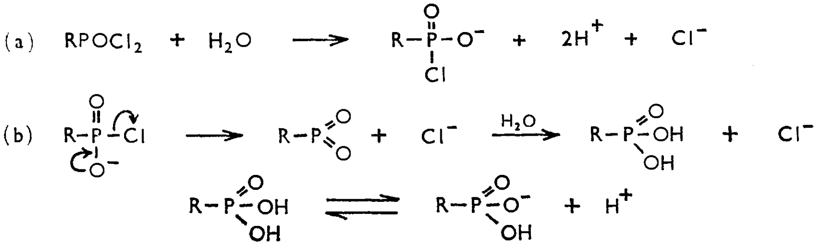
[16] Böhme, *Ber.*, 1941, *B*, **74**, 248.

ratio of the rates of solvolysis of dimethylphosphinic chloride and methylphosphonic dichloride in dioxan containing 5% alcohol (Table 7) was *ca.* 400. This very high reactivity suggests either that the second chlorine atom conjugates very strongly with the phosphonyl group, or a change in mechanism occurs. The high reactivity may be due to electrophilic catalysis, in view of the increased hydrogen-bonding tendency of the phosphinic oxygen atom[17] by electron release from the two alkyl groups, which may be represented as follows,



Phosphinic derivatives have received little attention, and systematic investigations of their reactivity should be made.

The hydrolyses of methyl- and chloromethyl-phosphinyl chlorides were of first order in all cases. Since the pK_1 of chloromethylphosphonic acid (1·45) is sufficiently high for the acid to be largely ionised in the presence of 10^{-2}—10^{-3}M-hydrochloric acid formed in the hydrolysis, no slow stage comparable to that observed in the hydrolysis of phosphonyl chloride is involved in the reaction. This suggests that the removal of the second chlorine atom proceeds in this case by the unimolecular mechanism (b) discussed previously,[5] involving an intermediate monomeric metaphosphate,



Experimental

Preparation of Materials.—Chloromethylphosphonic dichloride (I) was prepared[17] by the action of phosphorus trichloride on paraformaldehyde at 260° (yield 52%); it had b. p. 79°/10 mm., n_D^{20} 1·4980 (lit.,[17] b. p. 78—79°/10 mm., n_D^{20} 1·4978) [Found: Equiv. (acidimetric), 42·65. Calc. for CH_2Cl_3OP: Equiv., 41·84]. Diethyl chloromethylphosphonate was prepared[18] by the action of ethanol on (I) in the presence of pyridine (yield 88%); it had b. p. 54—55°/0·21 mm., n_D^{20} 1·4383 (lit.,[18] b. p. 101°/5 mm., n_D^{20} 1·4415) (Found: *M* (saponification), 186. Calc. for $C_5H_{12}ClO_3P$: *M*, 186·6). Ethyl chloromethylphosphonochloridate[19] was prepared by the reaction of an equimolecular mixture of ethanol, triethylamine, and (I) in ether at 0° (yield 30%); it had b. p. 64°/1·2 mm., n_D^{20} 1·4643 (lit.,[19] n_D^{25} 1·4659) (Found: P, 17·65. Calc. for $C_3H_7Cl_2O_2P$: P, 17·5%). Dimethylphosphinic chloride was prepared[20] by the reaction of methyl magnesium iodide on thiophosphoryl chloride, followed by oxidation of the disulphide to methylphosphonic acid with 30% nitric acid, and chlorination with thionyl chloride; it had b. p. 128°/16·5 mm. (lit.,[20] b. p. 202·4°) [Found: Equiv. (acidimetric), 56·25. Calc. for C_2H_6ClOP: Equiv., 56·24]. Methylphosphonic dichloride was purified by distillation; it had b. p. 163° (lit., b. p. 163°). Ethyl phosphorodichloridate[21] was prepared by the action of phosphoryl chloride on ethanol (yield 82%); it had b. p. 71°/23 mm., lit., b. p. 63°/19 mm. (Found: Cl, 43·1. Calc. for $C_2H_5Cl_2O_2P$: Cl, 43·5%).

Kinetic Measurements.—The rates of hydrolysis of methyl- and chloromethyl-phosphonic

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[17] Aksnes, *Acta Chem. Scand.*, 1960, **14**, 1475, 1526.

[18] Kabachnik and Shepeleva, *Izvest. Akad. Nauk S.S.S.R., Otdel. khim. Nauk*, 1951, 185 (*Chem. Abs.*, 1951, 10,191).

[19] Toy and Rattenbury, U.S.P. 2,922,810/1960.

[20] (*a*) Kosolapoff and Watson, *J. Amer. Chem. Soc.*, 1951, **73**, 5466; (*b*) Kabachnik and Shepeleva, *Izvest. Akad. Nauk S.S.S.R., Otdel. khim. Nauk*, 1949, 56.

[21] Gerrard, *J.*, 1940, 1464.

dichlorides were measured by the stopped-flow technique described elsewhere.[22] The alkaline hydrolysis of diethyl chloromethylphosphonate was followed acidimetrically as for other phosphonates.[23] Tests on the reaction mixtures showed that the chlorine atom was not removed during the hydrolysis. The rate of solvolysis in aqueous acetone was carried out by the method already described.[1] The rates of alcoholysis of dimethylphosphinic chloride and methylphosphonic dichloride were followed similarly, the former chloride being introduced into the reaction mixture on the end of a glass rod as described elsewhere. The reaction of this chloride did not obey the first-order rate law accurately, as the initial major portion was followed by a slow stage, which was probably due to the presence of anhydride introduced in the storage and handling operation. The anhydride (b. p. 140°/15 mm.) was isolated in the form of white needles,[20a] from the residues after the distillation of methylphosphinic dichloride, by evaporation on to a cold finger (Found: Equiv., 84·5. Calc. for $C_4H_{12}O_3P$: Equiv., 85·05). The rate of hydrolysis measured in water at pH 7 (k_1 = 0·084 min.$^{-1}$) corresponded approximately to the slow stage of the hydrolysis of dimethylphosphinic dichloride. The rate of hydrolysis of this anhydride is much greater than that of a tetra-alkyl pyrophosphate.

The rate constants are summarised in Tables 4—8.

TABLE 4.

Hydrolysis of ethyl chloromethylphosphonochloridate in aqueous acetone (5% water by volume).

Concn. (10^2M)	Temp.	10^3k_1 (min.$^{-1}$)	Mean 10^3k_1 (min.$^{-1}$)
3·90	1·30° ± 0·05	106	
2·49	,,	107	106
5·20	−9·5 ± 0·5	46·0	
1·71	,,	46·6	46·3
6·95	24·2 ± 0·3	13·6	
4·10	,,	13·5	13·5

E_A = 10·9 kcal./mole; log PZ = 5·94 (PZ in sec.$^{-1}$).

TABLE 5.

Hydrolysis of diethyl chloromethylphosphonate in 0·05N-aqueous sodium hydroxide solution.

Concn. (10^2M)	Temp.	k_2 (l. mole^{-1} hr.$^{-1}$)	Mean k_2 (l. mole^{-1} hr.$^{-1}$)
3·32	59·2	111	
2·96	60·0	110	
3·73	45·0	48·9	47·7
3·23	,,	48·8	
3·11	30·0	17·8	17·6
2·90	,,	17·4	

E_A = 12·03 kcal./mole; log PZ = 6·78 (PZ in hr.$^{-1}$).

TABLE 6.

Hydrolysis of ethyl phosphorodichloridate in aqueous acetone.

Water % (v/v)	Temp.	[EtO·POCl$_2$]	10^3k_1 (min.$^{-1}$)	$10^3k_1'$ (min.$^{-1}$)
1·0	0·3	0·050	31·7	7·3
,,	15·7	0·040	53·1	10·3
,,	24·7	0·040	80·3	18·5
2·0	−12·0	0·034	42·1	14·9
,,	0·3	0·056	73·3	28·3
,,	13·5	0·050	153	58·7
,,	16·3	0·036	169	60·1
10·0	−13·2	0·028	340	110
,,	0·6	0·033	735	325

k_1 and k_1' referring to the following reactions, were calculated by the method of Swain.[23]

$$\mathrm{EtO{\cdot}POCl_2 + H_2O \xrightarrow{k_1} EtO(O)P(OH)Cl \xrightarrow{k_1'\ H_2O} EtO(O)P(OH)_2}$$

TABLE 7.

Solvolysis in alcoholic dioxan at 25°.

Compound	Concn. (mole/l.)	Alcohol % (v/v)	k_1 (min.$^{-1}$)
Me_2POCl	0·042	2·0	0·15 (15°)
	0·025	5·0	0·40
	0·025	,,	0·35
	0·023	,,	0·45
$MePOCl_2$	0·011	,,	3·50 × 10^{-4}

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[22] Hudson and Moss, *J.*, 1962, 5157.

[23] Hudson and Keay, *J.*, 1956, 2463.

TABLE 8.

Hydrolysis of methylphosphonic dichloride and chloromethylphosphonic dichloride in aqueous dioxan.

Concn. (10^3M)	Vol. of water % (before mixing)	Temp.	k_1 (sec.$^{-1}$)	Mean k_1 (sec.$^{-1}$)	Concn. (10^3M)	Vol. of water % (before mixing)	Temp.	k_1 (sec.$^{-1}$)	Mean k_1 (sec.$^{-1}$)
				Methylphosphonic dichloride					
3·5	24·0	24·0	2·60		4·0	50·0	26·4	10·47	
,,	,,	,,	2·62	2·52	,,	,,	,,	9·53	10·27
,,	,,	,,	2·34		,,	,,	,,	10·80	
2·7	33·3	26·0	5·65		1·6	60·8	26·5	10·56	
,,	,,	,,	5·25	5·30	,,	,,	,,	10·45	10·51
,,	,,	,,	5·10		2·1	75·6	27·3	8·82	
4·5	50·0	29·0	10·25		,,	,,	27·4	9·92	9·50
,,	,,	28·9	9·36	9·61	,,	,,	,,		
,,	,,	,,	9·22		1·9	,,	26·2	9·77	
					,,	,,	,,	9·43	9·58
				Chloromethylphosphonic dichloride					
1·17	33·3	22·9	9·8	9·61	0·686	60·8	25·0	20·9	21·7
,,	,,	,,	9·41		,,	,,	,,	22·4	
1·75	50·0	23·2	19·1	19·0	0·855	75·6	,,	20·1	21·0
,,	,,	,,	19·0		,,	,,	,,	21·9	

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