

372. *The Mechanism of Hydrolysis of Phosphonochloridates and Related Compounds. Part II.* The Effect of the Solvent.*

By R. F. HUDSON and L. KEAY.

Phosphonochloridates are approximately 10^3 times less reactive in formic acid containing *ca.* 0.7% of water than in aqueous ethanol of comparable ionising power. Ethyl methylphosphonochloridate gave ethyl hydrogen methylphosphonate in both solvents. These observations, and the effect of the concentration of water on the rate of solvolysis in acetone-water mixtures, suggest that the reaction is bimolecular. The importance of steric hindrance is shown by the rapid decrease in rate of alcoholysis in the series $\text{MeOH} > \text{EtOH} > \text{Pr}^i\text{OH} > \text{Bu}^t\text{OH}$. The activation energy also decreases in this order, *i.e.*, with increasing basicity, which is attributed to the increase in the bond-forming energy.

In Part I* the effect of substituents on the rate of hydrolysis of phosphonochloridates and related compounds is interpreted consistently in terms of a bimolecular displacement reaction. Further information on the nature of the transition state may be obtained from studies of the influence of the solvent on the rate of reaction.¹ In the present work, the rates of solvolysis in formic acid and in aqueous ethanol are compared, and the effect of increasing the water content of the medium has been investigated.

Reaction in Formic Acid.—The importance of bond formation is shown by comparing the rates of solvolysis in solvents of similar ionising power but widely differing basicities. Ionisation (S_N1) reactions of alkyl¹ and acyl halides² proceed at similar rates in formic acid, 40% aqueous alcohol (v/v), and 65% aqueous acetone (see Table I). These reactions are promoted by short-range solvation³ of the ionic transition state, particularly of the incipient anion,⁴ but the rate of a bimolecular reaction also depends on the basicity of the solvent. (Basicity alone is not a satisfactory criterion of nucleophilic power, but may be used when different bases containing the same nucleophilic atom are compared.)

TABLE I. *Comparison of the reactivities of various halides in aqueous ethanol (*) containing 40% of water by volume, or aqueous acetone (†) containing 65% of water by volume, and formic acid containing *ca.* 0.7% of water.*

Halide	MeBr *	Bu ^t Cl *	<i>p</i> -C ₆ H ₄ Me·COCl †
Relative reactivity ‡	200	0.89	1.5
Halide	<i>p</i> -NO ₂ ·C ₆ H ₄ ·COCl †	(PrO) ₂ POCl *	C ₆ H ₁₃ ·CHMe·O·PMeOCl
Relative reactivity ‡	1560	2000	1840

‡ Rate in the aqueous solvent divided by the rate in formic acid.

Table I shows that 1-methylheptyl methylphosphonochloridate and di-isopropyl phosphorochloridate are more reactive, by several powers of ten, in the more basic, aqueous solvents than in formic acid. The rate ratios are similar to that for *p*-nitrobenzoyl chloride,² which is hydrolysed in moist formic acid by a bimolecular mechanism. The ratios for our reactions are considerably greater than that for methyl bromide given in Table I, suggesting that bond formation is almost complete in the transition state.

Dostrovsky and Halmann⁵ noted that the ester groups are removed in addition to the chlorine atom in the formolysis of di-isopropyl phosphorochloridate. The high activation energy compared with that for hydrolysis in aqueous ethanol (Table 2) suggests that the

* Part I, preceding paper.

¹ Dostrovsky and Hughes, *J.*, 1946, 167, 172; Grunwald and Winstein, *J. Amer. Chem. Soc.*, 1948, **70**, 846.

² Crunden and Hudson, *J.*, 1956, 501.

³ Gelles, Hughes, and Ingold, *J.*, 1954, 2918.

⁴ Hudson and Saville, *J.*, 1955, 4114.

⁵ Dostrovsky and Halmann, *J.*, 1953, 503.

rate-determining step in formic acid involves dealkylation rather than substitution at the phosphorus atom, and this is supported by the preferential alkyl-oxygen fission of dialkyl phosphonates in acid solution.⁶

For phosphonochloridates, however, the differences in the activation energy for the reaction in formic acid and in aqueous solvents are much smaller than for the phosphorochloridate (Table 2 where E refers to the experimental activation energy in kcal. mole⁻¹). Moreover, ethyl hydrogen methylphosphonate was isolated after reaction of ethyl methylphosphonochloridate in formic acid. The rates of reaction of phosphonochloridates in formic acid, therefore, refer to P-Cl fission.

TABLE 2.

	H·CO ₂ H		5% aq. COMe ₂		40% aq. EtOH	
	E	log PZ	E	log PZ	E	log PZ
EtO·MePOCl	13.9	7.62	8.5	5.80	—	—
C ₆ H ₁₃ ·CHMe·O·PMeOCl	12.6	6.50	9.2	5.72	10.7	8.24
(PrO) ₂ ·MePOCl	22.5	12.6	—	—	13.0	6.0

Reaction in Aqueous Acetone.—The effect of changing water concentration on the reaction rate also provides information on the charge dispersion in the transition state.¹ If the measurements are restricted to one particular reaction mixture, the following empirical relation proposed by Grunwald, Winstein, and Jones,⁷ involving an empirical parameter for solvating power Y , may be conveniently used, namely, $\log k/k^0 = mY$. The results given in Table 3 lead to an average value for m of *ca.* 0.43 for isopropyl methyl-

TABLE 3. *The hydrolysis of isopropyl methylphosphonochloridate in acetone-water mixtures.*

Water (v/v %)	Concn. (N)	Temp.	E			Water (v/v %)	Concn. (N)	Temp.	E		
			10 ³ k_1 (min. ⁻¹)	(kcal. mole ⁻¹)	log ₁₀ PZ				10 ³ k_1 (min. ⁻¹)	(kcal. mole ⁻¹)	log ₁₀ PZ
2	0.024	25.0°	26.9			20	0.025	-30.0°	23.3	11.1	8.3
5	0.023	-16.0	16.8	8.7	5.4		0.025	-20.0	59.6		
	0.023	-8.5	23.8				0.024	-10.0	136		
	0.024	0.0	41.2				0.024	0.0	46.5 *		
10	0.024	26.1	163				0.050	0.0	44.2 †		
	0.025	-20.0	29.0	10.1	7.1	100% (EtOH)	0.024	0.0	29.5		
	0.024	-8.5	69.1								
	0.025	0.0	125								

* Saturated with KCl. † Containing 0.12N-HCl.

phosphonochloridate compared with 0.33 for di-isopropyl phosphorochloridate.⁵ These values are considerably less than the values normally obtained for S_N1 reactions ($m \sim 1.0$), and similar to typical values obtained for bimolecular hydrolyses.

A significant increase in activation energy with water content is observed as the water content varies from 5% to 25% (Table 4).

TABLE 4. *Arrhenius parameters for the hydrolysis of isopropyl methylphosphonochloridate in acetone-water mixtures.*

Water content (v/v %)	5	10	20
E_A (kcal. mole ⁻¹)	8.7	10.1	11.1
log ₁₀ PZ	5.4	7.1	8.3

The similar increases in activation energy observed⁸ in the hydrolysis of benzoyl chloride in these solvent mixtures have been attributed to a gradual increase in the polarity of the transition state, rather than to changes in solvent structure alone. Thus, as the electrostatic field increases, the polarisation of the relatively weak P-Cl bond in the transition state increases. This may result in an increase in activation energy and a

⁶ Hudson and Keay, *J.*, 1956, 2463.

⁷ Grunwald, Winstein, and Jones, *J. Amer. Chem. Soc.*, 1951, **73**, 2700.

⁸ Archer and Hudson, *J.*, 1950, 3259.

compensating increase in the entropy of activation.^{9,10} Bond-breaking is more advanced in the hydrolysis of phosphorochloramidates,¹¹ owing to electron-release from the amino-group.

Reactions of Alcohols.—The rates of reaction of a series of alcohols with ethyl methylphosphonochloridate were measured in acetone solution, in a desire to investigate the influence of the structure of the substituting agent on reactivity. In interpreting the observed rates, the following factors have to be considered: (a) the energy of bond formation, (b) steric hindrance, and (c) specific solvation of the transition state by alcohol molecules. Substitution of alkyl groups in the alcohol increases the basicity and thus facilitates bond formation, but also increases the steric hindrance. The latter effect is considerably more important than changes in the bond-forming energy in the reactions between amines and phosphorochloridates⁵ and probably accounts for the rate decreases shown in Table 5. The slight increase in rate on changing from isopropyl to t-butyl alcohol must be due to the increase in basicity, hence in the bond energy.

TABLE 5. *The reactivity of EtO·MePOCl with water and alcohols (1·56M) in acetone at 25°.*

	H ₂ O	MeOH	EtOH	Bu ⁿ OH	PrOH	Bu ^t OH
10 ³ k (min. ⁻¹)	128	10·3	5·07	6·72	1·47	1·68
E (kcal. mole ⁻¹)	8·5	8·0	7·3	7·4	6·9	6·3
log ₁₀ PZ	5·37	3·88	3·07	3·23	2·26	1·86

The influence of factor (c) cannot be ascertained with certainty, since it is determined by the charge distribution in the transition state. If analogy with similar reactions catalysed by specific solvation of the transition state is valid, the differences may be assumed to be small. For example, the catalytic constant for water is about twice that for ethanol in S_N1 reactions of t-butyl bromide in nitromethane. Since the solvent effect is considerably greater in ionisation reactions than in bimolecular substitutions the differences in rate due to differences in solvation by the hydroxylic component are probably much smaller than the differences in Table 5.

The decreases in activation energy with substitution in the alcohol are also explained by increases in the bond-forming energy, and the corresponding large decreases in the PZ factor to increased steric hindrance. The rate of reaction with phenol (Table 7) is less than that with ethanol, which also follows from the greater acidity of the former. No specific catalysis by the second hydroxyl group of catechol was found (Table 7), in agreement with a previous conclusion¹² that only the singly ionised species is catalytically effective in the reactions of acyl halides and phosphonofluoridates.

EXPERIMENTAL

The rates of hydrolysis and alcoholysis were measured as described in the previous paper. The rate of reaction in formic acid ("AnalaR"; water content 0·7%) was followed conductimetrically.⁸ Ethyl methylphosphonochloridate, b. p. 40—41°/1 mm., and isopropyl methylphosphonochloridate, b. p. 47°/3 mm., were prepared as described in a previous paper. "AnalaR" acetone was boiled with phosphoric oxide for several hours and distilled through a 30 cm. glass column packed with Fenske helices. Methanol and ethanol were distilled from magnesium methoxide and ethoxide respectively; propyl, isopropyl, butyl, and t-butyl alcohol, phenol, and catechol were distilled over sodium before use.

1-Methylheptyl methylphosphonochloridate was prepared by the action of methylphosphonyl dichloride on octan-2-ol in the presence of triethylamine in ether at 0° and had b. p.

⁹ Brown and Hudson, *J.*, 1953, 3352.

¹⁰ Leffler, *J. Org. Chem.*, 1955, 20, 1202.

¹¹ Hall, *J. Org. Chem.*, 1956, 21, 248.

¹² Epstein, Rosenblatt, and Demek, *J. Amer. Chem. Soc.*, 1956, 78, 341; Churchill, Lapkin, Martinez, and Zaslowsky, *ibid.*, 1958, 80, 1944.

84°/0.2 mm. (yield 79%) (Found: C, 48.1; H, 8.6; Cl, 15.7%; equiv., 224.9. $C_9H_{20}O_2PCl$ requires C, 47.7; H, 8.8; Cl, 15.7%; equiv., 226.7).

Product of Solvolysis of Ethyl Methylphosphonochloridate in Formic Acid.—The ester (3 g.) was heated at 50–60° for 24 hr. with formic acid (100 ml.; ca. 0.7% of water). The formic acid was removed at the water-pump, and the residual oil distilled (yield, 2.0 g.; b. p. 105–110°/0.2 mm.) (b. p. of $EtO \cdot PMeO \cdot OH$ is 120°/0.3 mm.) (Found: C, 28.5; H, 7.24; P, 25.4%; equiv., 124. $C_3H_9O_3P$ requires C, 28.6; H, 7.1; P, 24.6%; equiv., 126).

Alcoholysis of Ethyl Methylphosphonochloridate.—The chloridate (1.2 g.) was added to acetone (100 ml.) containing the appropriate alcohol (5 ml.), and the mixture set aside for 24 hr. The solvent was removed, and the residual oil distilled under reduced pressure. The following were obtained:

Ethyl methyl methylphosphonate (61%), b. p. 87–89°/20 mm. (Found: C, 34.6; H, 7.9; P, 22.3. $C_4H_{11}O_3P$ requires C, 34.8; H, 8.0; P, 22.5%).

Ethyl isopropyl methylphosphonate (60%), b. p. 90–92°/20 mm. (Found: C, 43.6; H, 9.4; P, 18.5. $C_6H_{15}O_3P$ requires C, 43.4; H, 9.3; P, 18.7%).

Butyl ethyl methylphosphonate (66%), b. p. 100–102°/20 mm. (Found: C, 47.1; H, 9.7; P, 16.9. $C_7H_{17}O_3P$ requires C, 46.7; H, 9.4; P, 17.2%).

Diethyl methylphosphonate (70%), b. p. 92–94°/17 mm. (lit., b. p. 192–194°).

Ethyl methylphosphonochloridate with *t*-butyl alcohol gave ethyl hydrogen methylphosphonate in 55% yield.

Results.—The rate data are summarised in Tables 4, 6, and 7.

TABLE 6. *Comparison of the reactivity of 1-methylheptyl methylphosphonochloridate in aqueous acetone, aqueous ethanol, and formic acid.*

Medium	Concn. (N)	Temp.	$10k$ (min. ⁻¹)	Medium	Concn. (N)	Temp.	$10k$ (min. ⁻¹)
5% of H ₂ O in acetone	0.020	0.0°	21.9	40% of H ₂ O in EtOH	0.023	–21.0°	86.0
	0.020	12.0	44.6	EtOH	0.019	0.0	446
	0.22	20.2	69.9	0.7% of H ₂ O in H·CO ₂ H	0.021	25.0	1.71
					0.015	50.0	11.7

TABLE 7. *Rate of reaction of ethyl methylphosphonochloridate with water, alcohols, and phenols in acetone.*

Medium	Concn. (N)	Temp.	10^3k_1 (min. ⁻¹)	Medium	Concn. (N)	Temp.	10^3k_1 (min. ⁻¹)
2.8% of H ₂ O	0.045	25°	128	5% of BuOH	0.055	24.8°	7.62
5% of H ₂ O	0.046	–24	19.8		0.060	34.0	11.4
	0.049	–10.5	47.7		0.048	43.7	16.5
	0.051	0.0	87.6	5% of Bu ^t OH	0.056	24.8	0.781
5% of MeOH	0.043	0.0	2.92		0.082	34.0	1.06
	0.042	24.8	10.3		0.083	43.7	1.50
	0.047	35.0	15.2	11.6% of Bu ^t OH	0.071	25.0	1.68
5% of EtOH	0.057	24.7	2.47	5% of PhOH	0.053	44.0	1.15
	0.046	34.0	3.41	5% of catechol	0.058	44.8	1.01
	0.053	43.7	5.03	0.7% of H ₂ O in H·CO ₂ H	0.041	25.0	2.64
7.19% of EtOH	0.047	25.0	5.07		0.023	40.0	8.10
5% of Pr ⁱ OH	0.054	24.8	0.882		0.027	50.0	16.2
	0.050	34.0	1.26				
	0.050	43.7	1.80				
9.38% of Pr ⁱ OH	0.055	25.0	1.47				

QUEEN MARY COLLEGE (UNIVERSITY OF LONDON),
MILE END ROAD, LONDON, E.1.

[Received, July 10th, 1959.]