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Chlorophosphate solvolyses. Evaluation of third-order rate laws and rate–product correlations for diphenyl phosphorochloridate in aqueous alcohols †

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Rate constants and product selectivities for solvolyses of diphenyl phosphorochloridate in aqueous ethanol and methanol have been determined, along with additional kinetic data for solvolyses in acetone–water, D_2O, MeOD, 2,2,2-trifluoroethanol–water, and CF_3CH_2OH–EtOH. Kinetic data for solvolyses of bis(4-chlorophenyl) phosphorochloridate in the above solvents have also been obtained. The results show that these solvolyses have the following features: (*i*) no evidence for mechanistic changes over the solvent range ethanol to water; (*ii*) the largest kinetic solvent isotope effect (KSIE in MeOH/MeOD) yet reported for a chloride solvolysis; (*iii*) large rate decreases in CF_3CH_2OH-rich solvents, indicating a very high sensitivity to solvent nucleophilicity. The large KSIE and the product selectivities are well explained by the accepted $S_N2(P)$ mechanism, extended to incorporate two solvent molecules in the rate-determining step; *i.e.* reactions are third-order, with one molecule of solvent acting as nucleophile and the other acting as general base. This relatively simple theory accounts well for several important features of these solvolyses (including solvolyses in trifluoroethanol–water and –ethanol), but the third-order rate constants derived from product selectivities lead to calculated first-order rate constants which are not always in agreement with experimental values. The unexpected failure of the rate–product correlation may be due to initial-state effects, reducing values of third-order rate constants as alcohol is added to water.

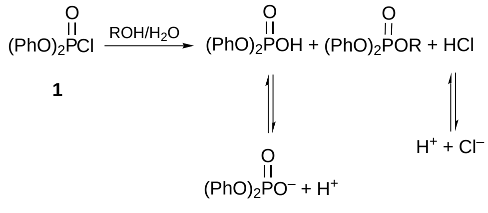
When an acid chloride such as the chlorophosphate, diphenyl phosphorochloridate **1** reacts in an alcohol–water mixture both an acid and an ester are formed (Scheme 1). If a suitable chromophore (*e.g.* an aromatic ring) is present, the product ratio can be obtained by reversed-phase high-performance liquid chromatography (RPHPLC), and the product selectivity, *S* [equation (1)], can be calculated.[1] A new challenge, to explain

$$S = [\text{ester}][\text{water solvent}]/[\text{acid}][\text{alcohol solvent}] \qquad (1)$$

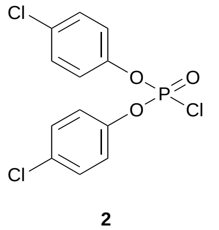
quantitatively both the rates and products, is further complicated in the cases of carboxylic acid[2,3] and sulfonyl[4] chlorides by the possibility of mechanistic changes over the wide range of solvent polarity from ethanol to water.

Chlorophosphate solvolyses, like other phosphorus acyl group transfers,[5] are known to occur by an $S_N2(P)$ mechanism;[6a,b,7] *e.g.* $(Pr^iO)_2POCl$ reacts 5000-fold faster than $(Pr^iO)_2POF$ in water,[8] $(EtO)_2POCl$ does not undergo ^{18}O exchange in 1,4-dioxane–water,[9] and there is no evidence for the acid or base catalysis often observed for addition/elimination mechanisms.[10,11] The mechanistic uniformity of chlorophosphate solvolyses provides an excellent opportunity to test a recently developed theory explaining the rates and products of solvolyses in aqueous alcohols in terms of competing third-order reactions.[12,13]

Since earlier work,[7–11] considerable progress has been made by investigating the rates of solvolyses in alcohol–water mixtures: *e.g.* studies of trifluoroethanol–water mixtures have led to a better understanding of the role of the solvent as a nucleophile in heterolytic reactions,[14] and linear free-energy relationships have been expanded to include the effects of solvent nucleophilicity.[15] Also, solvent isotope effects in methanol have been used to assess the role of solvent as a general base catalyst.[16–19]



Scheme 1 Solvolyses of diphenyl phosphorochloridate **1** in alcohol–water



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We now report rate and product data for solvolyses of diphenyl phosphorochloridate **1** and rate data for solvolyses of bis(4-chlorophenyl) phosphorochloridate **2**. The results will be interpreted with the aid of rate–product correlations and linear free-energy relationships.

Results

First-order solvolysis rate constants at 0 °C were calculated from the appearance of the two acid products (Scheme 1); data are given for solvolyses in aqueous acetone, ethanol and methanol at 0 °C for diphenyl phosphorochloridate (Table 1) and

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Non-SI units employed: cal = 4.184 J, mmHg ≈ 133 Pa, in = 2.54 × 10^{-2} m.

Table 1 First-order rate constants (k) for solvolyses of diphenyl phosphorochloridate **1** in aqueous binary mixtures at 0.0 °C[a]

Solvent (% v/v)	$k/10^{-4}$ s^{-1} Acetone	Ethanol	Methanol
100		0.48 ± 0.01[b]	3.04 ± 0.10[b]
95	1.09 ± 0.04[b]		
90	3.44 ± 0.09[b]	5.63 ± 0.08[b]	14.7 ± 0.2[b]
80	9.56 ± 0.10[b]	8.54 ± 0.29[b]	26.5 ± 0.5[b,c]
70	18.0 ± 0.2[b,c]	11.8 ± 0.1[c]	36.8 ± 0.2[c]
60	28.4 ± 0.1[c]	15.0 ± 0.1[c]	51.4 ± 0.2[c]
50	42.7 ± 0.6[c]	20.8 ± 0.1[c]	73.6 ± 0.3[c]
40	67.5 ± 1.0[c]	38.1 ± 0.2[c]	115 ± 1[c]
30	115 ± 1[c]	104 ± 1[c]	180 ± 3[c]
20	196 ± 1[c,d]	237 ± 2[c,d]	280 ± 10[c,d]
10	400 ± 20[c,d]	350 ± 20[c,d]	370 ± 10[c,d]
Water	450 ± 20[c–e]		

[a] Determined at least in duplicate; errors shown are average deviations. [b] Titrimetric analysis. [c] Conductimetric analysis for 5–8 cm^3 of solvolysis media, typically containing 20 µl of a 1% solution of substrate in acetonitrile. [d] Injected 10 µl aliquots of a fresh 0.1% solution of phosphorochloridate in acetonitrile into degassed solvent; during the solvolysis the first 10 µl injection produced HCl which reacted with residual carbonate from carbon dioxide, and usually the second or third injection of a 10 µl aliquot gave reproducible results. [e] A very similar result was obtained for 2% acetone–water.

Table 2 First-order rate constants (k) for solvolyses of bis(4-chlorophenyl) phosphorochloridate **2** in aqueous binary mixtures at 0.0 °C[a]

Solvent (% v/v)	$k/10^{-4}$ s^{-1} Acetone	Ethanol	Methanol
100		2.86 ± 0.11[b]	19.1 ± 0.6[b,d]
95	10.9 ± 0.6[b]		
90	37.5 ± 1.2[b]	51.9 ± 1.8[b,d]	100 ± 1[c]
80	95.5 ± 4.0[b]	85.5 ± 1.9[b,d]	159 ± 2[c]
70		100 ± 1[c]	206 ± 1[c]
60		113 ± 2[c]	248 ± 1[c]
50		136 ± 2[c]	302 ± 2[c]
40		183 ± 3[c]	378 ± 4[c]
30		138 ± 4[c]	443 ± 7[c]
20		507 ± 20[c]	600 ± 50[c]
10			930 ± 140[c]

[a–c] As for Table 1, except a more dilute solution (*ca.* 0.1%) of substrate in acetonitrile was used. [d] Conductimetric results: 100% MeOH (18.8), 90% EtOH (54), 80% EtOH (81).

bis(4-chlorophenyl) phosphorochloridate (Table 2). Slower reactions were monitored titrimetrically, faster reactions conductimetrically, with very good agreement between the two methods in the five cases where both methods were used. Solvolyses of compound **1** at 25 °C in ethanol and 80% ethanol–water have been reported previously.[10] The low solubility of the substrates led to experimental difficulties particularly for solvolyses in 20% v/v methanol–water and 10% compositions, for which larger error estimates have been made (Table 1). For typical solvolysis reactions of chlorides the pH is mainly determined by the HCl liberated (*ca.* 10^{-3} M). A spectrophotometric investigation of diphenyl phosphorochloridate in 50% ethanol–water at 17 ± 1 °C showed that the rate of solvolysis was independent of pH (<5% change in rate constants) between pH 3 and 7.

Kinetic data for mixtures of CF_3CH_2OH with water or ethanol were determined titrimetrically (Table 3); products (investigated by RPHPLC) contained such small amounts of CF_3CH_2OH esters (<1%) that further quantification was not attempted. Kinetic solvent isotope effects (Table 4), and some activation parameters (Table 5) were determined conductimetrically.

Table 3 First-order rate constants (k) for solvolyses of phosphorochloridates **1** and **2** in binary mixtures containing 2,2,2-trifluoroethanol at 0.0 °C[a]

Solvent	$k/10^{-6}$ s^{-1} **1**	**2**
CF_3CH_2OH–water[b]		
97	0.35 ± 0.02	0.67 ± 0.02
90	4.82 ± 0.20	9.97 ± 0.43
80	23.2 ± 0.3	51.5 ± 2.6
70	54.5 ± 1.1	118 ± 6
50		279 ± 16
CF_3CH_2OH–EtOH[c]		
80	1.21 ± 0.03	3.49 ± 0.05
60	7.85 ± 0.25	29.7 ± 1.1
40	23.5 ± 0.7	112 ± 5
20		257 ± 8

[a] Determined titrimetrically from two or more kinetic runs; errors shown are standard deviations. [b] % w/w. [c] % v/v.

Table 4 Kinetic solvent isotope effects for solvolyses of phosphorochloridates in methanol[a]

Substrate	T/°C	$k/10^{-3}$ s^{-1} MeOH	MeOD	k_{MeOH}/k_{MeOD}
1	25.0	1.73 ± 0.05	0.566 ± 0.019	3.06 ± 0.21
2	25.0	8.34 ± 0.02	2.65 ± 0.03	3.15 ± 0.04
	0.0[b]	1.88 ± 0.09	0.57 ± 0.01	3.30 ± 0.05
1	5.0	(67)[c]	(23)[c]	(2.9 ± 0.3)[c]

[a] Determined conductimetrically in duplicate in the order MeOH, MeOD (×2), MeOH. [b] Activation parameters: $\Delta H^{\ddagger} = 9.1$ kcal mol^{-1}; $\Delta S^{\ddagger} = -38$ cal K^{-1} mol^{-1}. [c] Less reliable results determined for water and D_2O.

Product selectivities [equation (1)], determined by RPHPLC using an ion-pair reagent to increase the retention time of the acid, are given in Table 6; under the dilute reaction conditions ($<10^{-2}$ M) no diphosphate product was observed. A rapid equilibrium between the products was excluded, and the acid and ester products were shown to be stable over 10–20 half-lives of reaction, but not over 100 half-lives. The two products gave different ^{31}P NMR signals, but for convenient NMR analysis times (*e.g.* 15 min) 10^{-1} M solutions were required. The HPLC analysis of a more concentrated (10^{-1} M) equimolar product mixture was in agreement with the integrated areas from ^{31}P NMR signals. Mixing problems may explain the less reliable results given in parentheses in Table 6, and it appears that more ester is formed during solvolyses in the more concentrated solutions, as observed previously when mixing did not occur sufficiently rapidly.[1] For solvolyses in the highly aqueous mixtures more reproducible results were obtained at 25 °C (Table 6).

Discussion

Kinetic data

Correlations of solvolysis rate constants with Grunwald–Winstein Y values have been carried out for substitutions occurring at for example Co^{III}[20a] and Pd^{II},[20b] as well as carbon.[21] To correct for nucleophilic participation of solvent in solvolyses of *tert*-butyl chloride, the model compound for Y values, a Y_{Cl} scale has been defined based on solvolyses of the caged substrate 1-adamantyl chloride, for which rearside attack and elimination are not possible.[22a] Unusual sinusoidal logarithmic plots of rate constants for solvolyses of compounds **1** and **2** *vs.* Y_{Cl} for three aqueous mixtures (Figs. 1 and 2) were obtained (discussed later), particularly for solvolyses of **2** in aqueous ethanol.

Activation parameters (Table 5) show highly negative $\Delta S^{\ddagger}$ values (*ca.* −30 cal K^{-1} mol^{-1}), consistent with the high degree

Table 5 First-order rate constants (k) and activation parameters ($\Delta H^{\ddagger}$ and $\Delta S^{\ddagger}$) for solvolyses of diphenyl phosphorochloridate **1**

	$k/10^{-4}\ s^{-1}$			$\Delta H^{\ddagger b}$/	$\Delta S^{\ddagger c}$/
Solvent	0 °C^{a}	10 °C	25 °C	kcal mol^{-1}	cal K^{-1} mol^{-1}
MeOH	3.04 ± 0.10	6.58 ± 0.01	17.3 ± 0.6	10.7	−35
70% MeOH	36.8 ± 0.2	80.4 ± 1.2	202 ± 4	10.4	−31
EtOH	0.48 ± 0.01	1.17 ± 0.01	2.97 ± 0.08	11.1	−37
70% EtOH	11.8 ± 0.1	26.7 ± 0.2	78.2 ± 0.9	11.7	−29

[a] Data from Table 1. [b] Typical error 0.5 kcal mol^{-1}. [c] Typical error 1.5 cal K^{-1} mol^{-1}.

Table 6 Product selectivities S [equation (1)] for solvolyses of diphenyl phosphorochloridate **1** in alcohol–water[a]

Solvent	S	
(% v/v)	Ethanol	Methanol
99.8^{b}	0.030^{c}	0.108^{c}
99.5^{b}	0.035^{c}	0.111^{c}
99.0^{b}	0.042^{c}	0.119^{c}
98.0^{b}	0.055^{c}	0.142^{c}
95.0^{b}	0.108^{c}	0.200^{c}
90^{d}	0.15^{e}	0.30^{e}
80^{d}	0.21^{e}	0.46^{e} (0.46)^{b,c}
70^{d}	0.28^{e}	0.60^{e} (0.69)^{b,c}
60^{d}	0.34^{e}	0.73^{e} (0.78)^{b,c}
50^{d}	0.44^{e} (0.53)^{b,c}	0.82^{e} (0.97)^{b,c}
40^{d}	0.44^{e} (1.0)^{b,c}	0.88^{e} (1.04)^{b,c}
30^{d}	0.58^{e} (1.0)^{b,c}	0.90^{e}
20^{d}	0.39^{e}	0.90^{e}
10^{d}	0.41^{e}	0.80^{e}

[a] Calculated from the ester : acid mole ratio determined by HPLC by duplicate analyses on two independent samples; typical error ± 2%. [b] At 0 °C. [c] Typical injection of substrate was 20 µl of a 5% solution in acetonitrile; HPLC analyses included 0.6% acetic acid in the eluent. [d] At 25 °C. [e] Typical injection of substrate was a total of 50 µl of a 1% solution in acetonitrile, injected in 10 or 20 µl aliquots.

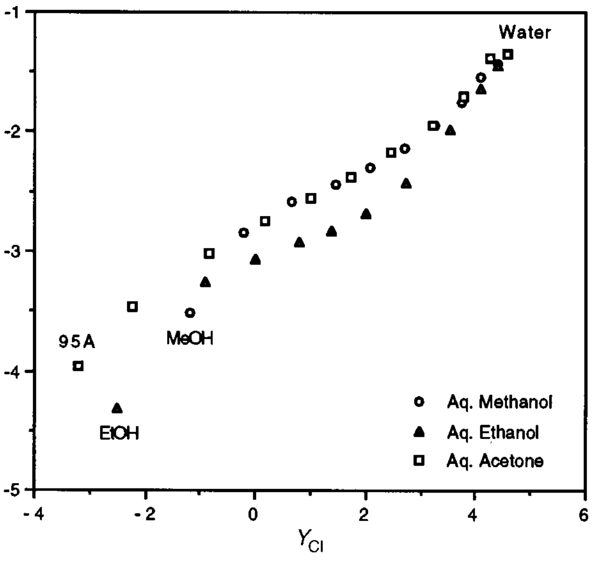


Fig. 1 Logarithms of solvolysis rate constants for diphenyl phosphorochloridate **1** at 0 °C *versus* Y_{Cl}; kinetic data from Table 1 and Y_{Cl} values from ref. 22; 95Å symbolises 95% acetone–water

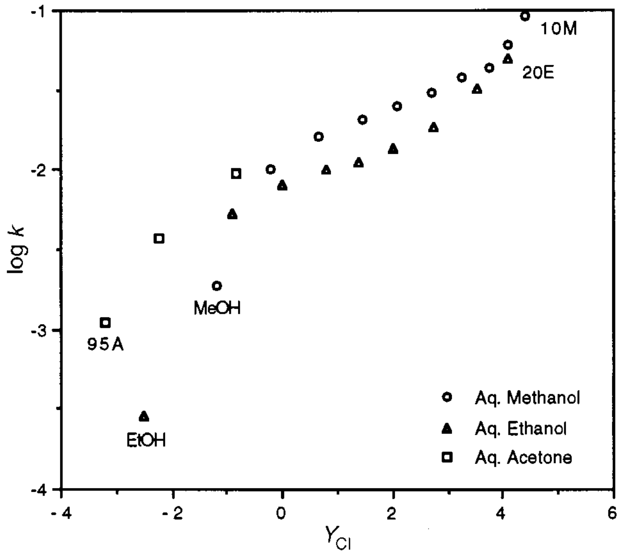


Fig. 2 Logarithms of solvolysis rate constants for bis(4-chlorophenyl) phosphorochloridate **2** at 0 °C *versus* Y_{Cl}; kinetic data from Table 2 and Y_{Cl} values from ref. 22; symbols A, E and M refer to cosolvent, *e.g.* 10M is 10% methanol–water

of order in the $S_N2(P)$ transition states.[6c,23] As expected,[1,2,4,12,13] values of S (Table 6) are greater for methanol–water than for ethanol–water and show only a small temperature dependence, but all of the S values are lower than for solvolyses of other substrates in comparable solvents.

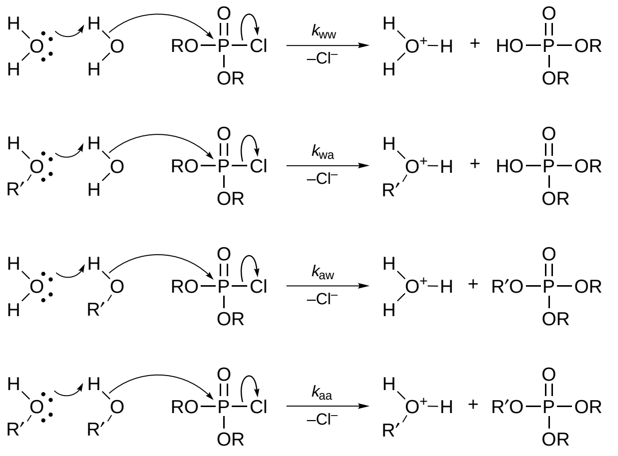
The kinetic solvent isotope effects (KSIEs) of greater than 3 (Table 4) are the largest ever reported for chloride solvolyses in MeOD, comfortably exceeding the previous highest value of 2.3 for solvolyses of *p*-nitrobenzoyl[13,17] and *p*-nitrobenzenesulfonyl chlorides[18] and 2.5 for solvolyses of *p*-nitrophenyl chloroformate.[24] These results suggest that the MeO–H bond is partially broken in the rate-determining step, consistent with the recent proposal[12,13] that solvolyses of these acid chlorides in aqueous and alcoholic media are third-order with one molecule of solvent acting as nucleophile while the other acts as a general base catalyst. In contrast, typical S_N1 and S_N2 reactions at saturated carbon give very low KSIEs (*ca.* 1.2).[16,19,25] Third-order kinetics is long established from the rate laws for solvolyses of acid chlorides in non-aqueous mixtures such as methanol–acetonitrile.[26]

A third-order mechanism readily fits the data for acetone–water mixtures; for solvolyses of compound **1** a plot (not shown) of log k *vs.* log [water] has a slope of 1.95 ± 0.14, which is the kinetic order in solvent[27] if other medium effects are negligible;[28] the plot is gently curved ($r = 0.982$), but k/[water]^2 varies only two-fold and reaches a minimum in 50% acetone.

Rate–product correlations

Both rate constants (Tables 1 and 2) and S values [equation (1), Table 6] increase as water is added to ethanol or to methanol. The increases in rates can be explained in various ways (*e.g.* by an increase in solvent polarity as the water content of the solvent increases), but the increase in S is more difficult to explain. Competing second-order reactions would give constant S values, in the absence of a medium effect on the nucleophilicity of the water and/or alcohol molecules,[29] but the increase in S can be explained by a third-order mechanism, as follows.

If reaction in water is denoted by a third-order rate constant k_{ww} (calculated from k_{obs}/[water]^2), the other terms (Scheme 2) are: k_{wa}, water acts as nucleophile and alcohol acts as general



Scheme 2 Four competing general base-catalysed reactions for nucleophilic attack on phosphochloridates; R = aryl

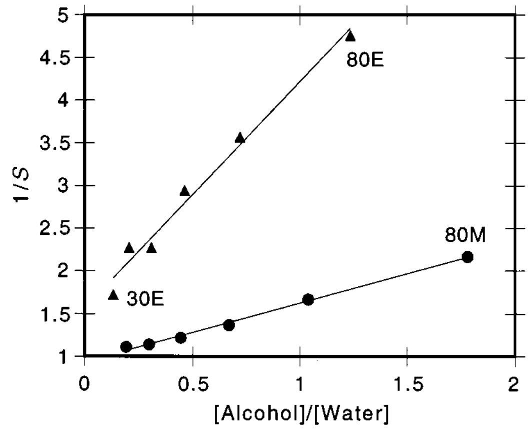


Fig. 3 Plots of 1/*S* [equation (3)] *versus* molar ratio of solvents, [alcohol]/[water], for solvolyses of diphenyl phosphorochloridate **1** at 25 °C; *S* values from Table 6. For ethanol–water: slope = 2.654 ± 0.183, intercept = 1.557 ± 0.116, *r* = 0.991. For methanol–water: slope = 0.688 ± 0.022, intercept = 0.939 ± 0.020, *r* = 0.998

base; k_{aw}, alcohol acts as nucleophile and water acts as general base; k_{aa}, alcohol acts as nucleophile and a second molecule of alcohol acts as general base. The k_{aa} term (k_{aa}[alcohol]^2) was shown to be unimportant for solvolyses of carboxylic acid[12] and sulfonyl[13] chlorides in solvent compositions more aqueous than about 80% v/v alcohol, and attack by alcohol appears to be even less important for phosphorochloridates (see below). If the k_{aa} term is ignored, *S* [equation (1)] is given by equation (2),

$$S = (k_{aw}[\text{alcohol}][\text{water}]/\{k_{wa}[\text{alcohol}][\text{water}] + k_{ww}[\text{water}]^2\}) \times [\text{water}]/[\text{alcohol}] \quad (2)$$

and the reciprocal of this simplifies to equation (3).[12,13] Hence,

$$1/S = (k_{wa}/k_{aw})([\text{alcohol}]/[\text{water}]) + (k_{ww}/k_{aw}) \quad (3)$$

1/*S* increases (so *S* decreases) as the alcohol content of the solvent increases, or conversely *S* increases as the water content of the solvent increases to reach a maximum given by k_{aw}/k_{ww}.[28]

Similarly, for solvolyses in alcohol-rich solvents, when k_{ww}[water]^2 is negligible it can be shown[12,13] that *S* is given by equation (4).

$$S = (k_{aw}/k_{wa})([\text{water}]/[\text{alcohol}]) + (k_{aa}/k_{wa}) \quad (4)$$

From the slopes of plots (Figs. 3 and 4) for 1/*S* [equation (3)] over the solvent range 30–80% alcohol and *S* [equation (4)] over the solvent range 95–99.8% alcohol we obtained two completely independent measures of the ratios of the two 'hidden' rate constants (k_{aw} and k_{wa}). The results (Table 7) show excellent agreement for ethanol–water (k_{aw}/k_{wa} = 0.40 ± 0.02) with a wider range for methanol–water (k_{aw}/k_{wa} = 1.1 ± 0.3), and provide strong support for the validity of the third-order model.

Knowing k_{ww} [equation (3)] or k_{aa} [equation (4)], absolute values of k_{aw} and k_{wa} were calculated. The results (Table 8) show that values of k_{aw} and k_{wa} are 2–4 fold higher when calculated using 1/*S* [equation (3)] and k_{ww}, compared with those obtained from the *S* [equation (4)] and k_{aa}. Also, the third-order rate constants (Table 8) lead to calculated values of first-order rate constants[13] which are up to 10-fold faster than observed values (*e.g.* in 50% ethanol–water), mainly because of the dominant contribution from the k_{ww}[water]^2 term. Initial-state stabilisation may affect rates of solvolyses of *tert*-butyl chloride in aqueous alcohols,[30] and rate decreases due to stabilisation of non-ionic diphenyl phosphorus esters on addition of organic solvent to water have recently been proposed for reactions with hydroxide ions.[31]

Product ratios for solvolyses of compound **1** in ethanol- and methanol–water can be explained quantitatively (mol% ester within 3% of observed values) by a decrease in k_{ww} from 1.5 × 10^{-5} (Table 8) to 4 × 10^{-6} M^{-2} s^{-1}; the lower value of k_{ww} also leads to much better agreement between the two values of

Table 7 Ratios of third-order rate constants k_{aw}/k_{wa} derived from 1/*S* and *S* plots for solvolyses of diphenyl phosphorochloridate **1** in alcohol–water mixtures

Plot	Solvent range	Slope	k_{aw}/k_{wa}	Equation
1/*S*[a]	30–80% EtOH	2.65 ± 0.18	0.38 ± 0.03	(3)
S[b]	98–99.8% EtOH	0.42 ± 0.02	0.42 ± 0.02	(4)
1/*S*[a]	30–80% MeOH	0.69 ± 0.02	1.45 ± 0.04	(3)
S[b]	95–99.8% MeOH	0.82 ± 0.02	0.82 ± 0.02	(4)

[a] Fig. 3. [b] Fig. 4.

Table 8 Calculated third-order rate constants (M^{-2} s^{-1}) for the product–rate correlations for solvolyses of diphenyl phosphorochloridate **1** in alcohol–water mixtures at 0 °C[a]

	Ethanol–water		Methanol–water	
Rate constant	1/*S* [eqn. (3)]	*S* [eqn. (4)]	1/*S* [eqn. (3)]	*S* [eqn. (4)]
k_{ww}[b]	1.5 × 10^{-5}		1.5 × 10^{-5}	
k_{wa}	2.5 × 10^{-5}	6.1 × 10^{-6}	1.1 × 10^{-5}	4.9 × 10^{-6}
k_{aw}	9.3 × 10^{-6}	2.5 × 10^{-6}	1.5 × 10^{-5}	4.0 × 10^{-6}
k_{aa}[c]	1.5 × 10^{-7}		5.0 × 10^{-7}	

[a] Details of slopes and intercepts are given in the legends to Figs. 3 and 4. [b] From $k_{obs}/[H_2O]^2$. [c] From k_{obs}/[ROH]^2.

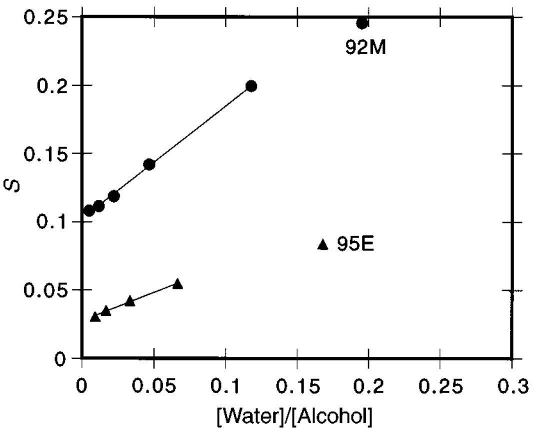
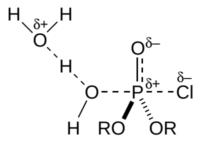


Fig. 4 Plots of *S* [equation (4)] *versus* molar ratio of solvents, [water]/[alcohol], for solvolyses of diphenyl phosphorochloridate **1** at 0 °C; *S* values from Table 6. For ethanol–water: slope = 0.419 ± 0.023, intercept = 0.0275 ± 0.0009, *r* = 0.997. For methanol–water: slope = 0.824 ± 0.018, intercept = 0.103 ± 0.001, *r* = 0.999



3 R = aryl

k_{aw} and k_{wa} (Table 8), and to satisfactory predictions of first-order rate constants in 50–90% methanol–water mixtures. Even lower values of k_{ww} are required to explain rate constants in ethanol–water mixtures, as expected for a hydrophobic stabilisation of the initial state; also the sinusoidal plots *versus* Y_{Cl} (Figs. 1 and 2) are increasingly curved for the more hydrophobic substrate **2** and for the more hydrophobic solvent (ethanol).

Although initial-state effects on k_{ww} appear to be the main cause of discrepancies between calculated and observed first-order rate constants, initial-state effects on k_{aw} and k_{wa} are significant in the solvent ranges 40% methanol or 50% ethanol to water. We also explored the possibility of using an mY treatment to allow for differences in polarity between initial and transition states,[28] but it was found that a single m value was not able to reproduce the observed trends in rates for both highly aqueous mixtures (for which an m value of 0.2 or 0.3 is required) and highly alcoholic media for which m appears to be negligible.

The mechanistic information discussed above can be incorporated into a picture of a possible $S_N2(P)$ transition state **3** for hydrolyses of diaryl chlorophosphates. The high kinetic solvent isotope effect (Table 4) is explained by cleavage of the O–H bond of the nucleophile in a highly ordered transition state, consistent with the large negative values of $\Delta S^{\ddagger}$ (Table 5). As **2** is more reactive than **1**, the reaction is favoured by electron withdrawal, and positive charge may develop on P as well as on the water molecule acting as general base; negative charge may develop on oxygen and chlorine, but charge development between initial and transition states is small and charges are delocalised, so the reaction is relatively insensitive to changes in solvent polarity.

Trifluoroethanol mixtures

Solvolyses in mixtures containing 2,2,2-trifluoroethanol are so slow that they do not appear within the range of k_{obs} values used for Figs. 1 and 2. Comparing rate constants for solvolyses in 40% ethanol–water with those for 97% CF_3CH_2OH–water (two solvents having the same Y_{Cl} value but different nucleophilicities)[22a] for compound **1** gives a rate ratio of 1.1×10^4 which is the largest value we are aware of, and which confirms the strong effect of solvent nucleophilicity on these solvolyses.[10] Previously, similar comparisons were made between 40% ethanol–water and formic acid.[10]

An alternative to the third-order treatment of the rate data (discussed above) is to analyse the data using linear free-energy relationships such as equation (5), to account for solvolyses

$$\log(k/k_0) = lN_T + mY_{Cl} + c \qquad (5)$$

over a wide range of solvent nucleophilicities; k refers to the rate constant for solvolysis relative to 80% ethanol–water (k_0), and m and l measure the response of the specific rates of solvolyses of the substrate to changes in the solvent properties of ionizing power Y_{Cl} and nucleophilicity N_T and c is the intercept.[32]

The results show very high l values (1.7–1.8) for solvolyses of compounds **1** and **2**, compared with $l = 1.0$ for solvolyses of methyl toluene-*p*-sulfonate. However, results for acetone–water mixtures are predicted to be much too slow (over 10-fold in some cases) and results for CF_3CH_2OH–ethanol are predicted to be much too fast (again over 10-fold). Details of the correlations using Y_{Cl}[22] and N_T[32] for all of the solvents listed in Tables 1–3 are as follows: for solvolyses of **1**, $m = 0.68 \pm 0.06$, $l = 1.72 \pm 0.18$, $c = 0.42 \pm 0.15$, $r = 0.885$; for solvolyses of **2**, $m = 0.58 \pm 0.08$, $l = 1.79 \pm 0.20$, $c = 0.11 \pm 0.18$, $r = 0.863$.

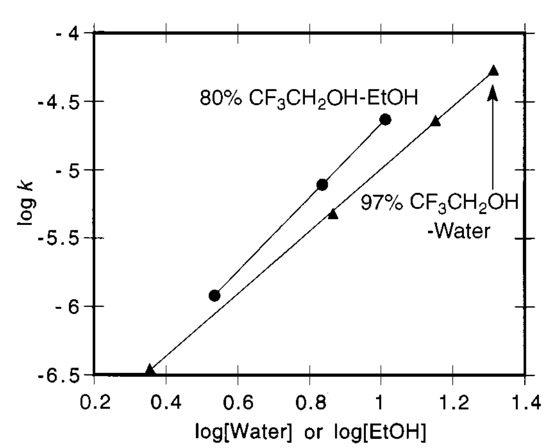


Fig. 5 Logarithms of solvolysis rate constants for diphenyl phosphorochloridate **1** in binary mixtures containing trifluoroethanol at 0 °C *versus* logarithms of water or ethanol concentrations; kinetic data from Table 3. Slopes 2.29 ± 0.02, 2.70 ± 0.01; intercepts -7.28 ± 0.02, -7.36 ± 0.01; $r = 1.00$

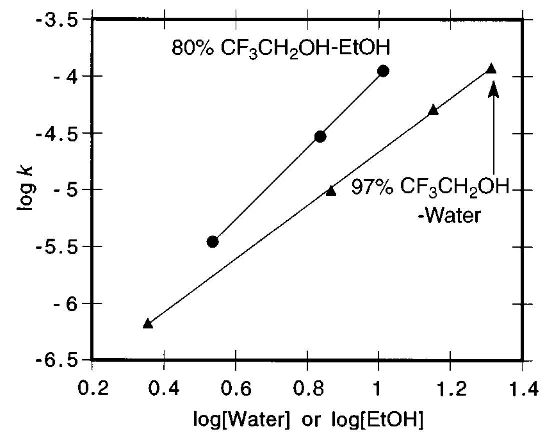


Fig. 6 Logarithms of solvolysis rate constants for bis(4-chlorophenyl) phosphorochloridate **2** in binary mixtures containing trifluoroethanol at 0 °C *versus* logarithms of water or ethanol concentrations; kinetic data from Table 3. Slopes 2.36 ± 0.03, 3.15 ± 0.05; intercepts -7.02 ± 0.03, -7.15 ± 0.04; $r = 1.00$

A theory based on third-order reactions can be developed from our observations that the amounts of trifluoroethyl ester products are negligible, so at least two of the four third-order terms can be neglected. If it is also assumed that third-order terms involving CF_3CH_2OH as base (*e.g.* k_{wa} in CF_3CH_2OH–water) and medium effects can be neglected, then the relative rates are dependent on the dominant third-order contributions, *i.e.* the $[\text{water}]^2$ term in CF_3CH_2OH–water mixtures and the $[\text{ethanol}]^2$ term in ethanol–CF_3CH_2OH mixtures, and a plot of log k *vs.* log[water] or log[ethanol] should have a slope of 2.0. The results (Figs. 5 and 6) show very good linearity for all four plots, and the slopes of 2.3 for CF_3CH_2OH–water mixtures are in accord with a third-order mechanism dominated by the contribution from the k_{ww} term. The higher slopes (2.7, 3.1) for ethanol–CF_3CH_2OH mixtures may be explained by medium effects (ethanol has a much lower Y_{Cl} value than that of CF_3CH_2OH[22a]) or by increasingly significant third-order contributions involving ethanol as nucleophile and CF_3CH_2OH as base.

Addition of >50% CF_3CH_2OH has a strong rate-retarding effect on all solvolyses, possibly because of strong hydrogen bonding between one molecule of it and one molecule of the nucleophilic component of the solvent. However, it appears that ethanol and water have very similar third-order reactivities under CF_3CH_2OH-rich conditions. From the intercepts of Figs. 5 and 6 it appears that the third-order rate constant involving two ethanol molecules in CF_3CH_2OH is only marginally less than the corresponding rate constant involving two water molecules (k_{ww}); for comparison, for solvolyses of *p*-nitrobenzenesulfonyl chloride the k_{aa} rate constant in ethanol was calculated to be about five-fold less than the k_{ww} rate constant in water.[13]

Conclusion

Rates of solvolyses of diphenyl phosphorochloridate **1** and the dichloro-derivative **2** are strongly retarded in solvents rich in trifluoroethanol and give large *l* values [equation (5)], consistent with strong rate accelerations in solvents of greater nucleophilicity (*e.g.* ethanol–water mixtures). A third-order mechanism explains the rates of solvolyses in trifluoroethanol-rich media, as relative rates are dominated by a third-order rate constant involving [nucleophilic cosolvent]^2, see Figs. 5 and 6. Kinetic solvent isotope effects (Table 4) and the increase in selectivity as water is added to ethanol or to methanol (Table 6) are also consistent with competing third-order reactions, involving the four possible combinations of water and/or alcohol acting as nucleophile or as base. Quantitative evaluation of this theory shows that, in addition to the two third-order terms calculated from solvolyses in pure solvents (*e.g.* water and methanol), satisfactory ratios of the other two terms (k_{wa} and k_{aw}) can be calculated by two independent methods (Table 7). Surprisingly, in contrast to previous studies of solvolyses of *p*-nitrobenzenesulfonyl chloride[13] and *p*-nitrobenzoyl chloride,[12] the third-order rate constants lead to inaccurately high predictions of the observed first-order rate constants for solvolyses of **1**. Probably, initial-state effects decrease the magnitude of the contributing third-order terms in more alcoholic media.

Experimental

Materials

Diphenyl phosphorochloridate (Aldrich) was distilled prior to use (b.p. 120 °C at 0.1 mmHg; lit.,[33] 141 °C at 1 mmHg), and was shown to contain <0.3% acid by HPLC analysis of the methanolysis product. Titrimetric studies of bis(4-chlorophenyl) phosphorochloridate utilised a commercial sample (Lancaster 98%), whereas conductimetric studies were done on a sample prepared from the acid (Lancaster) by reaction with PCl_5[34] at 180 °C in the presence of Aliquat (Lancaster) (b.p. 155–160 °C at 0.1 mmHg; lit.,[34] 199–201 °C at 1.8 mmHg); HPLC analysis of the methanolysis product showed 3–4% acid. Materials for response calibration of the HPLC were diphenylphosphoric acid and $(PhO)_2PO(OMe)$ (Aldrich), shown to be pure by HPLC, and standard solutions of $(PhO)_2PO(OEt)$ obtained by ethanolysis of the acid chloride.

Solvents for kinetics were dried and distilled and solvolysis media were prepared as described elsewhere.[32a,35] The accurate water contents of the low% water–alcohol mixtures, determined by Karl Fischer titration using a Mettler-Toledo DL18 apparatus and Hydranal™ titrant (2 mg ml^{-1}), were usually within ±0.02% of the nominal values given in Table 6: the more exact compositions were used for calculations. The compound MeOD (Aldrich) was recycled from previous work and shown by ^{1}H NMR spectroscopy to contain <0.05% OH.

Materials for chromatography were AR grade methanol and acetic acid, distilled water, and tetrabutylammonium bromide (Lancaster).

Kinetic methods

Titrimetric measurements were made as described elsewhere;[32a] first-order rate constants were integrated values determined from infinity titres (10 half-lives). Conductimetric measurements were made by the rapid-injection method,[12] and calculations were performed on a personal computer version of LSKIN. Spectrophotometric measurements were made at 17 ± 1 °C using a Unicam SP1800 spectrophotometer at 262 nm.

Other computer methods

Calculations of the equations for linear free energy were made using a personal computer version of Microsoft Excel™, and we established that identical values of the desired parameters were obtained to those using the ABSTAT statistical package[36] as well as 'in house' programs originally written by Dr F. L. Schadt (Princeton) and Dr M. S. Garley (Swansea).

Other analytical methods

For product studies up to 90% alcohol–water, chromatography was performed using a 15 cm × ¼ in Spherisorb ODS 2 column, eluted at a flow rate of 1 cm^3 min^{-1} with 65% v/v methanol–water containing 0.01 M tetrabutylammonium bromide. The acid signals for some product mixtures (*e.g.* 90% ethanol–water) were split into two overlapping peaks the areas of which were combined; phenol was shown to be absent and it was assumed that only one acid (in equilibrium with the corresponding anion) was present; addition of 0.6% acetic acid to the eluent sharpened the overlapping signal into a single peak, and this eluent was used for product ratios above 90% alcohol (recalibration of ester/acid response was then required). The HPLC equipment was a Milton Roy Constametric 3000 solvent-delivery system and a Milton Roy Spectromonitor 3100 variable-wavelength detector (typically set to $\lambda = 255$ nm, $A = 0.01$–0.05), fitted with a Promis II autosampler operated in the partial loop-fill injection method. Integration of peak areas was done using a C4100 integrator.

Proton NMR spectra were determined on a Bruker AC400 spectrometer and ^{31}P NMR spectra on a Bruker WM250 spectrometer. The ^{31}P chemical shifts in aqueous alcohols were δ *ca.* −10 with 0.3 ppm difference between the acid and ester signals. Other ^{1}H NMR spectra were determined on a Hitachi Perkin-Elmer R-24B instrument.

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