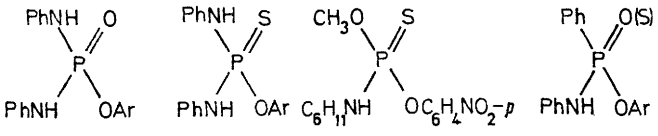
Aminolysis and Base-catalysed Hydrolysis of Aryl Phenylphosphonamidates and amidothionates: Reactions close to the *E*1cB–Bimolecular Nucleophilic Mechanistic Borderline

By **Andrew Williams,* Kenneth T. Douglas,** and **John S. Loran,** University Chemical Laboratory, University of Kent, Canterbury, Kent CT2 7NH

Trapping experiments with amine nucleophiles of high negative Brønsted-type exponent confirm that *O*-aryl *NP*-diphenylphosphonamidates [PhPO(NPh)OAr] release phenolate in base *via* an *E*1cB process. The corresponding phosphonamidothionates, however, hydrolyse in base *via* an addition–elimination pathway. These conclusions are consistent with the poorer electron-donating power of the thioanion (P–S$^-$) compared with oxyanion (P–O$^-$) to expel phenolate from the corresponding conjugate base [PhPS($\bar{N}$Ph)OAr].

THE alkaline hydrolysis of aryl *NN*-diphenylphosphorodiamidates (I) and diamidothionates (II) in alkaline media has been shown with little doubt not to involve a bimolecular nucleophilic (AE) † but an *E*1cB (EA) mechanism.[1,2] Alkaline hydrolysis of other aryl phosphoramidates such as (III) appear to follow the bimolecular nucleophilic mechanism as judged by, for example,



the inversion of stereochemistry at phosphorus during the reaction.[3]

The AE mechanism for the alkaline hydrolysis of the phosphate derivative (III) is almost certainly related to the replacement of one of the nitrogens [in (II)] by an oxygen atom which is not sufficiently electron donating to expel the phenolate anion from the conjugate base of the substrate. Replacement of P=S by P=O will probably favour the *E*1 elimination from the conjugate base of the P=O species because P–S$^-$ is less likely to donate its electrons than P–O$^-$. In the diamidate esters,[1,2] replacing P=O by P=S has no effect on the mechanistic path taken presumably because the system is so far from the borderline between EA and AE mechanisms.

The purpose of this work is to investigate the effect of changing from P=O to P=S in a borderline region where a mechanistic change is possible. We chose to study phenylphosphonamidate derivatives (IV) where the PhNH group of (I) or (II) is replaced by the far less electron donating phenyl group. These substrates also have the added advantage of being fairly labile and are therefore more easily studied than those esters with oxygen substitution as in (III).

EXPERIMENTAL

Materials.—Phenyl phosphonodichloridate and phosphonodichlorothionate were purchased from R. N. Emanuel. 4-Chlorophenyl *NP*-diphenylphosphonamidothionate was prepared by adding a mixture of 4-chlorophenol (12.9 g) and triethylamine (10 g) in dichloromethane (30 ml) dropwise to a stirred solution of phenyl phosphonodichloridothionate (21 g) in dichloromethane (50 ml). The mixture was stirred for *ca.* 6 h and then aniline (9.3 g) in dichloromethane (20 ml) was added and stirring was continued overnight. The product was filtered, the filtrate evaporated, and the residual oil taken up in ethanol. A few drops of water were added and the mixture kept in a refrigerator; crystals appeared which were collected at the pump and washed with ethanol and a small amount of ether. Other aryl *NP*-diphenylphosphonamidothionates were prepared in this way as were the corresponding morpholidothionates. Aryl *NP*-diphenylphosphonamidates and morpholidates were prepared in a similar fashion using pyridine instead of triethylamine.

The series of aryl diphenylphosphinothioates was prepared by the route outlined below [4] and the preparation of the 4-nitrophenyl derivative is described in detail. Commercial chlorodiphenylphosphine (R. N. Emanuel) was distilled under vacuum from an oil-bath to yield a liquid, b.p. 119° at 0.06 Torr, n_D^{20} 1.6360 lit., n_D^{20} 1.6352; to a

† We use here the abbreviation AE for any mechanism involving addition as the initial process and EA for elimination as the first step in a nucleophilic substitution; this nomenclature is used in a review on elimination–addition mechanisms of acyl transfer.[3a]

[1] A. Williams and K. T. Douglas, *J.C.S. Perkin II*, 1972, 1444.
[2] A. Williams and K. T. Douglas, *J.C.S. Perkin II*, 1973, 318.
[3] (*a*) A. F. Gerrard and N. K. Hamer, *J. Chem. Soc.* (*B*), 1969, 369; (*b*) A. F. Gerrard and N. K. Hamer, *J. Chem. Soc.* (*B*), 1967, 1122; (*c*) A. Williams and K. T. Douglas, *Chem. Rev.*, in the press.
[4] (*a*) F. G. Mann and J. Watson, *J. Org. Chem.*, 1948, **13**, 502; (*b*) C. Stuebe, W. M. LeSuer, and G. R. Norman, *J. Amer. Chem. Soc.*, 1955, **77**, 3526; (*c*) T. R. Hopkins and P. W. Vogel, *J. Amer. Chem. Soc.*, 1956, **78**, 4447.

stirred solution of the oil (4.4 g, 0.02 mol) in benzene (50 ml) at 27°, sulphur (0.64 g, 0.02 mol) was added in portions over 10 mins. The sulphur dissolved and the solution was refluxed gently for 2 h. Diphenylphosphinothioic chloride was obtained as an oil on evaporation of the reaction solution *in vacuo*. A solution of 4-nitrophenol (1.39 g, 0.01 mol) and triethylamine (1.01 g, 0.01 mol) in dichloromethane (30 ml) was added with stirring to an ice-cooled solution of diphenylphosphinothioic chloride (2.53 g, 0.01 mol) in dichloromethane (20 ml). The solution was stirred overnight at room temperature and washed twice with dilute HCl to remove triethylammonium chloride; an oil was obtained after drying the solution (Na_2SO_4) and evaporation. The oil gave, on trituration with absolute alcohol, crystals which were recrystallised with benzene–light petroleum to yield a micro-crystalline solid.

The series of aryl phosphorodimorpholidothionates was prepared by the general method outlined for the 4-nitrophenyl derivative. Thiophosphoryl chloride (Maybridge Chemical Company; 7.8 g, 0.046 mol) was added slowly to an ice-cooled solution of 4-nitrophenol (6.35 g, 0.046 mol) and pyridine (14.6 ml, 0.138 mol) in dichloromethane (50 ml). A solution of morpholine (26 g, excess) in dichloromethane (30 ml) was then added dropwise with stirring and cooling in ice. After stirring the mixture at room temperature for *ca.* 1 h the solvent was removed under vacuum and the resultant oil crystallised from ethanol–water to give needles.

Identities and structures of the substrates were confirmed by i.r. and n.m.r. (Perkin-Elmer R10 and JEOL PS 100 MHz instrument), and by mass spectrometry. Table 1 collects the physical data for the substrates. Analytical, spectral, and some selected kinetic data are given in Supplementary publication No 21371 (5 pp.).*

Buffer components were of analytical reagent grade or were recrystallised before use; amines were purified by recrystallisation of their hydrochloride salts or by distillation. 4-Nitrophenyl *NN*-diphenylphosphorodiamidate was from a previous study.[1]

Methods.—Reaction rates were measured by observing the change in visible or u.v. absorbance with time using a Unicam SP 800 instrument fitted with a repetitive scanning attachment (SP 825) and a Servoscribe recording potentiometer. Scanning experiments gave the best wavelength (Table 1) for following the hydrolyses and also gave an indication as to stoicheiometry and identity of products (see Table 1 for isosbestic wavelengths). A typical kinetic procedure involved equilibrating the hydrolysis mixture [for example 2.5 ml of a solution of NaOH in 50% ethanol–water (v/v)], in a quartz cell sealed with a Teflon stopper, for 10 min at the operating temperature and then adding a stock solution of the ester in ethanol (0.025 ml), mixing, and recording the change of absorbance with time. Pseudo-first-order rate constants were determined using infinity values taken after 5—6 half-lives and random checks using the Guggenheim method gave identical results. Some hydrolyses were followed using a Unicam SP 600 u.v. spectrophotometer connected to a Servoscribe recorder. Very slow rate constants were measured by the method of initial rates using as an infinity value for each rate the optical density calculated from the known molarity of the ester and the extinction coefficient of the released phenolate anion in the solvent.

* For details of Supplementary Publications see Notice to Authors No. 7 in *J.C.S. Perkin II*, 1974, Index issue.

Table 1 includes wavelengths used for spectral titration of some of the esters in increasing hydroxide concentrations. The very reactive esters were not titrated because the absorption changed too rapidly for a reading to be obtained at zero time without elaborate extrapolation. In any case an extrapolation technique had to be employed even for the less reactive esters. The results were analysed using equation (1); for an ionisation equilibrium the absorbance of the solution at a given hydroxide ion concentration is the sum of the absorbances of both ionised (S^-) and unionised (SH) forms of the substrate. The absorbance at partial

$$A_x - A_0 = A_{tot}\,(1 + K_w/K_a\,[OH^-]) \qquad (1)$$

ionisation is A_x, at zero ionisation A_0, and the absorbance change for full ionisation is A_{tot}.

TABLE 1

Physical properties of substrates

Substituent [d]	M.p.(°C) [b]	λ_k/nm [e]
Substituted phenyl *NP*-diphenylphosphonamidates		
4-NO_2	130—133	400
4-CN	131—134	280
4-CH_3CO	117—119	330
4-Cl	148.5—151	250
H[a](EtOH–H_2O)	143—144	290
Substituted phenyl *NP*-diphenylphosphonamidothionates		
4-NO_2	162—163	400
3-NO_2	123.5—125	280
4-Cl(EtOH–H_2O)	90—92	310
4-CH_3(EtOH–H_2O	98.5—100	270
Substituted phenyl phenylphosphonomorpholidothionates		
4-NO_2(EtOH)	149—150	400
3-NO_2(EtOH)	90—92	300
4-Cl(EtOH)	131—132	302
H(EtOH)	91—92	290
Phenyl phenylphosphonomorpholidate		
H(EtOH)	134—135	290
Substituted phenyl diphenylphosphinothioates		
4-NO_2	88—90	400
4-CH_3CO	69—71	330
4-Cl	75—77	300
H	123—125 [c]	290
Substituted phenyl phosphorodimorpholidothionates		
H	91—92	
4-Cl	166—168	
4-NO_2	185—187	400
4-CH_3CO	114—116	330
2,4-$(NO_2)_2$	113—114	416
2-Cl-4-NO_2	168—171	404
3-NO_2	116—119	

[a] A. Michaelis, *Annalen*, 1896, **293**, 193; 1896, **294**, 1, finds m.p. 63°. However, mass spectral analysis of our material indicates M^+ 309 consistent with ester rather than dianilide which is the only reasonable alternative product. Nitrogen analysis for the dianilide (9.1%) and the i.r. spectrum of an authentic sample of dianilide were significantly different from that of the ester. [b] Determined using a Kofler Thermospan instrument. [c] Hopkins and Vogel [4c] find m.p. 124°. [d] Recrystallisation solvent in parenthesis except when noted in text. [e] Wavelength used for kinetics.

Fitting of the experimental data to theoretical equations was accomplished using Basic Language programmes and the Kent On-line system. The help of Dr. K. T. Taylor and Dr. D. Cook is gratefully acknowledged.

Measurements of pH were carried out using a Radiometer pH meter 25 or a Pye Dynacap instrument both calibrated with E.I.L. standard buffer powders.

Product Analysis.—The principle of the analytical technique used for product analysis in the reaction carried

out in amine buffers was the use of the aromatic hydrogen atoms of the released 4-nitrophenol as markers or standards to compare with the aliphatic hydrogens of the amino-function of the amide product (using n.m.r. signals). A typical procedure involved incubating the 4-nitrophenyl ester (1 g) (added in solution in methanol) in amine buffer (500 ml) under the conditions of the kinetic experiment. The reaction mixture was basified after allowing time for complete reaction and evaporated under vacuum to remove water and excess of amine. The semi-solid residue was twice taken up with water and re-evaporated; the final residue was taken to acid pH, evaporated, and the residue taken up in methanol. The mixture was filtered to remove salt and evaporated; the residue was subjected to n.m.r. spectroscopy and the ratio of one of the four 4-nitrophenol resonances to the amino-hydrogen atoms was a measure of the yield of amide compared with the acid. It was found that our usual technique of acidifying the buffer and extracting 4-nitrophenol with amide using chloroform was not successful owing to the amide not partitioning well out of water.

RESULTS

Hydrolysis.—Hydrolysis of substituted phenyl esters in alkaline media involves a simple 1 : 1 stoicheiometry since

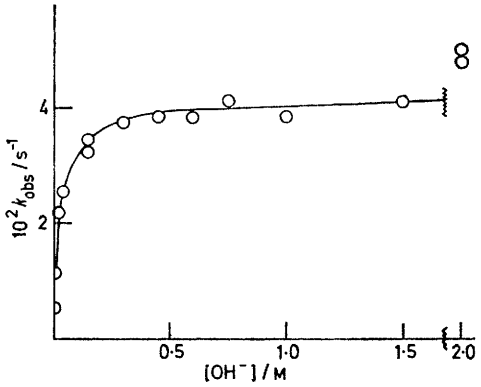


FIGURE 1 Hydroxide ion dependence of the rate of release of 4-nitrophenol from the *NP*-diphenylphosphonamidothionate ester [58.3°; 50% ethanol–water (v/v); ionic strength below 1M- is 1M and above 1M-hydroxide is 2M adjusted with NaCl]. Line is theoretical from parameters in Table 2.

excellent isosbestic wavelengths are observed in many cases during repetitive u.v.–visible scanning of the reaction mixture (Table 1). Checking the absorbance at 400 nm for the hydrolysis of the 4-nitrophenyl derivatives against the expected absorbance calculated from the concentration of the ester and the extinction coefficient of the phenolate in the same solutions indicates that one mole of 4-nitrophenol is released per mole of ester consumed. Since ester concentration was always kept low (*ca.* 10^{-4}M) compared with hydroxide ion or amine buffer concentration pseudo-first-order kinetics in ester were ensured; logarithmic plots were linear up to 80% of the total reaction and in most cases up to 90%. Hydrolysis rate constants for those esters with a labile NH were not proportional to hydroxide ion concentration (Figures 1 and 2) but became constant at high pH. These kinetics may be described by equation (2)

$$k_{obs} = k'/\{1 + K_w/(K_a[OH^-])\} \quad (2)$$

and dissection into the component kinetic constants k' and K_w/K_a for each ester gives values which are collected in Table 2. At even higher concentrations of hydroxide ion

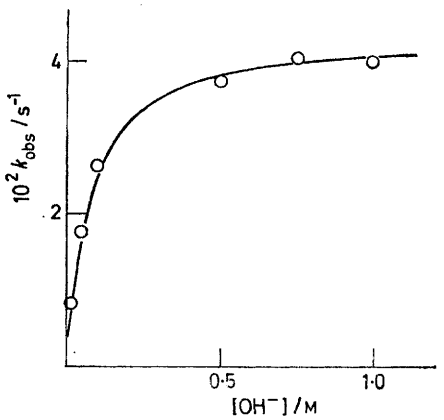


FIGURE 2 Hydroxide ion dependence of the rate of release of 4-nitrophenol from the *NP*-diphenylphosphonamidate ester [27°; 50% ethanol–water (v/v); ionic strength made up to 1M with NaCl]. Line is theoretical from parameters in Table 2

4-nitrophenyl *NP*-diphenylphosphonamidothionate showed a further increase in rate constant and this may be accommodated by equation (2) provided the k' term is replaced by a function linear in hydroxide ion concentration ($k' + k_b[OH^-]$). As we are not interested in the k_b term in this study we have not examined the other esters with a view to its estimation. Hammett ρ values for the various parameters are collected in Table 2 and illustrated in part in Figure 3.

Values of K_w/K_a, obtained by spectrophotometric titration, are given in Table 2 together with the corresponding Hammett selectivity. Values were not obtained for the 4-nitro and 4-cyano esters of the phosphono-series owing to the rapidity with which these esters hydrolyse.

Pseudo-first-order rate constants for the hydrolysis of morpholino, and diphenylphosphinothionate, esters are

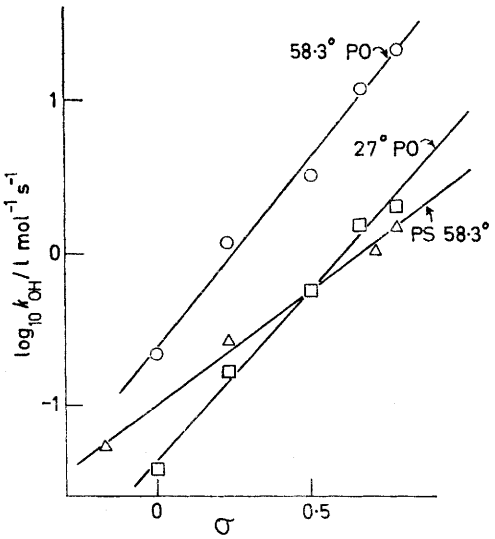


FIGURE 3 Hammett dependencies of apparent bimolecular rate constants ($k'K_a/K_w$) for aryl *NP*-diphenylphosphon-amidate and phosphon-amidothionate ester hydrolysis. σ Values are from G. B. Barlin and D. D. Perrin, *Quart. Rev.*, 1966, **20**, 75, and the lines are theoretical from parameters in Table 2

proportional to hydroxide ion concentration and the bimolecular rate constants are collected in Tables 3—5 together with the corresponding Hammett selectivities.

TABLE 2

Base-catalysed hydrolysis of substituted phosphonamidates [a]

Substituent	$10^2k'/s^{-1}$	$pK_w - pK_a$ [g,h]	k_{OH}–/l mol^{-1} s^{-1}		[OH$^-$]/M [b]
Substituted phenyl *N*-phenylphosphonamidates [e]					
4-NO_2	8.3	1.77	1.9	21 [c]	0.01—1.0 (6)
4-CN	7.1	1.34	1.5	12 [c]	0.001—1.0 (7)
4-CH_3CO	4.4	1.11 (1.24) [a,e]	0.57	3.1 [c]	0.001—1.0 (7)
4-Cl	3.2	0.72 (0.80) [a,e]	0.17	1.2 [c]	0.02—1.0 (6)
H	1.3	0.46 (0.52) [a,e]	0.37	0.22 [c]	0.02—1.0 (6)
ρ [d,f]	0.99 (0.980)	−1.24 (0.993)	2.23 (0.994)	2.49 (0.992)	
Substituted phenyl *NP*-diphenylphosphonamidothionates [e]					
4-NO_2	4.1	1.56	1.5		0.005—2.0 (14)
3-NO_2	3.8	1.43	1.0		0.025—0.75 (6)
4-Cl	1.5	1.23	0.26		0.025—0.6 (5)
4-CH_3	0.77	0.84	0.53		0.049—1.0 (6)
ρ [d,f]	0.78 (0.999)	−0.69 (0.979)	1.48 (0.997)		

[a] 50% Ethanol–water (v/v), 1.0M ionic strength made up with NaCl. [b] Figure in parentheses is the number of concentrations employed. [c] Values for 58.3°. [d] ρ = slope of $pK_a - pK_w$ against σ. [e] Values for 27°. [f] Correlation coefficients in parentheses. [g] $pK_w - pK_a$ Values in parentheses are thermodynamically derived from titration experiments (Table 1 and Results section); $\rho = -1.4$ (r 0.0994). [h] Wavelengths for titration were: 4-CN, 240 nm; 4-CH_3CO, 250 nm; 4-Cl, 250 nm; H, 290 nm.

TABLE 3

Base-catalysed hydrolysis of morpholidate esters [b]

Substituent	10^4k_{OH}–/l mol^{-1} s^{-1}
Substituted phenyl phenylphosphonomorpholidothionate [a]	
4-NO_2	43
3-NO_2	25
4-Cl	3.9
H	1.2
Phenyl phenylphosphonomorpholidate	
H	19

[a] ρ 1.9 (r 0.998). [b] 50% Ethanol–water (v/v); 58.3°; 1.0M ionic strength made up with NaCl.

TABLE 4

Rate parameters for the hydrolysis of substituted phenyl phosphorodimorpholidothionates [a]

Substituent	pK_a of leaving phenol [b]	10^5k_{OH}–/ l mol^{-1} s^{-1}
4-NO_2	7.14	2.32
4-CH_3CO	8.05	1.43
2,4-$(NO_2)_2$	3.96	65.8
2-Cl-4-NO_2	5.45	15

[a] 50% Ethanol–water (v/v); 60°; 1.0M ionic strength made up with NaCl; $\beta_{lg.} = -0.4$. [b] Values for pK_a taken from W. P. Jencks and J. Regenstein, 'Handbook of Biochemistry, Section J-187,' ed. H. A. Sober, Chemical Rubber Company, Cleveland, 1970, 2nd edn.

Trapping Experiments.—In the presence of amine buffers with increasing concentration of basic species at constant buffer ratio and pH the rate of release of 4-nitrophenol from 4-nitrophenyl *NP*-diphenylphosphonamidate and *NN*-diphenylphosphorodiamidate is constant within the limits of experimental observation; we observed a maximum variation in rate constant of *ca.* 3% over a range of 0.1—1.0M total buffer concentration; piperidine, diethylamine, and ethylamine buffers with fraction of base at 0.5 were used for the former ester and ethylamine for the latter (SUP 21371). At a total concentration of 1M-ethylamine buffer the product analysis for both the above ester reactions indicates that the amide and 4-nitrophenol are the major products of the reaction which occur in the ratio 1 : 1.0 ± 0.1 in both cases. The pH of the buffer (1% in methanol), before and after reaction, only varied in the preparative experiments by *ca.* 0.05 units and the experiments only differed from the analytical ones in that a certain amount of precipitation of reactants occurred. We checked that the ethylamine resonances were not due to *residual* ethylammonium salt (which escaped the purging treatment) by repeating the experiment without the addition of ester but with 4-nitrophenol (1 g). The resonances employed for assay of products were the methyl (triplet) and methylene (multiple splitting by methyl protons, the proton on nitrogen, and on phosphorus) of the ethyl group; since the 4-nitrophenyl resonances are not very well resolved in our system ([$^2H_6$] dimethyl sulphoxide) from the other aromatic peaks the error in the analysis we estimate to be of the order ±10%. Product analysis was carried out only for ethylamine buffers.

TABLE 5

Rate parameters for the hydrolysis of substituted phenyl diphenylphosphinothioates [a]

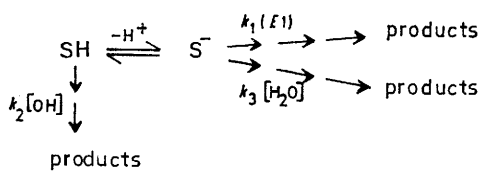
Substituent	σ [b]	10^3k_{OH}–/ l mol^{-1} s^{-1}
4-NO_2	0.78	190
4-CH_3CO	0.50	52
4-Cl	0.23	17
H	0	6.2

[a] 50% Ethanol–water (v/v); 25°; 0.1M ionic strength made up with NaCl; ρ 1.9. [b] σ taken from G. B. Barlin and D. D. Perrin, *Quart. Rev.*, 1966, **20**, 75.

The rate constant for release of 4-nitrophenol from the *NP*-diphenylphosphonamidothionate in the presence of piperidine buffers is linear in total amine concentration (SUP 21371); second-order rate constant for attack of free amine on neutral ester [25°, 1M ionic strength; 20% ethanol–water (v/v)] is 1.6×10^{-4} l mol^{-1}s^{-1} and the overall change in rate constant for a concentration range 0.1—0.8M is 25%.

DISCUSSION

The non-linear dependence of rate of release of phenol on hydroxide ion concentration is consistent with a minimal kinetic scheme [equation (3)] involving hydroxide attack (AE) on an ester whose concentration is depleted (by ionisation) as the pH rises, the *E*1 decomposition of a conjugate base, or water attack (AE) on the



(3)

conjugate base. Attack of hydroxide ion in a bimolecular mechanism on the conjugate base although present is not included in the mechanism [equations (3)] as it only interferes at high pH and in the experiments reported here a sufficiently high pH for this to be important was

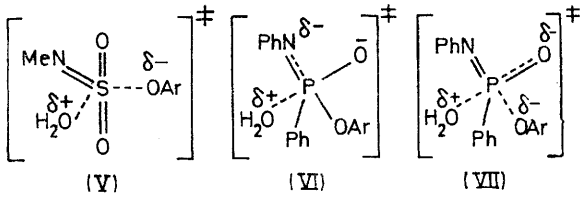
not usually reached (for an example see Figure 1). Steady-state analysis of equation (3), omitting the extra hydroxide term, yields the kinetic equation (4) for the numerator of empirical equation (2).

$$k' = (k_1 + k_3 + k_2K_w/K_a) \qquad (4)$$

NP-*Diphenylphosphonamidates*. Attack of hydroxide ion on aryl diphenylphosphinates, phosphorodimorpholidates, and diethyl phosphates has Hammett ρ selectivities of 1.55,[5] 1.47,[1] and 1.26 [6] respectively. At 27 and 58.3° the Hammett selectivity for alkaline hydrolysis of aryl *NP*-diphenylphosphonamidates is 2.23 and 2.49 respectively; the parameter used here is the apparent bimolecular rate constant which is essentially the effect of low hydroxide concentrations on the rate where little conjugate base is present. The high selectivity towards substituent variation suggests a mechanism different from the AE type and it is possible to calculate the ρ value for k' assuming the AE mechanism holds using a ρ value of 1.4 for k_2, the ρ value for K_w/K_a (known to be −1.24), and the equation $k' = k_2K_w/K_a$; this value (1.4 − 1.24 = 0.16) is very much less than that observed for k' (0.99). A further assumption is that a single mechanism holds for the hydrolysis and this is partially justified over the range of substituents employed by the existence of a linear Hammett relationship.

It is possible to eliminate the mechanism involving water attack on phosphorus in an AE process (k_3) provided we can assume that a single mechanism holds. Thus, if $k' \equiv k_3$ then the latter has the value 4.38×10^{-2} s^{-1} at 27° for the acetyl phenyl ester and the rate of attack of water on the neutral molecule should be greater than on the anionic species if both reactions were of the same AE type; since the rate constant is 6.49×10^{-3} s^{-1} at 0.001M-hydroxide ion we can exclude the mechanism giving rise to k_3.

Participation of Solvent in the Transition State.—The mechanism giving rise to k_3 deserves further comment as it is easy to confuse this with one involving participation of water in the *E*1 mechanism (k_1) and it may not be clear from our earlier papers that we believe there to be two distinct processes or extremes. In all probability water is involved with weak binding to the acyl centre in the reactions involving an *E*1cB mechanism. There is indirect evidence that this is so for transfer of phosphate dianions [7] and sulphate [8] and we have recently concluded [9] that aminosulphonate transfer (V) from poor leaving groups involves binding of water with the electrophile. The 'k_3' mechanism involves water attacking the conjugate base in an AE pathway (VI).* The involvement of water in the *E*1 step leads to expulsion of the aryloxy-group and formation of a planar phosphorimidate weakly bonded to water (VII) whereas the 'k_3' mechanism involves water strongly bonded to a four-co-ordinate phosphorus.



(V) (VI) (VII)

Just as there is a continuum between S_N2 and solvent-aided S_N1 mechanisms, so there is a possibility of a continuity between uni- and bi-molecularity for the present case. We have alluded to this in an earlier paper [1] where we try to explain Gerrard and Hamer's observation of inversion of configuration in the hydrolysis of 4-nitrophenyl *N*-cyclohexyl-*p*-methylphosphoramidate (probably wrongly) in terms of an *E*1cB mechanism with solvent participation. For many of the reactions already mentioned [1,2,6-9] the transition states have been shown unambiguously to possess high degrees of *E*1 character, for example by Hammett-σ^- dependence and a large negative Brønsted exponent for the leaving group. Unfortunately, the probes generally employed to demonstrate solvent participation in the transition state such as activation parameters, solvent isotope effects, or solvent changes prove to be ambiguous in this case and although these techniques might be used to indicate *some* solvent participation in the transition state they cannot do so on a quantitative basis. Even leaving aside the possibility of partially rate-determining proton transfer in some cases.[10,11] the distinction between differential solvation of ground and transition states and specific nucleophilic interaction with the solvent shell (providing part of the driving force for fragmentation) is difficult to make, even in principle.

Although one might predict no solvent isotope effect on k' the observed values of k_H/k_D range above unity in many cases (see Table 6) indicating interaction of solvent with conjugate base either by solvation or as a nucleophile. In the case of phosphate and phosphoroamidates there is the possibility of rate-determining proton transfer to the leaving groups either directly or *via* a solvent molecule. The insensitivity of rate to solvent composition [11] indicates that P–O cleavage is not critically dependent on the solvent shell. As pointed out for acetoacetates [12] the ionisation of the second proton would be expected to exert its own solvent isotope effect

* Although there are cases of transphosphorylation where a pentacovalent intermediate would seem to be proven the situation at present is by no means such that we can assume the AE mechanism involves an intermediate as opposed to a concerted S_N2-like process. It makes no difference to our arguments whether or not an intermediate is formed.

[5] A. Williams and R. A. Naylor, *J. Chem. Soc.* (*B*), 1971, 1967.
[6] D. F. Heath, 'Organo-phosphorus Poisons,' Pergamon, Oxford, 1961, p. 79.
[7] (*a*) A. J. Kirby and W. P. Jencks, *J. Amer. Chem. Soc.*, 1965, **87**, 3209; (*b*) S. J. Benkovic and K. J. Schray, 'The Enzymes,' ed. P. D. Boyer, Academic Press, New York, 1972, 3rd edn., vol. 8, p. 209.
[8] S. J. Benkovic and P. A. Benkovic, *J. Amer. Chem. Soc.*, 1966, **88**, 5504.
[9] A. Williams and K. T. Douglas, *J.C.S. Perkin II*, 1974, 1727.
[10] A. J. Kirby and A. G. Varvoglis, *J. Amer. Chem. Soc.*, 1967, **89**, 415.
[11] C. A. Bunton, *Accounts Chem. Res.*, 1970, **3**, 257.
[12] R. F. Pratt and T. C. Bruice, *J. Amer. Chem. Soc.*, 1970, **92**, 5956.

in these cases leading to non-unity values. The results are explicable in terms of a pre-equilibrium formation of zwitterion [10] for the phosphate esters although this explanation is unlikely for the phosphorodiamidates.[1,2]

TABLE 6

Solvent deuterium isotope effects on $E1$ reactions

Substrate	k_H/k_D	Reference
$^-O–SO_2–OC_6H_4NO_2$-*p*	1.26	13
$^-O–P(O)(OH)OC_6H_3(NO_2)_2$	1.45	10
$^-O–P(O)(OH)SC_6H_4NO_2$-*p*	1.78	*a*
$^-O–P(O)(OH)SPh$	1.44	9
$Ph–\bar{N}–P(O)(NHPh)–OC_6H_4NO_2$-*p*	1.30	1
$CH_3–\bar{N}–SO_2–OC_6H_4NO_2$-*p*	1.35	9

[a] S. Milstien and T. H. Fife, *J. Amer. Chem. Soc.*, 1967, **89**, 5820.

In the absence of further information such as the deviations from the Brønsted plots observed for phosphate monoanions mechanistic distinctions are not possible.

Since a near zero entropy of activation is expected for a unimolecular heterolysis, the observed value for 4-nitrophenyl sulphate [8] shows considerable reduction of solvent degrees of freedom. The stricture is also considerable for the anion of 4-nitrophenyl methylaminosulphonate ($\Delta S^{\ddagger} = -8$ cal K^{-1} mol^{-1}) [9] and comparable with the value for water attack on the neutral species (-14 cal K^{-1} mol^{-1}).[9] Studies of the effect of added electrolytes on solvation of aryl sulphates are in favour of no water attack on the monoanion as the hydrolytic route.[13]

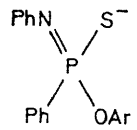
Support for a low degree of nucleophilic involvement by the solvent in $E1cB$ transition states comes from studies of aminolysis reactions of phosphoramidate,[14] 4-nitrophenyl phosphate dianion,[15] and 4-nitrophenyl sulphate [8] which have low Brønsted type exponents (β_{nuc}) of 0.22, 0.13, and 0.20 respectively *versus* the pK_a of the attacking amine. This may indicate very little bond formation in the nucleophilic reactions (*e.g.* solvolysis) of these species compared with the usual high degree of interaction of acyl centres with amines. The interaction involved may be more akin to a solvation of the developing electrophilic centre than to nucleophilic attack on an acyl centre.

In the case of 4-nitrophenyl *NN'*-diphenylphosphorodiamidate and *NP*-diphenylphosphonamidate there is no acceleration of phenol release in amine buffers of increasing concentration at constant pH indicating a rate-determining step *prior* to amine attack and complete absence of bond formation between nucleophile and phosphorus except in a later fast step. By analogy, solvent participation is expected also to be minimal as far as bond formation with the phosphorus is concerned. Product isolation experiments confirm that amide is the product and that the absence of amine buffer effect is not simply due to an absence of reaction.

NP-*Diphenylphosphonamidothionates*. The sensitivity of the apparent hydroxide ion rate constant for aryl *NP*-diphenylphosphonamidothionates to Hammett σ values is $+1.48$; σ values for hydroxide attack at P=S esters where the mechanism is a bimolecular one are $+1.9$ for substituted phenyl phenylophosphonomorpholidothionates (Table 3) and diphenylphosphinothionates (Table 5). The low reactivity of phosphorodimorpholidothionates (Table 4) precludes the use of ordinary Hammett substituents and a $\beta_{1.g.}$ value is the only reasonable measure of selectivity; this value (-0.4) is equivalent to $\rho +0.9$ (we use $\rho +2.23$ from the reference in footnote *b* of Table 5). These data provide no compelling reason to involve an $E1cB$ mechanism for the thio-substrates and the 'saturation' observed for rate with increasing hydroxide concentration (Figure 2) is caused by the depletion of neutral substrate by ionisation which is counterbalanced by an exactly equal increase in hydroxide ion concentration. Care has to be taken in the interpretation of the comparatively large difference in hydroxide rate constant between the 4-nitrophenyl *NP*-diphenylphosphonamidothionate and the corresponding morpholidate (*ca.* 200-fold). Differences of this magnitude have been observed previously by Hamer and Tack [16] who imply that the rate difference lies in a different steric requirement. We believe this explanation is probably correct for our amidothionate as it is well known that substitution at phosphorus in the four-co-ordinate state provides large steric constraint on expansion of the co-ordination number.[17] It is very unlikely, however, that effects of the order of 10^6 for the alkaline hydrolysis of aryl *NN'*-diphenylphosphorodiamidates and -diamidothionates [1,2] are due to anything other than a change in mechanism. The rate difference between phenyl *NP*-diphenylphosphonamidate and its corresponding morpholidate (*ca.* 100-fold) is due to both steric and mechanistic effects because the phenyl ester is extremely close to the borderline between AE and EA mechanisms (see later).

The bimolecular mechanism for solvolysis of the aryl *NP*-diphenylphosphonamidothionates is consistent with the observation that rate acceleration of 4-nitrophenol release from the corresponding ester occurs in amine buffers with increasing concentrations (see Results section).

Comparison of Oxygen and Sulphur Derivatives.—Replacing the oxygen by sulphur in phenyl esters of phenylphosphonamidates swings the mechanism of alkaline



(VIII)

hydrolysis from $E1cB$ to a true bimolecular pathway and the reason for this change in mechanism is probably due to the poorer electron-donating power of the thioanion

[13] E. F. Fendler and J. H. Fendler, *J. Org. Chem.*, 1968, **33**, 3852.
[14] W. P. Jencks and M. Gilchrist, *J. Amer. Chem. Soc.*, 1965, **87**, 3199.
[15] A. J. Kirby and W. P. Jencks, *J. Amer. Chem. Soc.*, 1965, **87**, 3209.
[16] N. K. Hamer and R. D. Tack, *J.C.S. Perkin II*, 1974, 1184.
[17] J. R. Cox and O. B. Ramsay, *Chem. Rev.*, 1964, **64**, 317.

compared with the oxyanion in expelling the phenolate ion [from (VIII)]. This relative ability is not important in the phosphorodiamidates which have the extra driving force of the amine nitrogen lone pairs.

The Government of Northern Ireland and the Ministry of Defence are thanked for grants for K. T. D. and J. S. L. respectively.

[5/032 *Received, 7th January,* 1975]