*E*1cB Mechanisms. Part IV.[1] Base Hydrolysis of Substituted Phenyl Phosphoro- and Phosphorothio-diamidates

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Hydrolysis of substituted phenyl *NN'*-diphenylphosphorothiodiamidates has been measured over a range of hydroxide ion concentration (up to 2M) in 50% ethanol–water (v/v). The pseudo-first-order rate constants in ester obeyed the equation: $k_{obs} = (k_a + k_b[OH])/\{1 + K_w/(K_a'[OH])\}$. The 4-nitrophenyl ester however hydrolysed according to a simple bimolecular rate law: $k_{obs} = k_b[OH]$ which is shown to be a special case of the more complicated equation where $k_a = k_b \, . \, K_w/K_a'$. Spectroscopic titration of the esters yielded values of K_w/K_a' (for ionisation of NH) which when utilised in the above equation enabled values of k_a and k_b to be calculated. The ionisation constant (K_w/K_a') has a high Hammett selectivity ($\rho = -1{\cdot}47$, $r = 0{\cdot}828$) in accord with considerable linkage between the substituent and NH *via* the O–P bond. The parameter k_a ($\rho = +1{\cdot}37$, $r = 0{\cdot}977$) is argued to represent a unimolecular elimination of phenol from the conjugate base (monoanion) of the ester to form a phosphorothioimidate which rapidly decomposes to acid. The parameter k_b, on account of its high Hammett selectivity and its dependence on σ^- ($\rho = +3{\cdot}08$, $r = 0{\cdot}987$), represents the ionisation of the monoanion to yield a conjugate base (dianion) which eliminates a phenolate anion to give a phosphorothioimidate anion. Phenolate-ion character is displayed in the transition-state of the rate-determining step in k_b (the elimination reaction) but not in that for k_a.

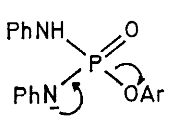
The deuterium oxide solvent isotope effect on k_a was previously suggested to be zero for the general case for the *E*1cB mechanism. We provide evidence to show that this is not true for some esters known unequivocally to hydrolyse *via* the elimination mechanism.

The corresponding phosphyl oxygen esters also show evidence of a hydrolysis reaction proceeding *via* the dianion.

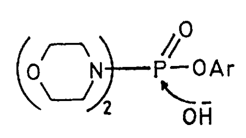
RECENTLY we showed that the hydrolysis of substituted phenyl *NN'*-diphenylphosphorodiamidates hydrolysed in the presence of base according to the kinetic law expressed in equation (1).[2] The term k_a obeyed a good

$$\text{Rate} = [\text{ester}] \, . \, k_a/\{1 + K_w/(K_a' \, . \, [OH])\} \quad (1)$$

Hammett σ relationship ($\rho = 1{\cdot}58$) and this was interpreted as due to insignificant P–O cleavage in the transition-state of the rate-determining step. The selectivity of 1·58 was argued to arise from a mechanism involving decomposition of the conjugate base of the amido-ester (I) and this agreed with the 20,000-fold difference in rate constants between amido-esters possessing ionisable NH groups and phosphorodimorpholidates (II).



(I)



(II)

The good correlation of k_a with Hammett σ values deserves further investigation since this contributor to k_{OH} for aryl carbamates and aryl acetoacetates is σ^- dependent.[3,4] It was considered[2] that the advanced C–O bond cleavage in the transition-state of the carbamate and acetoacetate cases (as opposed to little P–O cleavage) was connected with the greater stability of the isocyanate and keten intermediates compared with the phosphoroimidate (relative to the ground-state). Gerrard and Hamer[5a] discussed factors affecting the relative stability of the 'metaphosphate'-type intermediates and proposed that small electronegative elements on the phosphorus will favour a five-co-ordinated transition-state relative to a trigonal metaphosphate. The relative differential reactivities for P=S and P=O esters reacting *via* elimination–addition rather than addition–elimination mechanisms have been discussed by Katz and Breslow.[5b] The P=S esters favour the former mechanism as the sulphur prefers to remain doubly bound to phosphorus. In this investigation we replace the phosphoryl oxygen (P=O) by a sulphur atom (P=S) as in series (III). It was hoped that the 'metaphosphorimidate' (V) would be stabilised

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[1] Part III, A. Williams and K. T. Douglas, *J.C.S. Perkin II*, 1972, **2112**.

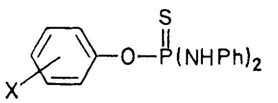
[2] A. Williams and K. T. Douglas, *J.C.S. Perkin II*, 1972, **1454**.

[3] A. Williams, *J.C.S. Perkin II*, 1972, 808.

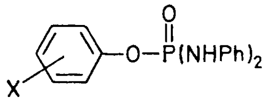
[4] R. F. Pratt and T. C. Bruice, *J. Amer. Chem. Soc.*, 1970, **92**, 5956.

[5] A. F. Gerrard and N. K. Hamer, *J. Chem. Soc.* (*B*), 1969, 369; (*b*) I. R. Katz and R. Breslow, *J. Amer. Chem Soc.*, 1968, **90**, 7376.

sufficiently [over the P=O, (VI)] for the P–O bond to be considerably broken in the transition-state of the rate-determining step for a Hammett σ^- dependence to be observed.



(III)



(IV)

$$PhN{=}P(X)NHPh$$
$$\text{(V) } X = S$$
$$\text{(VI) } X = O$$

EXPERIMENTAL

The phosphorothioate esters (III) were prepared by the following general techniques based on the work described in Part II.[2]

(*A*) Phenol (0·078 mol) and triethylamine (0·078 mol) in dry ether (75 ml) were added dropwise to thiophosphoryl trichloride (from Maybridge Chemical Company; 13·2 g, 0·078 mol) in dry ether (75 ml) and kept for 2 h. The mixture was filtered and evaporated to yield an oil. Aniline (28·1 g, 0·3 mol) in benzene (20 ml) was added to the oil dissolved in dry benzene (50 ml) and stirred for 2 h in an ice-bath. The benzene solution was then washed with dilute HCl and dried (Na_2SO_4). Evaporation yielded crystalline product.

TABLE 1

Analytical and physical properties of substrates [a, e]

Substituted phenyl *NN'*-diphenylphosphorothiodiamidate

Compound	M.p. (*t*/°C)	Found (%) C	Found (%) H	Found (%) N	Formula	Calc. (%) C	Calc. (%) H	Calc. (%) N
4-Nitro [c]	189—191	55·9	4·3	10·7	$C_{18}N_{16}N_3O_3PS$	56·2	4·2	10·9
3-Nitro [c]	159—160	56·1	4·4	10·8	$C_{18}H_{16}N_3O_3PS$	56·2	4·2	10·9
4-Chloro [c]	198—200	57·6	4·4	7·5	$C_{18}H_{16}N_2OPSCl$	57·7	4·3	7·5
4-Acetyl [d]	160—161	63·0	5·2	7·0	$C_{20}H_{19}N_2O_2PS$	62·9	5·0	7·3
Unsubst.[d]	122—123 [b]	63·6	5·1	8·1	$C_{18}H_{17}N_2OPS$	63·6	5·0	8·2

[a] Analyses were by Mr. G. M. Powell of this laboratory using a Hewlett–Packard 185 CHN Analyser. M.p.s. were determined using a Kofler Thermospan instrument. [b] Lit., m.p. 122—123 °C (E. J. Reist, I. G. Junga, and B. R. Baker, *J. Org. Chem.*, 1960, **25**, 666; W. Autenrieth and O. Hildebrand, *Chem. Ber.*, 1898, **31**, 1094, 1111; W. Autenrieth and W. Meyer, *Chem. Ber.*, 1925, **58**, 840, 848. [c] Method (*A*). [d] Method (*B*). [e] Mass-spectral analyses were carried out on the esters to check purity and identity.

(*B*) This method was identical to (*A*) except that dichloromethane was used instead of ether and benzene. The dichloromethane was not evaporated prior to interaction with aniline.

All products were recrystallised from ethanol and the analytical and physical properties are recorded in Table 1. The oxygen analogues of the above esters (IV) are from an earlier investigation.[2] Dioxan was AnalaR grade material and before use was purged of peroxides by percolation through an alumina column. Potassium iodide solution was used to test for the absence of these impurities.

Mass spectral analyses were carried out on an A.E.I. MS 902 high-resolution mass spectrograph.*

Kinetics.—Rates of hydrolysis were measured spectroscopically (Table 2) using a Unicam SP 800 instrument fitted with repetitive scanning attachment (SP 825) and a Servoscribe recording potentiometer. Scanning experiments gave the best wavelength for following the hydrolyses and also gave an indication as to stoicheiometry and identity of products. A typical kinetic procedure involved equilibration of the hydrolysis medium (2·5 ml NaOH in 50% ethanol–water) in Teflon-stoppered silica u.v. cells for 5 min at the operating temperature, followed by addition of the ester and recording of the absorbance change with time. Pseudo-first-order rate constants were determined using calculated infinity values [$A_\infty = A_t^2/(2A_t - A_{2t})$ where A_t = absorbance at times t and it is assumed that absorbance at $t = 0$ is set at zero]. Random checks were made with the Guggenheim [6a] method.

Apparent ionisation constants were determined from the spectral change at different hydroxide ion concentrations (Table 2) and the results were analysed using the equation $A^x - A^\circ = A^c/\{1 + K_w/(K_a' \, . \, [OH])\}$ where A^x and A° are the absorbancies at concentration x and zero of hydroxide ion and A^c is the change in absorbance from non-ionised to ionised species. Where reaction of substrate caused absorbance to change rapidly as in the case of the 4-nitrophenyl ester extrapolation to zero time was employed.

Computer programmes written in Dartmouth Basic were based on improved versions of algorithms already published.[6b] The programmes were run on an Elliott 4130 central computer.†

TABLE 2

Spectral data for substrates *

Substituted phenyl *NN'*-diphenylphosphorothiodiamidate

Compound	λ_t/nm †	λ_k/nm ‡	λ_i/nm §
4-NO_2	280	400	343·8, 250
3-NO_2	275	275	360
4-Cl	275	275	288·8
Unsubst.	285	293	284, 305·5
4-Ac	250	330	293

* Data for the corresponding phosphyl oxygen esters are in Table 2 of reference 2. § Isosbestic wavelength varies according to hydroxide ion concentration. ‡ Kinetic wavelength. † Titration wavelength.

RESULTS

Hydrolysis of the substituted phenyl *NN'*-diphenylphosphorothiodiamidates in alkaline media was judged to be a simple 1 : 1 reaction on account of the excellent isosbestic wavelengths observed during repetitive u.v. scanning of the reacting mixture. Check of the absorbance

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* Carried out by Mr. R. B. Turner under the supervision of Dr. J. F. J. Todd.

† The help of Mr. K. T. Taylor is acknowledged.

[6] (*a*) E. A. Guggenheim, *Phil. Mag.*, 1926, **2**, 538; (*b*) A. Williams, 'Introduction to the Chemistry of Enzymes,' McGraw–Hill, London, 1969.

at 400 nm for the hydrolysis of the 4-nitrophenyl derivative indicated release of 1 mole of 4-nitrophenolate anion per mole ester. Since ester concentration was always kept much lower than the hydroxide ion concentration pseudo-first-order kinetics in ester were observed; logarithmic plots were linear up to 80% of the total reaction and in most cases up to 90%. Hydrolysis rate constants were not however proportional to hydroxide ion concentration (Figure 1—see also Figure 2) but obeyed a kinetic law [equation (2)]:

$$k_{obs} = (k_a + k_b \cdot [OH])/\{1 + K_w/(K_a' \cdot [OH])\} \quad (2)$$

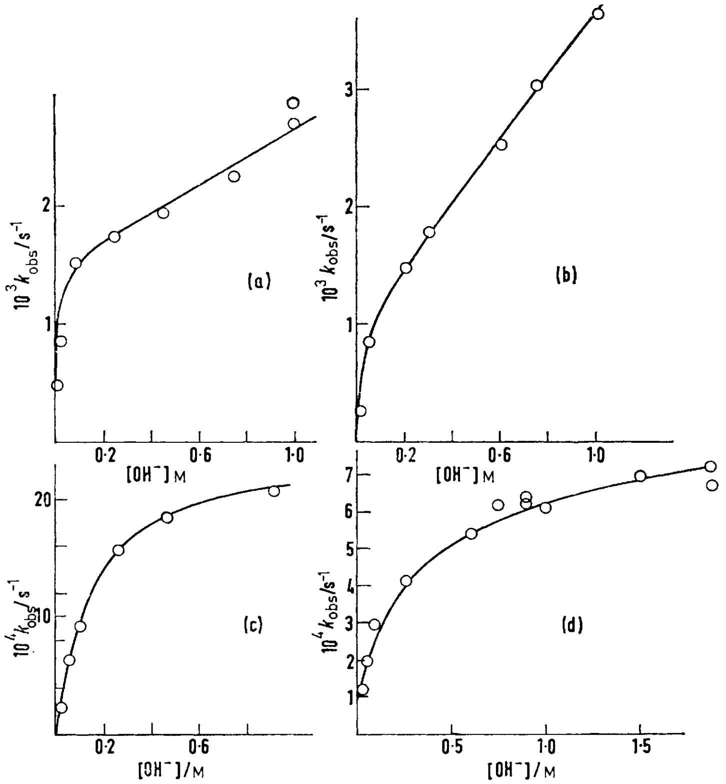


FIGURE 1 Rate constants for hydrolysis of substituted phenyl *NN'*-diphenylphosphorothiodiamidates (III) as a function of hydroxide ion concentration. Lines are theoretical calculated from data of Table 3 and equation (2): (a) = 3-NO_2, (b) = 4-Ac, (c) = unsubst., (d) = 4-Cl

In fact, equation (2) is a simplified version of a more complicated one (see later) involving an extra $[OH]^2$ term in the denominator. However, the hydroxide-ion concentrations available to us are unable to increase the squared term to become experimentally important. Parameters k_a and k_b (Table 3) were obtained for each ester by plotting the function $k_{obs} \cdot ([OH] + K_w/K_a')/[OH]$ *versus* hydroxide ion concentration (Figure 3); the K_w/K_a' term is that determined spectroscopically (Table 3). However, in the case of the 4-chloro- and 3-nitro-esters (III) a slightly different ionisation constant had to be employed to obtain a good fit with the kinetic data. The values were respectively 0·10 and 0·025M but the only significance we place on this difference between 'kinetic' and 'titration' ionisation constants is that the method is sensitive to changes in ionisation constant. For the unsubstituted ester K_b was negligible and the hydrolysis rate constant obeyed a simple Michaelis-Menten saturation type rate law; k_a was derived by methods described in Part II.[2] The identities of k_a and k_b are discussed later in terms of composite rate parameters referring to different mechanisms.

Spectrophotometric titration of the esters yielded values of K_w/K_a' ranging from *ca.* 0·15 to 0·03M (Table 3). A typical titration is shown in Figure 4 for the ionisation of the 4-nitrophenyl ester (III). Unfortunately K_w is unknown for a 50% ethanol–water (v/v) mixture at 58·3° and

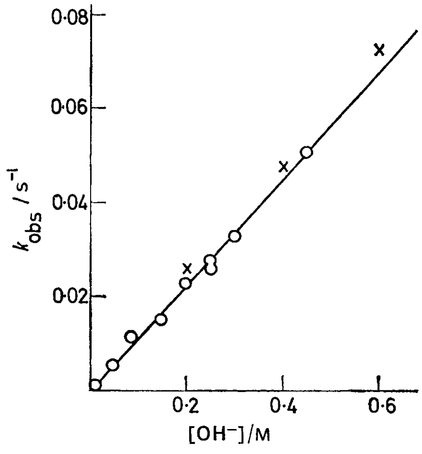


FIGURE 2 Rate constants for the hydrolysis of 4-nitrophenyl *NN'*-diphenylphosphorothiodiamidate as a function of hydroxide ion concentration. Line is theoretical calculated from the data of Table 3 (see Results section); ×, ionic strength = 1·0M; ○, variable ionic strength

TABLE 3

Kinetic and ionisation parameters of substituted phenyl *NN'*-diphenylphosphorothiodiamidates [a]

Compound	(K_w/K_a')/M	$10^4 k_a$/s^{-1}	$10^4 k_b$/l mol^{-1} s^{-1}
Unsubst.[b]	0·153 ± 0·015	2·24 ± 0·14	
3-NO_2	0·0378 ± 0·0058	16·8 ± 0·7	10·8 ± 1·2
4-Cl	0·137 ± 0·03	5·95 ± 0·13	0·85 ± 0·12
4-NO_2 [c]	0·0344 ± 0·0053	37·8 ± 9·3	1110 ± 31
4-Ac	0·0343 ± 0·0061	12·3 ± 0·5	25·6 ± 1·0

[a] 58 3°, 50% ethanol–water (v/v). [b] Plot of k_{obs} *versus* [OH] levelled out completely so a Michaelis–Menten type analysis was used which assumes $k_b = 0$. Value of K_w/K_a' derived from this kinetic analysis was 0·125 ± 0·023 M. [c] Value of K_w/K_a' at 25° is 0·0512 ± 0·0097M.

it is therefore impossible to calculate K_a' from these data. Values of K_w/K_a' follow the Hammett equation: $\log_{10}(K_w/K_a') = -1{\cdot}47\sigma - 0{\cdot}236$.

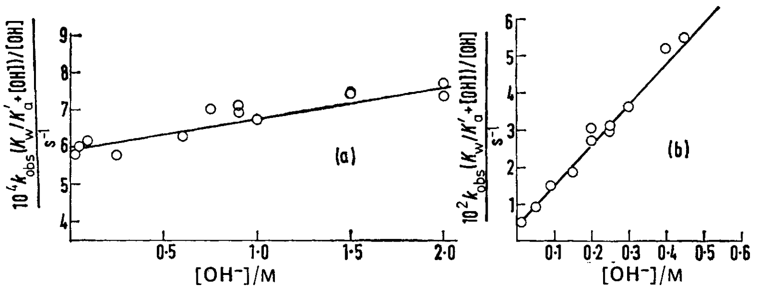


FIGURE 3 Typical hydrolysis data for 4-chlorophenyl (a) and 4-nitrophenyl (b) *NN'*-diphenylphosphorothiodiamidates fitted to a linear function of hydroxide ion concentration. Line is theoretical calculated from the data of Table 3 and rearranged form of equation (2) (see Results section)

The 4-nitrophenyl ester (Figure 2) is interesting because the hydrolysis rate constant does not sensibly deviate from a first-order dependence on hydroxide ion concentration despite the ionisation constant (K_w/K_a' determined spectroscopically) occurring well within the range of hydroxide ion concentrations employed (0·025—1M). Inspection of the kinetic equation (2) reveals that if $k_a = k_b \cdot K_w/K_a'$ then the pseudo-first-order rate constant is given by the equation $k_{obs} = k_b \cdot [OH]$. Effect on the hydrolytic reactivity of a change in ionic strength is minimal as evidenced by inspection of Figure 2. Moreover the change in ionic strength has a minimal effect on the ionisation constant of the 4-nitrophenyl ester (III). The ionic strength kept at 1M yielded $K_w/K_a' = 0{\cdot}0358 \pm 0{\cdot}0040$M whereas under an ionic strength which varied from 0·01 to 1M the value 0·0344 ± 0·0053M was obtained.

The parameter k_a follows the Hammett equation: $\log_{10} k_a = 1{\cdot}37\sigma - 3{\cdot}61$ whereas the parameter k_b fits an equation utilising σ^- $\log_{10} k_b = 3{\cdot}08\sigma^- - 4{\cdot}95$.

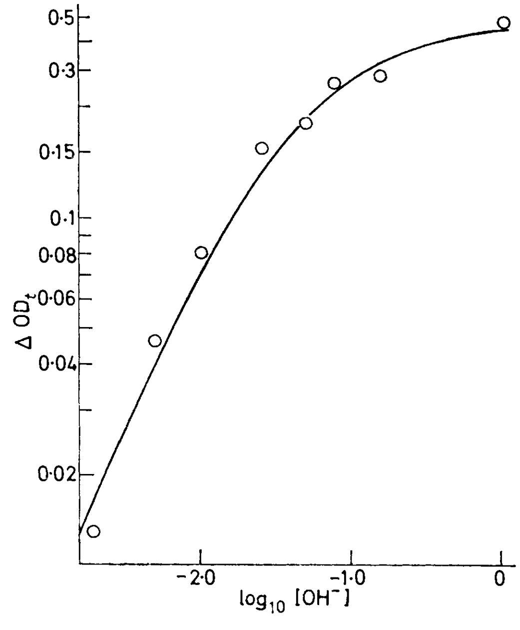


FIGURE 4 Spectrophotometric titration of 4-nitrophenyl *NN'*-diphenylphosphorothiodiamidate. Line is theoretical calculated from data of Table 3 and equation in Experimental section

The hydrolysis of the 4-nitrophenyl ester (IV) was determined at high hydroxide ion concentration to check whether a further hydroxide term was involved. Figure 5 shows that a small but observable extra hydroxide term participates and that equation (2) holds for the oxygen series as well. Study of the hydrolysis of the 3-nitrophenyl, 4-cyanophenyl, 4-chlorophenyl, and 4-acetylphenyl esters (IV) up to 2M-sodium hydroxide in 50% ethanol–water (v/v) at 58·3° revealed a definite increase in k_{obs} in the higher concentration region in concert with a k_b term for all except the 4-chloro-ester. The increase was low as expected from work on the 4-nitrophenyl ester (IV) and not sufficient to enable accurate calculation of k_b.

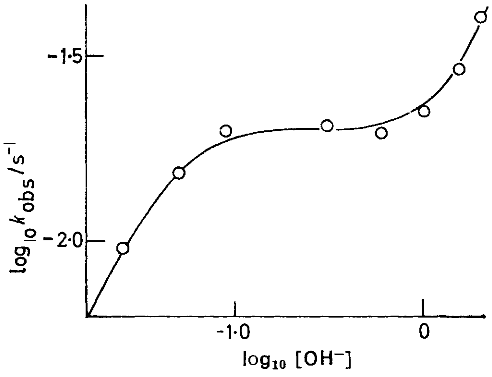


FIGURE 5 Dependence of rate constant for hydrolysis of 4-nitrophenyl *NN'*-diphenylphosphorodiamidate on hydroxide ion concentration (58·3°, 50% ethanol–water, v/v). A k_b term of approximately $2 \cdot 10^{-2}$ l mol^{-1} s^{-1} is calculated for the above conditions

The deuterium oxide solvent isotope effect on kinetic parameters for selected esters of the (III) and (IV) series is shown in Table 4.

TABLE 4

Deuterium oxide solvent isotope effect [a]

Phenyl *NN'*-diphenylphosphorothiodiamidate ($k_a = k_1$) [b]

[OH]/M	0·5	0·6	
$10^4k/s^{-1}$	1·2	1·12	$k_1^H = 1{\cdot}16 \,.\, 10^{-4}\ s^{-1}$
[OD]/M	0·5	0·6	
$10^4k/s^{-1}$	1·21	1·28	$k_1^D = 1{\cdot}24 \,.\, 10^{-4}\ s^{-1}$ $k_1^H/k_1^D = 0{\cdot}93$

4-Nitrophenyl *NN'*-diphenylphosphorodiamidate ($k_a = k_1$)

[OH]/M	0·5	0·6	
$10^3k/s^{-1}$	7·61	7·54	$k_1^H = 7{\cdot}57 \,.\, 10^{-3}\ s^{-1}$
[OD]/M	0·5	0·6	
$10^3k/s^{-1}$	5·86	5·73	$k_1^D = 5{\cdot}80 \,.\, 10^{-3}\ s^{-1}$ $k_1^H/k_1^D = 1{\cdot}3$

4-Acetylphenyl *NN'*-diphenylphosphorothiodiamidate ($k_b = k_5 \,.\, K_a''/K_w$) [c]

[OH]/M	1·0	0·75	0·5	
$10^3k/s^{-1}$	3·29	2·80	2·05	$k_b^H = 2{\cdot}58 \,.\, 10^{-3}\ l\ mol^{-1}\ s^{-1}$
[OD]/M	0·952	0·714	0·476	
$10^3k/s^{-1}$	4·10	3·49	2·43	$k_b^H = 3{\cdot}25 \,.\, 10^{-3}\ l\ mol^{-1}\ s^{-1}$ $k_b^D/k_b^H = 1{\cdot}37$

4-Nitrophenyl *NN'*-diphenylphosphorothiodiamidate [d]

[OH]/M	0·1	0·1	
$10^2k/s^{-1}$	1·12	1·2	$(k_1K_a'/K_w)^H = 1{\cdot}16 \,.\, 10^{-1}\ s\ mol^{-1}\ s^{-1}$
[OD]/M	8·13	8·13	
$10^2/ks^{-1}$	1·62	1·65	$(k_1K_a'/K_w)^D = 2{\cdot}02 \,.\, 10^{-1}\ l\ mol^{-1}\ s^{-1}$ $k^D/k^H = 1{\cdot}74$

[a] 58·3°. [b] 40% Dioxan–water (v/v). [c] 25% Dioxan–water (v/v). [d] 50% Dioxan–water (v/v); the measurements in deuterium oxide were made at concentrations below that of K_w/K_a' to ensure no incursion of k_b; in the case of water such precautions are not necessary owing to the special relationship between k_a and k_b (see Results section).

TABLE 5

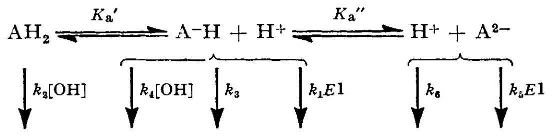
Comparison of kinetic and equilibrium parameters for oxygen and sulphur esters [a,c]

Parameter	Oxygen	Sulphur
K_w/K_a'/M	0·204	0·153
k_1/s^{-1}	$7{\cdot}15 \,.\, 10^{-4}$	$2{\cdot}24 \,.\, 10^{-4}$
k_{OH}/l mol^{-1} s^{-1} [b]	$3{\cdot}48 \,.\, 10^{-3}$	$3{\cdot}42 \,.\, 10^{-3}$
k_b [d] l mol^{-1} s^{-1}	$2{\cdot}10^{-2}$	$11{\cdot}1 \,.\, 10^{-2}$
Hammett ρ (K_w/K_a')	−1·27	−1·47
Hammett ρ (k_1)	+1·58	+1·37
Hammett ρ (k_{OH}) [b]	+2·84	+2·84

[a] 50% Ethanol–water (v/v), 58·3°. [b] $k_{OH} = k_1 \,.\, K_a'/K_w$ and is a composite parameter 'bimolecular' in ester and hydroxide ion concentration. [c] The unsubstituted phenyl ester is compared. [d] For the 4-nitrophenyl ester.

DISCUSSION

The alkaline hydrolysis of substituted phenyl *NN'*-diphenylphosphorothiodiamidates theoretically goes *via* the mechanism of Scheme 1. Analysis of this scheme yields the theoretical kinetic equation (3). Since only one kinetic inflection is observed in the profile of k_{obs} *versus* hydroxide ion concentration (Figure 1) we can assume that the term $K_a'' \,.\, [OH]/K_w$ is negligible.



SCHEME 1

$$k_{obs} = \frac{k_2(K_w/K_a') + k_3 + k_1 + (k_4 + (K_a''/K_w)k_5 + k_6)[OH]}{\{1 + K_a''/K_w)[OH] + K_w/(K_a' \,.\, [OH])\}} \quad (3)$$

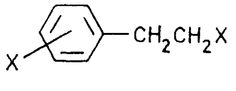
The $K_a'' \,.\, k_5 \,.\, [OH]/K_w$ term in the numerator of equation (3) is not necessarily negligible. Rearranging equation (3) with this assumption yields equation (4)

$$k_{obs}\{1 + (K_w/K_a')/[OH]\} = K_w \,.\, k_2/K_a' + k_3 + k_1 + (k_4 + k_6 + K_a'' \,.\, k_5/K_w)[OH] \quad (4)$$

which is analogous to the experimental kinetic expression [equation (2)]. The parameter k_3 refers to bimolecular attack of water on the monoanion (AH$^-$); argument similar to that employed for the elimination of the analogous term from hydrolysis of carbamates [3] and phosphoramidates [2] eliminates k_3 as a contributor. For example the 4-nitrophenyl ester (III) has $k_a = 3{\cdot}78 \,.\, 10^{-3}$ s^{-1} and if this is dominated by the k_3 term then k_3 has this value which is larger than the smallest observed rate constant for hydrolysis of the ester ($1{\cdot}15 \,.\, 10^{-3}$ s^{-1} at [OH] = 0·01M); thus k_3 is negligible.

A sensitivity argument is used to eliminate the k_2 term as a contributor to k_a (bimolecular attack of hydroxide ion on the neutral ester, *B*Ac2). If k_2 is dominant then the Hammett sensitivity of k_a to change in substituent ($k_a = k_2 \,.\, K_w/K_a'$) is that for k_2 plus that for K_w/K_a'. The sensitivity for k_2 can be estimated since a study to be reported from this laboratory [7] shows *B*Ac2 attack of hydroxide on a P=S(OAr) ester to have a ρ value of *ca.* +1·6 and correlates with σ.* The sensitivity for K_w/K_a' determined spectroscopically is −1·47 thus the sensitivity of k_a is calculated to be 1·6−1·47 ≈ +0·1 which does not agree with the observed value of +1·37.

Thus the k_a parameter is probably a measure of k_1 the *E*1 expulsion of an aryloxide anion from the conjugate base (AH$^-$). The Hammett sensitivity to σ is close to that observed in the analogous phosphyl oxygen series.[1] It is not possible to compare this sensitivity with other *E*1 reactions; Bunnett has tabulated ρ values for the



(VII)

elimination of HX from phenylethyl derivatives (VII) and these range from +2 to +3·8 but are not analogous

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* Studies from this laboratory [7] to be reported in the future indicate that 4-nitrophenyl phosphorothiodimorpholidate has a bimolecular rate constant of 3·8 10^{-5} l mol^{-1} s^{-1} at 80° in 50% ethanol–water (v/v) for reaction with hydroxide ion. Allowing for differences in temperature between these studies and the present one the rate enhancement of the 4-nitrophenyl ester (III) over the corresponding dimorpholidate is greater than 10,000-fold in accord with a different mechanism. There is little doubt that the alkaline hydrolysis of the dimorpholidate is *B*Ac2. The Hammett ρ value of *ca.* 1·6 refers to hydroxide ion attack on substituted phenyl *NN*-phenylphenylphosphonothioamidates and substituted phenyl phenylphosphonothiomorpholidates; the mechanisms of both these reactions are shown to be *B*Ac2.[7]

[7] A. Williams and K. T. Douglas, unpublished data.

to that for k_1 since the substituent variation is not on the leaving group and the reactions probably involve considerable $E2$ character. The dependence of k_1 on σ rather than on σ^- indicates little P–O bond cleavage in the transition-state for the $E1$ reaction; the oxygen analogue (IV) shows similar behaviour and the sulphur is presumably not able to stabilise the metaphosphate-type intermediate sufficiently.

The inclusion of a strong k_b term marks a qualitative difference between the phosphoryl sulphur (III) and oxygen (IV) series; in the latter only a small k_b term is detectable (Figure 5). It is unlikely that water is an efficient nucleophile for reaction with the dianion and we therefore exclude k_6 as a contributor to k_b. Contribution from k_4, the rate constant for reaction of hydroxide ion with mono-anion (*B*Ac2) is a possibility if the charge is spread sufficiently in the electrophile because hydroxide ion–anion reactions are known.[1,8] It is unlikely however that the sensitivity of k_4 would be as high as $+3{\cdot}1$ and be correlated with σ^-. There is a remote possibility that k_b is *B*Ac2 with a high sensitivity to σ owing to the low reactivity compared with other phosphorus ester series.[9e] However, reactivity changes in a series of similar compounds has been observed concurrent with only small changes in sensitivity.[10] Thus the $E1$ mechanism probably dominates the k_b term; * it is impossible to dissect k_b ($= K_a'' \,.\, k_5/K_w$) into its components owing to the ionisation term being greater than the attainable hydroxide concentrations but the high ρ value is in accord with that for other mixed terms involving an $E1$ mechanism.[2-4] The σ^- dependence is also in accord with other observations on an *E*lcB mechanism.[3,4] If we estimate the selectivity of K_a''/K_w as *ca.* $+2$ then the k_5 has a selectivity of *ca.* $+1$ not significantly different from that for the $E1$ degradation of the mono-anion. Significantly the k_b term has a σ^- Hammett relationship and since it is unlikely that K_a''/K_w contributes this character (there is no possible conjugation of substituent with nitrogen across the phosphorus atom) it can be inferred that the transition-state for the $E1$ mechanism has considerable phenolate anion character.

The relative reactivity of the oxygen and sulphur esters is close to unity (see Table 5); *B*Ac2 attack of hydroxide on the phosphorus atom as a major contributor to k_a would be expected to yield a relative reactivity of *ca.* 100-fold (oxygen to sulphur),[9] since the ionisation constants are similar between oxygen and sulphur derivatives for a given substituent (see Tables 3 and 5 and Table 2 of reference 2). This provides further evidence against participation of the *B*Ac2 mechanism as a major contributor to k_a. The greater reactivity for k_b for sulphur probably resides in the greater ease with which sulphur will donate electrons as the dianion probably has a lot of P–S$^-$ character. This relative reactivity also excludes a *B*Ac2 mechanism.

Selectivity of k_1 to change in substituent is also virtually identical for both ester types (Table 5). Although the value of K_w/K_a' for the unsubstituted esters is similar the sensitivity to change in substituent is larger for the sulphur case; this reflects a 'linkage' through oxygen and phosphorus [in (III)] which is more efficient than that in the oxygen case (IV) [2] which is itself larger than expected.[2]

Deuterium Oxide Solvent Isotope Effect.—Tobias and Kézdy [11] proposed a kinetic isotope method for distinguishing *E*lcB from *B*Ac2 mechanisms where the ionisation of the substrate lies within the range of hydroxide ion concentration used. They rely on the assumption that k_a should have no isotopic dependence if k_1 predominates (since the mechanism for k_1 involves no hydrogen-bond breaking) whereas if the *B*Ac2 term predominates ($k_2 \,.\, K_w/K_a'$) the effect of isotope on k_a is calculated from the known effects on the constituent parameters to be $k_a^D/k_a^H \approx 0{\cdot}65$. The reaction chosen by the above workers to illustrate their proposal was the hydrolysis of 5-nitrocoumaranone [11] which has a plateau rate constant (k_a) with solvent isotope effect of 0·58 (H/D); and they concluded that a *B*Ac2 mechanism held for hydrolysis. No independent evidence was cited to convince us that this secondary isotope effect was not due to differential solvation of the ground and transition-states during an $E1$ process. Convincing evidence has been quoted by Pratt and Bruice [4] that the hydrolysis of aryl acetoacetates is *E*lcB in nature. While doubt has been cast recently on the precise nature of the *E*lcB mechanism (*i.e.* whether it involves a keten intermediate or intramolecular attack at the ester carbonyl by the 3-carbonyl oxygen) [3] the deuterium oxide solvent isotope effect on the plateau rate constant (k_a) points to a *B*Ac2 mechanism if the Tobias and Kézdy criterion is applied. Results quoted in Table 4 indicate that $k_a^D/k_a^H \approx 0{\cdot}75$ for the hydrolysis of the oxygen and sulphur substrates [(IV) and (III) respectively] at variance [in the case of (IV)] with the criterion of Tobias and Kézdy. Finally the hydrolysis of aryl alkylaminosulphonates possesses a plateau solvent deutrium isotope effect of *ca.* 0·75 (D/H) while proceeding *via* an *E*lcB mechanism.[12] The deuterium

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* Another mechanistic possibility is that hydroxide ion could attack the aromatic ring and expel the phosphorus acid as a leaving group. This would give rise to a large Hammett ρ and would correlate with σ^-; oxygen-18 studies using 1·6% oxygen-18 enriched water at high pH (1M-NaOH) gave product 4-nitrophenol with percentage ratio 141/139 [$(M^+ + 2)/M^+$] of 0·850%. Percentage calculated for P–O fission is 0·835% and for Ar–O fission is 2·231%. Nucleophilic aromatic substitution is therefore eliminated. The value of k_b for the 4-nitrophenyl ester (III) is more than 10,000-fold faster than the *B*Ac2 attack of hydroxide ion on 4-nitrophenyl phosphorothiodimorpholidate [7] in agreement with a different mechanism for the two hydrolyses.

[8] R. P. Bell and B. A. W. Coller, *Trans. Faraday Soc.*, 1964, **60**, 1087.

[9] (*a*) J. A. A. Ketelaar, H. R. Gersmann, and F. Hartog, *Rec. Trav. chim.*, 1958, **77**, 982; (*b*) J. A. A. Ketelaar, H. R. Gersmann, and K. Koopmans, *Rec. Trav. chim.*, 1952, **71**, 1257; (*c*) B. Topley, *Chem. and Ind.*, 1950, 859; (*d*) J. A. A. Ketelaar, *Rec. Trav. chim.*, 1950, **69**, 649; (*e*) K. Ginjaar and S. Vel, *Rec. Trav. chim.*, 1958, **77**, 956.

[10] J. F. Kirsch, W. Clewell, and A. Simon, *J. Org. Chem.*, 1968, **33**, 127.

[11] P. S. Tobias and F. J. Kézdy, *J. Amer. Chem. Soc.*, 1969, **91**, 5171.

[12] A. Williams and K. T. Douglas, unpublished observations.

oxide solvent isotope effect is therefore not diagnostic between an *E*1cB or *B*Ac2 mechanism.

The diagnostic situation is similar if the overall bimolecular rate constant (k_{OH}) is employed; an inverse solvent isotope effect can arise from an equilibrium deprotonation followed by elimination[13] or by direct hydroxide ion attack.[3] The former is equivalent to $k_1 . K_a'/K_w$ and the latter to k_2. In the former case $k_{OH}/k_{OD} = (k_1^H/k_1^D) . (K_a'^H/K_a'^D) . (K_w^D/K_w^H)$ and this ratio is equal to $1{\cdot}3 . (K_a'^H/K_a'^D) . 0{\cdot}15$ and varies according to the isotope effect on the ionisation constant K_a' which rises as pK_a' rises).[14] For pK_a values in the region of that of water the calculated ratio would be greater than unity depending on the value taken for k_1^H/k_1^D. Kinetic isotope effects are therefore not reliable probes for this area of chemistry and results for k_b for the 4-acetylphenyl derivative (III) (see Table 4) are therefore only confirmatory evidence for an *E*1cB mechanism.

When the pre-equilibrium deprotonation is not exceptionally much faster than the overall reaction as in carbon acids product composition studies in deuterium oxide solvent are diagnostic;[15] this tool is not useful generally for nitrogen acids where proton exchange is infinitely faster than reaction.

Effect of general bases on the hydrolysis rate constant has been utilised as a criterion for the *E*1cB mechanism for carbon acids.[16a] This criterion is ambiguous unless combined with other data because although a curved plot of rate constant *versus* free base concentration is predicted for Scheme 2[16a] for a constant buffer ratio the

$$\mathrm{SH} \underset{k_{BH}[\mathrm{BH}]}{\overset{k_B[\mathrm{B}]}{\rightleftharpoons}} \mathrm{S}^- \xrightarrow{k_1(E1)} \text{products}$$

SCHEME 2

same can be predicted for the ' blind-alley ' mechanism of Scheme 3. The kinetic parameters governing the dependencies will have a different meaning in each case.

$$\mathrm{S}^- \underset{k_B[\mathrm{B}]}{\overset{k_{BH}[\mathrm{BH}]}{\rightleftharpoons}} \mathrm{SH} \xrightarrow[(BAc2)]{k_{OH}[\mathrm{OH}]} \text{products}$$

SCHEME 3

Kirby and Lloyd[16b] have recently found similar curved plots of rate constant *versus* *N*-methylmorpholine concentration in the hydrolysis of aryl hydrogen malonates. This criterion cannot in any case be applied to nitrogen or oxygen acids where proton exchange is too fast to be catalysed by general bases; the effect of added bases is minimal on such *E*1cB mechanisms.[13,*]

The Government of Northern Ireland is thanked for a Studentship (K. T. D.).

[2/2001 *Received*, 22*nd August*, 1972]

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[*] A referee posed the question ' is EtO⁻ or OH⁻ active in catalysis? ' The base serves only to absorb the proton removed from the amide group and since the transfer is fast, the base cannot act as a catalyst. The position of equilibrium which determines the overall rate depends on the pK_a of ethanol and water in the ethanol–water medium together with the total hydroxide concentration. Up to 1M-sodium hydroxide (constant ionic strength) for the ethanol–water (50/50; v/v) medium ionisation of the amides obeys the simple law—$[\mathrm{base}]/([\mathrm{OH}^-][\mathrm{acid}]) = \text{constant}$—exactly but this may not be true above that molarity despite keeping the ionic strength constant. These results imply that the use of an H_- function in discussing the kinetics is an unnecessary complication. Clearly our qualitative discussion of the kinetics in the hydroxide concentration range far greater than 1M (*e.g.* Figure 1 and for the other oxygen analogues) although correct would require use of an H_- function for quantitative study. Experimentally, the titration of these phosphoramidates and those amides reported in Parts II[2] and III[1] of the series gave clean isosbestic wavelengths and could possibly act as indicators for H_- function measurements.

The precise meaning of the experimental K_w/K_a' terms quoted in the Tables is not certain. A referee pointed out that some EtO^- exists in basic ethanol–water solutions (E. F. Caldin and G. Long, *J. Chem. Soc.*, 1954, 3737 and K. Bowden, *Canad. J. Chem.*, 1965, **43**, 2624). However, in media of a constant composition of ethanol–water the ratio $[\mathrm{EtO}^-]:[\mathrm{OH}^-]$ must remain constant; the observed K_w/K_a' term needs to be multiplied by the term $(1 + [\mathrm{EtO}^-]/[\mathrm{OH}^-])$ to obtain the ' true ' K_w/K_a'. Since a number of equilibria have not been measured we shall not pursue these calculations but note that the multiplication factor is a constant for the given medium.

[13] M. L. Bender and R. B. Homer, *J. Org. Chem.*, 1965, **30**, 3975.

[14] R. P. Bell, ' The Proton in Chemistry,' Methuen, London, 1959, p. 188.

[15] P. Müller, D. F. Mayers, O. R. Zaborsky, and E. T. Kaiser, *J. Amer. Chem. Soc.*, 1969, **91**, 6732.

[16] (*a*) B. Holmquist and T. C. Bruice, *J. Amer. Chem. Soc.*, 1969, **91**, 2993; (*b*) A. J. Kirby and G. J. Lloyd, *Chem. Comm.*, 1971, 1538.