*E*1cB Mechanisms. Part II.[1] Base Hydrolysis of Substituted Phenyl Phosphorodiamidates

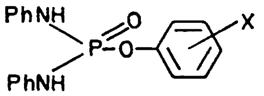
By **Andrew Williams** * and **Kenneth T. Douglas**, University Chemical Laboratories, Canterbury, Kent

Reaction of hydroxide ion with substituted phenyl *NN'*-diphenylphosphorodiamidates (I) was measured at 60 °C in 50% ethanol–water (v/v) medium. Rate constants followed the law $k_{obs} = k'/[1 + K_w/(K_a . OH)]$; K_a/K_w fitted a good Hammett relationship ($\rho = 1{\cdot}27$, $r = 0{\cdot}994$) indicating considerable ' linkage ' through oxygen and phosphorus. The term k' obeyed a good Hammett σ relationship ($\rho = 1{\cdot}58$, $r = 0{\cdot}980$); this is interpreted as insignificant P–O cleavage in the transition state of the rate-determining step. Selectivity of 1·58 is argued to arise from a mechanism involving decomposition of the conjugate base of (I). Arguments are presented which eliminate S_N2(P) attack of water on the anion of (I) and S_N2(P) attack of hydroxide ion on the neutral ester as contributors to k'. The ester 4-nitrophenyl phosphorodimorpholidate has a bimolecular rate constant for base hydrolysis some 20,000-fold *smaller* than the apparent bimolecular rate constant ($k_2 = k'K_a/K_w$) for alkaline hydrolysis of 4-nitrophenyl *NN'*-diphenylphosphorodiamidate (Ia) in accordance with a different mechanism for the latter. The difference is a reflection of a more favourable enthalpy and entropy of activation.

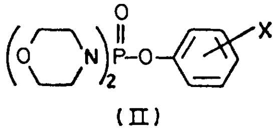
The absence of racemisation in alkaline hydrolysis of methyl 4-nitrophenyl *N*-cyclohexylphosphoramidothioate is suggested to be due to more rapid attack of solvent on the planar imidate intermediate (in the *E*1cB mechanism) than departure of 4-nitrophenolate anion from the solvent cage.

RECENT work from this laboratory has shown that a Hammett σ^- relationship with a high slope is diagnostic of an *E*1cB mechanism in the alkaline hydrolysis of substituted phenyl *N*-phenylcarbamates.[1] Another hydrolysis with an *E*1cB mechanism, the hydrolysis of aryl acetoacetates, also exhibits these symptoms.[2] For some time the *E*1cB mechanism has been supposed to operate in the alkaline hydrolysis of esters and halides of phosphoroamidates.[3] Evidence for the *E*1cB mechanism has been largely the great difference in alkaline rate constants between mono- and di-substituted nitrogen esters and halides. This was originally attributed by Heath [4a] to steric inhibition of the approach of hydroxide in an S_N2(P) mechanism (in the fully substituted substrate) and later [4b] to hydrogen-bonding of hydroxide ion to the NH of the substrate. However the magnitude of the effect is at least 100-fold larger than the steric effect expected by extrapolating from the results of Hudson and Keay;[5] moreover, Traylor and Westheimer [6] showed that nucleophiles other than hydroxide were not similarly activated. Crundon and Hudson [3c] showed that 2,6-lutidine catalysed the hydrolysis of *NN'*-diethylphosphorodiamidic chloride but not that of diethyl phosphoryl chloride. Gerrard and Hamer [7] recently showed that alkaline hydrolysis of methyl *N*-cyclohexylphosphoramidothioic chloride gave a racemic product in accord with a planar intermediate and was 45,000-fold faster than the corresponding dimethyl phosphorothioic chloride. Alkaline hydrolysis of methyl 4-nitrophenyl-*N*-cyclohexylphosphoramidothioate was some 100-fold faster than the corresponding phosphoromorpholidothioate; the difference reflected a more positive entropy of activation in the former case.[8] The products however had the same stereochemical configuration inconsistent with a planar intermediate in the ester hydrolysis. The alkaline hydrolysis of 4-nitrophenyl *NN'*-diphenylphosphorodiamidate and the corresponding *NN'*-dimethyl analogue was found by Coult and Green [9] to proceed more slowly than reaction with hydroperoxide anion a reactivity difference in accord with an S_N2(P) mechanism.

In this study we investigate the effect on rate constant of changing the substituent in the phenyl ester in compounds (I) and (II) as a diagnostic tool for mechanism.



(I)



(II)

a; X = 4-NO_2
b; X = 3-NO_2
c; X = 4-CN
d; X = 4-Ac
e; X = 4-Cl
f; X = 3-Cl
g; X = H
h; X = 4-Me
i; X = 4-MeO

EXPERIMENTAL

Materials.—Substituted phenyl phosphorodimorpholidates (Table 1) were prepared by the following general method (applied to the unsubstituted phenyl ester): phenyl phosphorodichloridate (5 g) in dichloromethane (5 ml) was added to a solution of morpholine (8·7 g) in dichloromethane (15 ml). The mixture was kept at room temperature for 2 h and then filtered to remove morpholine hydrochloride. The precipitate was washed with dichloromethane (10 ml) and the filtrate extracted with dilute hydrochloric acid (5N), dried ($MgSO_4$), and evaporated. The product was recrystallised from light petroleum (b.p. 120—160 °C).

Substituted phenyl-*NN'*-diphenylphosphorodiamidates

---

[1] A. Williams, *J.C.S. Perkin II*, 1972, 808, is considered to be Part I.

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

[3] (*a*) F. H. Westheimer, *Chem. Soc. Special Publ. No.* 8, 1957, 1180; (*b*) D. Samuel and F. H. Westheimer, *Chem. and Ind.*, 1959, 51; (*c*) E. W. Crundon and R. F. Hudson, *Chem. and Ind.*, 1958, 1478; *J. Chem. Soc.*, 1962, 3591.

[4] (*a*) D. F. Heath, *J. Chem. Soc.*, 1956, 3796; (*b*) D. F. Heath, ' Organo-phosphorus Poisons,' Pergamon Press, Oxford, 1961, p. 87.

[5] R. F. Hudson and L. Keay, *J. Chem. Soc.*, 1956, 2463.

[6] P. S. Traylor and F. H. Westheimer, *J. Amer. Chem. Soc.*, 1965, **87**, 553.

[7] A. F. Gerrard and N. K. Hamer, *J. Chem. Soc.* (*B*), 1968, 539.

[8] A. F. Gerrard and N. K. Hamer, *J. Chem. Soc.* (*B*), 1967, 1122.

[9] D. B. Coult and M. Green, *J. Chem. Soc.*, 1964, 5478.

were prepared by the following general methods. Method A[10] (described for the 4-acetyl ester) was used for the 4-acetyl- and 4-cyano-phenols.

A. 4-Acetylphenol (6·3 g), phosphoryl chloride (5·6 ml), and pyridine (14·6 ml) were dissolved in dichloromethane (50 ml) at 0 °C. This mixture, after being kept for ½ h, was added to a solution of aniline (28 ml) in dichloromethane (30 ml) cooled in an ice-bath. The solution was kept for 1 h at room temperature, evaporated, and taken up in ethanol–water (85%, v/v). Crystals of the product precipitated after a short while. The product was recrystallised from ethanol–water (85%, v/v).

TABLE 1

Analytical and physical properties of substrates [a]

Ester	M.p. (°C)	Found (%)			Formula	Calc. (%)		
		C	H	N		C	H	N
Substituted phenyl *NN'*-diphenylphosphorodiamidates (I)								
(Ia)	169—170 [b,e]	58·5	4·4	11·6	$C_{18}H_{16}N_3O_4P$	58·5	4·3	11·4
(Ib)	171—173 [e]	58·3	4·2	11·5	$C_{18}H_{16}N_3O_4P$	58·5	4·3	11·4
(Ic)	179—181	66·3	4·4	11·8	$C_{19}H_{16}N_3O_2P$	66·4	4·5	11·7
(Id)	175—177	65·7	5·0	7·5	$C_{20}H_{19}N_2O_3P$	65·5	5·2	7·7
(Ie)	169—171	60·1	4·6	7·7	$C_{18}H_{16}ClN_2O_2P$	60·3	4·5	7·8
(If)	162—165	60·0	4·7	7·8	$C_{18}H_{16}ClN_2O_2P$	60·3	4·5	7·8
(Ig)	165—168 [d]	66·4	5·1	8·9	$C_{18}H_{17}N_2O_2P$	66·6	5·3	8·7
(Ih)	154—156	70·3	5·8	8·4	$C_{19}H_{19}N_2O_2P$	70·5	5·6	8·3
(Ii)	163—164	64·5	5·4	7·8	$C_{19}H_{19}N_2O_3P$	64·5	5·4	7·9
Substituted phenyl phosphorodimorpholidates (II)								
(IIa)	124—125	47·1	5·8	11·6	$C_{14}H_{20}N_3O_6P$	47·0	5·6	11·8
(IIb)	84—86	47·2	5·7	11·7	$C_{14}H_{20}N_3O_6P$	47·0	5·6	11·8
(IIe)	118—120	48·3	5·9	8·2	$C_{14}H_{20}ClN_2O_4P$	48·5	5·8	8·1
(IIg)	82—85 [c]	54·0	6·9	8·8	$C_{14}H_{21}N_2O_4P$	53·9	6·7	9·0
(IIh)	87—89	55·0	7·0	8·8	$C_{16}H_{23}N_2O_4P$	55·2	7·1	8·6
(IIi)	81—82	52·4	6·8	8·1	$C_{16}H_{23}N_2O_5P$	52·6	6·7	8·2

[a] Analyses by Mr. G. Powell of this laboratory using a Hewlett–Packard-185 CHN analyser. M.p.s measured on a Kofler Thermospan instrument. [b] Lit.,[9] m.p. 159 °C. [c] Lit.,[10c] m.p. 85—86 °C. [d] Lit.,[10c] m.p. 179—180 and 169 and 179—180 °C (A. Michaelis, *Annalen*, 1903, **326**, 129). [e] Mass spectra showed M^+ 369 and fragmentation peaks 231 (M − 4-nitrophenol), 138 (4-nitrophenol), and 93 (aniline).

B. Phenyl phosphorodichloridate (4·2 g) was added gently to aniline (7·4 g) in a boiling tube. Considerable heat was evolved and liquefaction was effected with a bunsen flame (some dichloridates did not need extra heat). The material was crystallised as in A.

Substituted phenyl phosphorodichloridates were prepared by refluxing the phenol and excess of phosphoryl chloride for *ca.* 6 h in the presence of potassium chloride as catalyst.[11] Fractional distillation under vacuum gave the required dichloridate in good yield. This method was not suitable for the 4-acetyl- or 4-cyano-phenols which decomposed on refluxing with phosphoryl chloride.

Dioxan was AnalaR 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.

Kinetics.—Rates of hydrolysis were measured with a Unicam SP 600 u.v. spectrometer connected to a Servoscribe recorder. Some of the reactions with the morpholino-esters were very slow but the base line was found to be constant up to a time limit of two days. A Unicam SP 800 instrument (equipped with a repetitive scanning attachment, SP 825) was employed to determine the best wavelength for kinetic studies *via* repetitive scanning of a sample during reaction. A typical kinetic procedure involved equilibrating the hydrolysis mixture (2·5 ml NaOH in 50% ethanol–water) in a quartz cell sealed with a Teflon stopper for 5 min at the operating temperature and then adding a stock solution of the ester in ethanol (0·025 ml), shaking, and recording transmittance with time. Pseudo-first-order rate constants were determined by use of calculated infinity values for the slow reactions: $A_\infty = A_t^2/(2A_t - A_{2t})$ where A_t = absorbance at time t, and it is assumed that absorbance at time t = 0 is set at zero. For faster reactions experimental infinity values were employed. Random checks by use of the Guggenheim[12] method gave identical results.

Apparent ionisation constants were determined spectroscopically with a Unicam SP 800 machine. Where reaction of the substrate caused absorbances to change as in the 4-nitrophenyl ester (Ia) these were extrapolated to zero time.

Fitting of the experimental data to theoretical equations (see later) was accomplished by use of ' Basic Language ' programmes and the Kent ' on-line ' system. The help of Mr. K. T. Taylor and Dr. D. Cook is gratefully acknowledged. Copies of the programmes, which are related to earlier algorithms,[13a] are available on request.

Mass spectra were determined by Mr. R. B. Turner under the supervision of Dr. J. F. J. Todd (AEI MS902 high-resolution mass spectrometer).

RESULTS

Alkaline hydrolysis of aryl *NN'*-diphenylphosphorodiamidates in 50% ethanol–water obeyed good first-order kinetics up to 90% of the total reaction. Hydrolysis of the 4-nitrophenyl ester (Ia) gave the theoretical amount of 4-nitrophenol as judged from the product spectrum and extinction coefficient of 4-nitrophenol in the hydrolysis mixture. Good isosbestic wavelengths determined by repetitive scanning of the hydrolysis reaction (Table 2) also

---

[10] (*a*) L. F. Audrieth and A. D. F. Toy, *J. Amer. Chem. Soc.*, 1941, **63**, 2117; (*b*) 1942, **64**, 1337; (*c*) 1942, **64**, 1553.

[11] Houben and Weyl, ' Methoden der Organischen Chemie,' Georg Thieme Verlag, Stuttgart, 1963, vol. 12 (part 2), p. 216.

[12] E. A. Guggenheim, *Phil. Mag.*, 1926, **2**, 538.

[13] (*a*) A. Williams, ' Introduction to the Chemistry of Enzymes,' McGraw-Hill, New York, 1969, p. 119; (*b*) G. N. Wilkinson, *Biochem. J.*, 1961, **80**, 324.

TABLE 2

Base-catalysed hydrolysis of substituted phenyl *NN′*-diphenylphosphorodiamidates [a]

Ester	λ_k [b]/ nm	λ_i [c]/nm	$10^4k'$/s^{-1}	K_a/K_w / l mol^{-1}	k_{OH}/ l mol^{-1} s^{-1}
(Ia)	400	340, 247	154 ± 7	54·5 ± 0·5	0·838
(Ib)	300	292, 249	100 ± 3	44 ± 0·6	0·440
(Ic)	300	265	110 ± 2	35·4 ± 0·3	0·39
(Id)	300	292, 244	97 ± 3	18 ± 0·1	0·175
(Ie)	300	249	27 ± 0·3	8·7 ± 0·05	0·0235
(If)	300	285, 249	43·5 ± 0·4	12·4 ± 0·06	0·054
(Ig)	300	273	7·15 ± 0·41	4·9 ± 0·03	0·00348
(Ih)	300	254, 276	4·0 ± 0·06	3·6 ± 0·02	0·00144
(Ii)	300	253, 286	5·0 ± 0·09	2·2 ± 0·01	0·0011

[a] 60 °C, 50% ethanol–water (v/v). [b] Kinetic wavelength. [c] Isosbestic wavelengths. [d] Apparent bimolecular rate constant obtained from $k'K_a/K_w$.

indicate a 1 : 1 stoicheiometry (these wavelengths will depend on hydroxide concentration owing to ionisation of the NH group). Rate constants varied with hydroxide-ion concentration according to equation (1) and parameters k' and K_a/K_w were calculated by use of a regression analysis

$$\text{Rate} = [\text{ester}]k'/[1 + K_w/(K_a[\text{OH}])] \qquad (1)$$

devised by Wilkinson [13b] for the analogous enzymic rate law. Figure 1 illustrates typical dependencies of rate constant on hydroxide ion concentration. Typical data

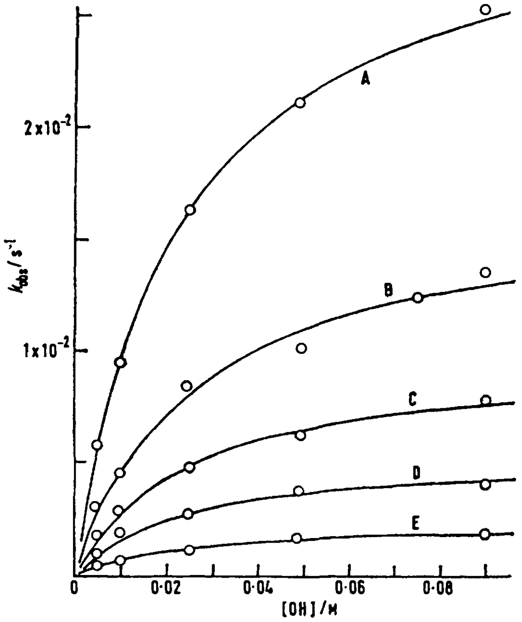


FIGURE 1 Rate constants for hydrolysis of 4-nitrophenyl *NN′*-diphenylphosphorodiamidate (Ia) as a function of hydroxide-ion concentration. Lines are theoretical calculated from data of Table 4 and equation (1); A, 68·4; B, 58·2; C, 49·35; D, 40·35; E, 29·35 °C

are fitted to a linear function of hydroxide ion concentration in Figure 2 $\{k_{obs} = k' - (k_{obs}/[\text{OH}](K_w/K_a\}$; comparative data from Coult and Green [9] for a different medium are incorporated and agree with our results. Values of k' and K_a/K_w for a number of phenyl esters are collected in Table 2.

Alkaline hydrolysis of substituted phenyl phosphorodimorpholidates was also measured. A good set of isosbestic wavelengths was obtained for the 4-nitrophenyl ester and the total 4-nitrophenol liberated (determined spectroscopically) agreed with the calculated quantity. Pseudo-first-order rate constants were proportional to hydroxide-ion concentration and the derived bimolecular rate constants are collected in Table 3.

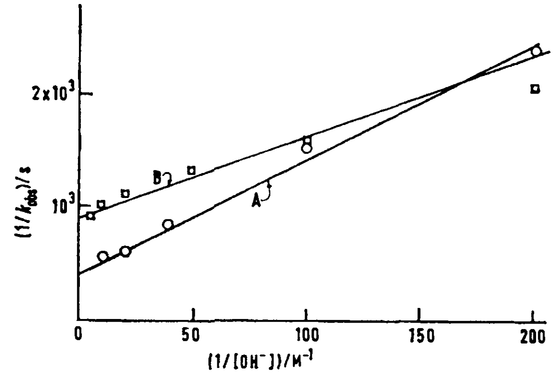


FIGURE 2 Typical hydrolysis data for 4-nitrophenyl *NN′*-diphenylphosphorodiamidate (Ia) fitted to a linear function of hydroxide-ion concentration; A, Data of Figure 1 (58·2 °C); B, data of Coult and Green (ref. 9)

TABLE 3

Base-catalysed hydrolysis of substituted phenyl phosphorodimorpholidates [a]

Ester	λ_k [b]/nm	10^5k_{obs}/s^{-1}	[OH]/M	10^5k_{OH} / l mol^{-1} s^{-1}
(IIa) [c]	400	4·80	1·00	
		2·45	0·5	
		1·24	0·25	4·74
(IIb)	355	3·32	1·00	
		1·62	0·5	
		0·8	0·25	3·37
(IIe)	300	0·83	1·00	
		0·87	1·00	
		0·80	1·00	0·83
(IIg)	245	0·295	1·00	
		0·300	1·00	
		0·286	1·00	0·294

[a] 60 °C, 100% water, hydrolysis of 4-methyl and 4-methoxy-esters was not studied owing to their slow reactivity. [b] Kinetic wavelength. [c] Isosbestic wavelengths were 250 and 310 nm.

TABLE 4

Effect of temperature on base-catalysed hydrolysis [a]

t/°C	$k'K_a/K_w$ / l mol^{-1} s^{-1}	$10^2k'$/s^{-1}	$10^2K_w/K_a$ / mol l^{-1}
4-Nitrophenyl *NN′*-diphenylphosphorodiamidate			
29·35	0·0955	0·242 ± 0·011	2·53 ± 0·30
40·35	0·227	0·540 ± 0·019	2·38 ± 0·22
49·35	0·395	0·979 ± 0·027	2·48 ± 0·18
58·2	0·626	1·705 ± 0·087	2·72 ± 0·38
68·4	1·38	3·113 ± 0·039	2·26 ± 0·08
$\Delta H^\ddagger_{30°}$	12·4 ± 0·5	12·79 ± 0·07	−1·01 ± 0·5
$\Delta S^\ddagger_{30°}$	−20 ± 2	−28·2 ± 0·2	−52 ± 2
4-Nitrophenyl phosphorodimorpholidate			
40·0	2·382 × 10^{-5}	$\Delta H^\ddagger_{30°}$	15·98 ± 0·14
50·0	5·54 × 10^{-5}	$\Delta S^\ddagger_{30°}$	−26·8 ± 0·4
58·3	1·095 × 10^{-4}		

[a] 50% Ethanol–water (v/v), enthalpy in kcal mol^{-1} and entropy in cal mol^{-1} K^{-1}

The effect of temperature on the rate constants was studied for esters (Ia) and (IIa) and good linear Arrhenius plots were obtained. Results are collected in Table 4 together with the corresponding enthalpies and entropies of activation derived from equation (2) from Benson.[14a]

$$k = 0{\cdot}2904 \times 10^{11}T \exp(\Delta S^{\ddagger}/R - \Delta H^{\ddagger}/RT) \qquad (2)$$

Ionisation of the *NN'*-diphenylphosphorodiamidates was determined from the spectral change at different hydroxide-ion concentrations and the results analysed according to the equation: $OD^x - OD^0 = OD^c/\{1 + K_w/(K_a[OH^x])\}$. Thermodynamic (collected in Table 5) and kinetic measurements gave near-identical values for K_a/K_w. Unfortunately it is not possible to evaluate K_a for the system as K_w is not available for our medium at the temperatures employed.

TABLE 5

Effect of hydroxide-ion concentration on spectra of substituted phenyl *NN'*-diphenylphosphorodiamidates [a]

Ester [c]	λ_t [b]/nm	10^2K [d]/mol l^{-1}
(Ia)	246·5	2·35 ± 0·19
(Ib)	255	2·22 ± 0·43
(Ic)	250	3·75 ± 0·55
(Id)	256	4·85 ± 0·43
(Ie)	255	8·92 ± 1·05
(If)	250	7·80 ± 0·5
(Ig)	255	0·143 ± 0·008
(Ih)	255	0·191 ± 0·011
(Ii)	254	0·236 ± 0·013

[a] 29·35 °C, 50% ethanol–water. [b] Wavelength for measurements. [c] Hydroxide concentration range from 0·005 to 0·45M. [d] Hammett ρ = 1·3.

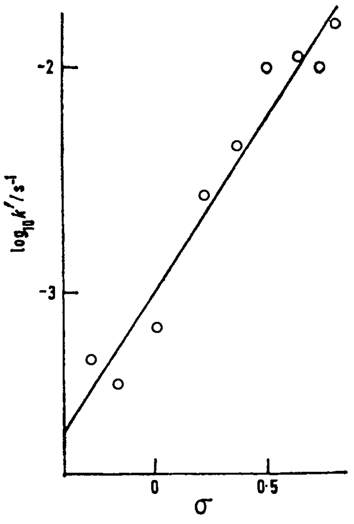


FIGURE 3 Dependence of $\log_{10}k'$ (Table 2) on σ; line is theoretical: $\log_{10}k' = -3{\cdot}00 + 1{\cdot}58\sigma$ ($r = 0{\cdot}980$)

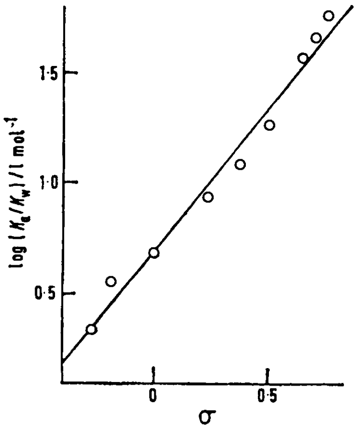


FIGURE 4 Dependence of $\log_{10}K_a/K_w$ (Table 2) on σ; line is theoretical: $\log_{10}K_a/K_w = 0{\cdot}69 + 1{\cdot}27\sigma$ ($r = 0{\cdot}994$)

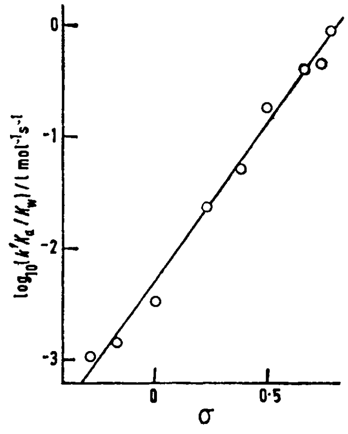


FIGURE 5 Dependence of $\log_{10}k'K_a/K_w$ (Table 2) on σ; line is theoretical: $\log_{10}k'K_a/K_w = -2{\cdot}31 + 2{\cdot}84\sigma$ ($r = 0{\cdot}997$)

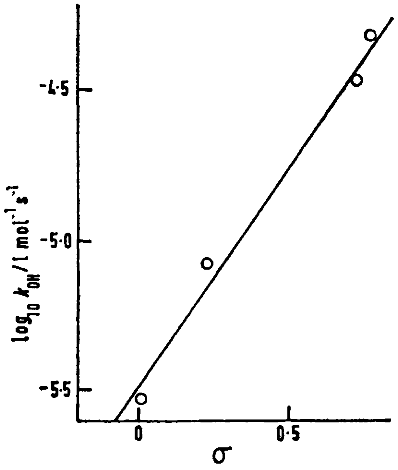


FIGURE 6 Dependence of $\log_{10}k_{OH}$ on σ for aryl phosphorodimorpholidates (II); line is theoretical: $\log_{10}k_{OH} = -5{\cdot}49 + 1{\cdot}47\sigma$ ($r = 0{\cdot}995$)

Dependencies of the various parameters on Hammett σ are illustrated in Figures 3—6. Values of σ are taken from the review of Barlin and Perrin [14b] and selectivities are quoted in legends to Figures.

DISCUSSION

There are three possible mechanisms (Scheme) for specific base-catalysed hydrolysis of an ester with a labile α-proton. Steady-state analysis yields the kinetic expression (3). Thus k' [of equation (1)] is a composite

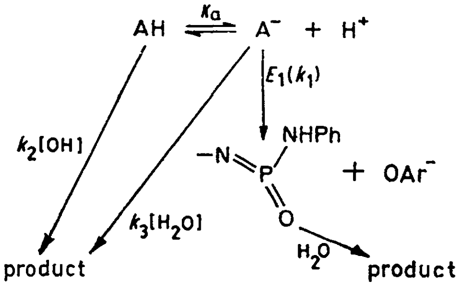
$$\text{Rate} = [\text{Ester}](k_2K_w/K_a + k_1 + k_3)/(1 + a_H/K_a) \qquad (3)$$

parameter involving rate constants for three mechanisms.

---

[14] (*a*) S. W. Benson, 'Foundations of Chemical Kinetics,' McGraw-Hill, New York, 1960, pp. 250, 279; (*b*) G. B. Barlin and D. D. Perrin, *Quart. Rev.*, 1966, **20**, 75.

The exact linearity of the Hammett correlations indicates that only one mechanistic pathway prevails (or, less likely, all three with identical selectivities). If k' has no k_1 or k_3 character then the expected selectivity can be estimated by use of the experimental selectivity for K_a/K_w (1·27) and an estimate for k_2. The latter should be of the order 1·2; Khan and Kirby[15] find $\rho = 1·18$ for alkaline hydrolysis of 2-(substituted phenoxy)-2-oxo-1,3,2-dioxaphosphorinans, Fukuto and Metcalf[16] find 1·26 for alkaline hydrolysis of aryl diethyl phosphates, and Heath[17] reports a Brønsted correlation for hydrolysis of diethyl phosphates with a variety of leaving groups (we determine from his figures a β of $-0·423$ which is equivalent to $\rho = 0·9$, ρ for phenol ionisation[18] being used). At 60 °C the alkaline hydrolysis of phenyl phosphorodimorpholidates is correlated by a Hammett relationship with $\rho = 1·47$. Thus the Hammett selectivity expected for k' is of the order 1·2—1·27 = —0·07 in disagreement with the observed value (1·58).



SCHEME

The mechanism involving water attack on the anion (k_3) should involve a selectivity higher than that expected for k_2 and could thus participate. If it is assumed that bimolecular attack of water on the anion of the 4-nitrophenyl ester (Ia) is predominant its rate constant ($k_3 = k'$) is $1·54 \times 10^{-2}$ s^{-1}. Reaction of water with *neutral* ester would be expected to be faster than this but the observed rate constant at 0·003N-hydroxide-ion concentration is only $1·98 \times 10^{-3}$ s^{-1} (at 60 °C).

It is impossible to predict a selectivity for k_1 but the composite parameter ($k'K_a/K_w$) has a Hammett ρ of 2·84 close to that for alkaline hydrolysis of substituted phenyl N-phenylcarbamates (2·86)[1] and phenyl acetoacetates (2·8)[2] which are also composite.

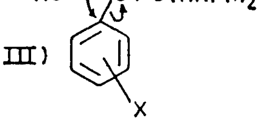
The E1cB mechanism is consistent with the smaller alkaline hydrolysis rate constant of compound (IIa) than the theoretical k_2 (derived from $k'K_a/K_w$) for (Ia) which has a labile α-proton. The enhancement is probably not due to strain in the transition state for S_N2(P) on the former substrate as both (I) and (II) have equally bulky substituents.

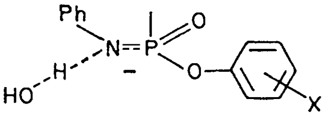
Arrhenius parameters (Table 5) indicate that the rate enhancement measured by the bimolecular rate constant ($k'K_a/K_w$) resides in both enthalpy and entropy terms. The large negative entropy of activation (—28 cal mol K^{-1}) for k' complies with Schaleger and Long's[19] criterion for a bimolecular reaction of a cation with solvent as a rate-determining step; the present reaction is *base*-catalysed where solvent effects could differ.

The nucleophilic aromatic substitution mechanism (III) and the E2 concerted mechanism (IV) where charge is spread over five atoms are not consistent with the σ correlations. The former mechanism is eliminated by Gerrard and Hamer's oxygen-18 study on a similar substrate.[8] The relative timings of departure of phenolate anion and the proton can be determined by the deuterium oxide solvent isotope effect (Table 6).

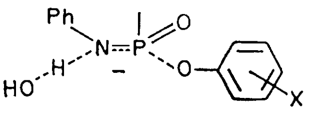
The inverse isotope effect ($k_{OD}/k_{OH} = 1·32$) indicates an ionisation step followed by a rate-determining E1 reaction[20a] rather than the timing indicated by transition states (IV) and (V) for the concerted mechanism; these should give large isotope effects (>5) since the α-proton is labile. Work of Crosby and Stirling[20b] and of Steffa and Thornton[20b] on E1cB mechanisms (k_{OD}/k_{OH} values 1·52, 1·28, and 1·78) is of relevance here.

(III)





(V)



(IV)

TABLE 6

Deuterium oxide solvent isotope effect on hydrolysis of 4-nitrophenyl NN'-diphenylphosphorodiamidate[a]

10^3[OH(D)]/M	10^3k_{obs}/s^{-1}	k_a[b] mol^{-1} s^{-1}
5·02(H)	3·96	
5·02(H)	3·83	0·777
5·42(D)	5·66	
5·42(D)	5·76	1·054
$k_2^{OD}/k_2^{OH} = 1·32$		

[a] 58·3 °C, 50% dioxan–water (v/v). [b] $k_2 = k'K_a/K_w$.

The good correlation of k' with Hammett σ values deserves comment especially as this contributor to k_{OH} for aryl carbamates and acetoacetates is dependent on σ^-. This result indicates that P–O cleavage is little advanced in the transition state of the E1 reaction (VI) as opposed to advanced C–O cleavage in the analogous carbamate case (VII).[1] Possibly this effect is caused

---

[15] S. A. Khan and A. J. Kirby, *J. Chem. Soc.* (*B*), 1970, 1172.

[16] T. R. Fukuto and R. L. Metcalf, *J. Agric. Food Chem.*, 1956, **4**, 930.

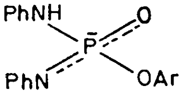
[17] D. F. Heath, ref. 4*b*, 79.

[18] J. E. Leffler and E. Grunwald, ' Rates and Equilibria of Organic Reactions,' Wiley, New York, 1963, p. 178.

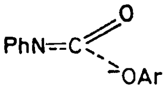
[19] L. L. Schaleger and F. A. Long, *Adv. Phys. Org. Chem.*, 1963, **1**, 1.

[20] (*a*) M. L. Bender and R. B. Homer, *J. Org. Chem.*, 1965, **30**, 3975; (*b*) J. Crosby and C. J. M. Stirling, *J. Amer. Chem. Soc.*, 1968, **90**, 6869; (*c*) L. J. Steffa and E. R. Thornton, *ibid.*, 1967, **89**, 6149.

by the lesser comparative stability of the intermediate phosphoimidate than isocyanate.



(VI)



(VII)

The absence of inversion during alkaline hydrolysis of 4-nitrophenyl *N*-cyclohexylphosphoramidothioate[8] could arise from attack of the solvent cage on the imidate intermediate being more rapid than departure of the 4-nitrophenolate anion from the solvent cage. The departing anion would have a shielding effect causing the planar imidate to react as though the phosphorus were chiral.

The greater reactivity to compound (Ia) of the hydroperoxide ion than hydroxide ion demonstrated by Coult and Green[9] is probably due to the S_N2(P) reaction (k_{HOO^-}) becoming more favourable for this α-nucleophile and does not eliminate the *E*lcB mechanism in the hydroxide case.

Transmission of Substituent Effects.—The Hammett selectivity of 1·27 for the ratio $K_a:K_w$ (at 60 °C) indicates considerable transmission of substituent effects through O and P compared with through carbonyl carbon of benzoic acids. This transmission (the selectivity for thermodynamic pK_a's from Table 5 at 29·35 °C is 1·3) is greater than expected from that for the first and second ionisation constants of benzenephosphonic acids (0·755 and 0·949 respectively)[21] and for phenylphosphinic acids.[22] However, the cause of this greater transmissive power is as yet unknown.

One of us (K. T. D.) thanks the University of Kent and the Northern Ireland Government for financial support.

[2/217 *Received, 2nd February,* 1972]

---

[21] H. H. Jaffe, L. D. Freedman, and G. O. Doak, *J. Amer. Chem. Soc.*, 1953, **75**, 2209.

[22] M. I. Kabachnik, *Doklady Akad. Nauk S.S.S.R.*, 1956, 577.