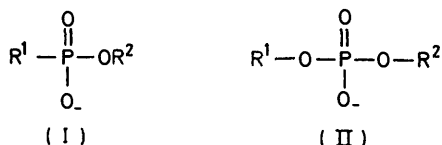


Hydrolysis of 2-Pyridylphosphonic Acid Mono- and Di-esters: Electrophilic Catalysis by Transition Metal Ions and the Irrelevance of Intramolecular Participation by the Pyridyl Group

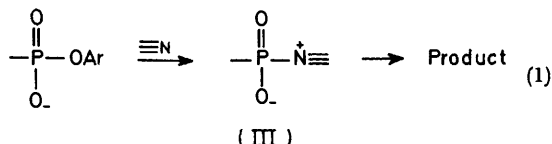
By John S. Loran, Richard A. Naylor, and Andrew Williams,* University Chemical Laboratories, Canterbury, Kent CT2 7NH

The hydrolysis of *O*-(4-nitrophenyl) 2-pyridylphosphonate possesses kinetic terms in hydroxide and hydrogen ion concentration and zwitterion and anion concentration. Comparison with suitable models where the proton is localised shows that the 'anion' term arises from hydroxide ion attack on the zwitterion rather than water attack on the monoanion; 'zwitterion' term involves attack of hydroxide ion on the cationic species. The hydrolysis of *O*-(4-nitrophenyl) (*N*-methyl-2-pyridinio)phosphonate possesses a 'neutral' term from hydroxide ion attack on the cationic species. 2-Pyridylphosphonate diesters hydrolyse *via* attack by water on the neutral form of the ester; there is no detectable anchimeric assistance by the pyridine nitrogen possibly due to the very low basicity of the base. The hydrolysis of *O*-(4-nitrophenyl) phenylphosphonate at neutral pH involves decomposition of the monoanion presumably by water attack rather than the equivalent reaction of hydroxide ion with the neutral form of the ester. *O*-(4-Nitrophenyl) 2-pyridylphosphonate is shown to complex with transition metal ions which also catalyse the hydrolysis of the ester possibly *via* electrophilic participation.

THE low reactivity to hydrolysis above pH 1 of phosphonate monoesters (I) and phosphodiester (II) is probably due to their existence as anions;¹ work in the



past decade has shown that these models of key biological processes may be catalysed by buffers *via* nucleophilic pathways if the leaving group is highly stabilised.² Pyridine and tertiary amine catalysed hydrolysis of substituted phenyl esters corresponding to (I) and (II) involves the initial formation of a phosphopyridine intermediate (III) which then decomposes rapidly to product [equation (1)].

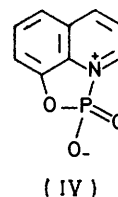


We are interested in factors which might change the mechanism from nucleophilic to general-base catalysis; even in a system where ring formation is strained as in the neighbouring group participation in the hydrolysis of 4-nitrophenyl quinolin-8-yl phosphate nucleophilic attack predominates to the exclusion of general-base catalysis.³ We therefore seek a model where strain in attaining the transition-state for neighbouring nucleophilic attack by tertiary nitrogen is impossibly high for

¹ R. F. Hudson, 'Structure and Mechanism in Organophosphorus Chemistry,' Academic Press, New York and London, 1965.

the reaction to accommodate the reaction flux. The question then arises: does general-base catalysis predominate or some other form of assistance?

We choose to study the hydrolysis of *O*-(4-nitrophenyl) 2-pyridylphosphonate (V) (see Table I) where intramolecular nucleophilic attack would require a highly strained three-membered ring transition state. Intramolecular general-base catalysis would necessitate a five-membered ring transition-state (N-C-P-O-H) while electrophilic catalysis by the pyridinium proton would



essentially neutralise the negative charge on the phosphoryl oxyanion *via* a five-membered ring.

Interpretation of the kinetic rate law for the hydrolysis of the substrate (V) by water and hydroxide presents a complex set of mechanistic ambiguities which are resolvable with suitable model systems (see Table 1) where the proton is effectively localised. Kinetic ambiguities are very important in mono- and di-phosphate ester hydrolyses and have been largely neglected. For example the hydrolysis of a phosphonate monoester

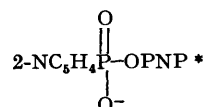
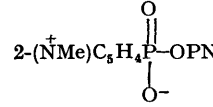
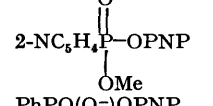


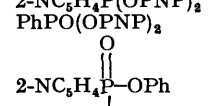
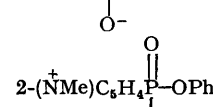
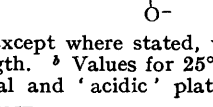
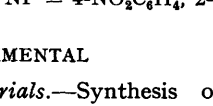
² A. J. Kirby and M. Younas, *J. Chem. Soc. (B)*, 1970 (a) p. 1165; (b) p. 510; E. J. Behrman, M. J. Biallas, H. J. Brass, J. O. Edwards, and M. Isaks, *J. Org. Chem.*, 1970, **35**, (c) p. 3063; (d) p. 3069; (e) H. J. Brass, J. O. Edwards, and M. J. Biallas, *J. Amer. Chem. Soc.*, 1970, **92**, 4675; (f) H. J. Brass, J. O. Edwards, and N. J. Fina, *J.C.S. Perkin II*, 1972, 726.

³ J. S. Loran and A. Williams, *J.C.S. Perkin II*, 1977, 64.

could involve decomposition of the anionic species or hydroxide ion attack on the neutral form of the ester. We provide an answer to this problem in this report.

The existence of a metal-binding ligand in the phosphonate ester should give rise to metal-chelating properties and possibly to electrophilic catalysis by the metal ion of the hydrolytic reaction; these expectations seem to be fulfilled.

TABLE I
Hydrolysis of phosphonate esters^a

Ester	$k_{H^+}/$ $1 \text{ mol}^{-1} \text{ s}^{-1}$	$k_{\text{plateau}}/$ s^{-1}	$k_{OH^-}/$ $1 \text{ mol}^{-1} \text{ s}^{-1}$
(V) 	$3.5 \cdot 10^{-5}$	$3.2 \cdot 10^{-7}$ ^c $6.3 \cdot 10^{-8}$ ^c	$4.5 \cdot 10^{-3}$
(VI) 	$6.3 \cdot 10^{-5}$	$6.5 \cdot 10^{-7}$	7.1
(VII) 	0.062	$4.4 \cdot 10^{-5}$	250
(VIII) 	$4.7 \cdot 10^{-5}$	$1.7 \cdot 10^{-7}$	$1.0 \cdot 10^{-3}$
(IX) 	$6.0 \cdot 10^{-5}$	$3.6 \cdot 10^{-8}$	17
(X) 	3.1	$3.0 \cdot 10^{-3}$	$1.1 \cdot 10^{-4}$
(XI) 	0.36^b	$4.0 \cdot 10^{-4}$ ^b	100^b
(XII) 			$2.3 \cdot 10^{-4}$
(XIII) 			0.13

^a Except where stated, values refer to 60° and 0.1M ionic strength. ^b Values for 25°. ^c Low and high values refer to neutral and 'acidic' plateaux respectively (see Figure 1).

* PNP = 4-NO₂C₆H₄, 2-NC₅H₄ = 2-pyridyl.

EXPERIMENTAL

Materials.—Synthesis of the substrates (V)—(VII), (XII), and (XIII) (see Table 1) has been described earlier.⁴

OO-(Bis-4-nitrophenyl) 2-pyridylphosphonate (X) was prepared by adding 4-nitrophenol (2.85 g, 20 mmol) and triethylamine (2.05 g, 20 mmol) in dichloromethane (20 ml) to a solution of 2-pyridylphosphonodichloridate⁴ (2 g, 10 mmol) in dichloromethane (100 ml). The solution was stirred at room temperature for 24 h, the precipitate filtered, and the solvent evaporated *in vacuo*. The resultant oil gave a white solid on trituration with ether; recrystallisation from ethanol gave *needles*, m.p. 108—111° (Found: C, 50.9; H, 3.1; N, 10.4. C₁₇H₁₂N₃O₇P requires C, 50.9; H, 3.0; N, 10.5%). I.r., n.m.r., and mass spectra confirm the structure and hydrolysis in NaOH (1M) gave two moles of 4-nitrophenol per one mole of substrate, each liberated at different rates.

OO-(Bis-4-nitrophenyl) phenylphosphonate (XI) was pre-

⁴ J. S. Loran, R. A. Naylor, and A. Williams, *J.C.S. Perkin II*, 1976, 1444.

⁵ A. I. Vogel, 'A Textbook of Practical Organic Chemistry', 3rd edn., Longman, London, 1967, p. 169.

pared by heating phenylphosphonodichloridate (Aldrich; 1.95 g, 100 mmol) and 4-nitrophenol (27.8 g, 200 mmol) at 160° using an oil-bath. The temperature was maintained for 4 h and the dark brown liquid taken up in ethyl acetate and treated with Norit several times. The solvent was evaporated *in vacuo* and the resultant oil triturated with ether to give crystals. The *material*, recrystallised from CCl₄ had m.p. 94—96° (Found: C, 53.4; H, 3.2; N, 6.8. C₁₇H₁₄NO₃P requires C, 53.9; H, 3.3; N, 7.0%). The structure was confirmed by its i.r. spectrum and by the release of two moles of 4-nitrophenol on hydrolysis in NaOH (1M) of one mole of substrate; release of the phenol took place in two stages.

O-(4-Nitrophenyl) phenylphosphonate (VIII) was prepared by suspending the bis-4-nitrophenyl ester (5 g) in water (100 ml) with NaOH (1 g). The mixture was boiled to dissolve the ester, cooled, and extracted with ether after adjusting the solution to pH 4. The aqueous phase was then acidified with concentrated HCl and the precipitated solid filtered and washed with water. Recrystallisation from CCl₄ gave *needles*, m.p. 117—119° (Found: C, 51.3; H, 3.9; N, 4.8. C₁₂H₁₀NO₅P requires C, 51.6; H, 3.6; N, 5.0%).

O-Methyl *O*-(4-nitrophenyl) phenylphosphonate (IX) was prepared by refluxing phenylphosphonodichloridate (5 g, 26 mmol) with 4-nitrophenol (3.58 g, 26 mmol) in sodium-dried benzene (200 ml) with KCl (100 mg) as a catalyst. The refluxing was continued for 10 days with suitable precautions to exclude moisture. The benzene was then removed *in vacuo* and pyridine (2.06 g, 26 mmol; previously distilled from NaOH pellets) was added carefully and the solution cooled in ice. Methanol (10 ml; dried by the method described by Vogel⁵) was added dropwise with stirring and the resultant solution allowed to stand at room temperature for 1 h. Benzene (100 ml) was added and the solution washed with saturated NaHCO₃ solution (4 × 50 ml) and saturated NaCl solution (4 × 50 ml). The benzene was then dried over MgSO₄ and the filtrate evaporated *in vacuo* to give a yellow liquid, b.p. 185° at 0.1 Torr (Found: C, 52.9; H, 4.3; N, 4.6. Calc. for C₁₃H₁₂NO₅P: C, 53.2; H, 4.1; N, 4.8%).⁶ I.r., n.m.r., and mass spectra confirmed the structure and a stoichiometric amount of 4-nitrophenol was released from the substrate on alkaline hydrolysis.

The complex between *O*-(4-nitrophenyl) 2-pyridylphosphonate and copper was prepared by suspending the phosphonate (298 mg, 1 mmol) in water (10 ml) with methanol (5 ml). The suspension was warmed to dissolve the ester and addition of a solution of Cu(NO₃)₂ (241 mg) in water (2 ml) precipitated a complex which was collected and washed well with water and methanol. The pale blue solid was dried overnight at *ca.* 70° in a vacuum drying pistol (yield 320 mg, *ca.* 100%). The compound was insoluble in a large range of organic solvents and recrystallisation was therefore not possible. The *solid* has m.p. >320° and analysed as a 2 : 1 complex [Found: C, 42.7; H, 2.4; N, 8.9. (C₁₁H₈N₂O₅P)₂Cu requires C, 42.5; H, 2.6; N, 9.0%]. The i.r. spectrum (Nujol) of the complex was significantly different from that of the free ester especially in the P-O region.

Substituted pyridines were obtained from B.D.H. and

⁶ This compound has been reported in the patent literature: H. M. Bode and G. Kötz, E.Ger.P. 9568/1955 (*Chem. Abs.*, 1959, 53P, 1625g); Y. Hayakawa, Y. Ura, and F. Suzuki, *Jap.P.* 14,624/1967 (*Chem. Abs.*, 1968, 68P, 95961e).

were distilled after storage over NaOH pellets for 24 h. Other materials were of analytical reagent grade or were recrystallised or redistilled from bench grade products. Deuterium oxide (99.8% D) was obtained from Prochem, and water doubly distilled from an all glass apparatus was used throughout. Acetonitrile was purified according to the method of Lewis and Smyth⁷ and dioxan was purged of peroxides by percolating the AnalaR material through a column of activated alumina; potassium iodide was used to test for the absence of peroxides.

Microanalyses were carried out by Mr. G. M. S. Powell, Miss F. Duckworth, and Miss L. Tidy using a Hewlett-Packard model 185 CHN analyser and were accurate to $\pm 0.3\%$. I.r. spectra were recorded on a Perkin-Elmer model 237 instrument using Nujol mulls or neat liquid samples. ¹H N.m.r. were recorded on a Perkin-Elmer R10 machine or by Dr. D. O. Smith using a JEOL P.S. 100 MHz instrument both with tetramethylsilane as internal or external standard. Mass spectra were obtained by Dr. R. B. Turner with an A.E.I. MS902 high resolution instrument.

Methods.—Kinetics. Reactions were studied spectrophotometrically using the cell compartment of Unicam SP 800, 600, or Beckman DBG instruments equipped with Servoscribe chart recorders. Thermostatting was attained using a Tecam Tempunit accurate to $\pm 0.1^\circ$ or a Shandon Circotherm device. The general procedure involved pipetting 2.5 ml of the appropriate buffer into a 1 cm path length silica cell in the cell compartment. The reaction was initiated by addition of a small portion (50–100 λ) of a solution of the ester in a suitable solvent (acetonitrile, water, or dioxan). For temperatures over 25° the buffer was allowed to equilibrate thermally for *ca.* 15 min before the ester was added. For reasonably fast reactions the measurements were continued to obtain an infinity reading; for the slow reactions the method of initial rates was employed: a portion of the ester was hydrolysed under 'strong' conditions, *e.g.* high pH or temperature and then diluted in the appropriate buffer to give the correct dilution and the optical density measured to obtain an infinity reading under the conditions of the initial rate experiment. Very slow reactions required a third technique: *ca.* 4 mg of the phosphonate were weighed accurately (to ± 0.01 mg) into a 2 ml volumetric flask. Buffer of the required pH was added to the mark and, after ensuring complete dissolution, the flask placed in a thermostatted water-bath at 60°. At successive intervals 250 λ portions of the reaction solution were pipetted into 2 ml portions of borate buffer (pH 10) and the optical density read at 400 nm. The final absorption was measured on an amount of 4-nitrophenol equivalent to that of the substrate. First-order rate constants were obtained from plots of $A_t - A_\infty$ versus time using semilogarithmic paper (A = absorption).

Measurements of pH were made with a Radiometer pH meter 25 or a Pye-Dynacap instrument both calibrated with E.I.L. standard buffer powders. pD was measured using the observed meter reading and the equation pD = meter reading + 0.4.

Spectrophotometric titration was carried out using a series of buffer solutions with pH close to the pK_a of the acid to be measured. A portion of the substrate was added to 2.5 ml of the buffer in the 1 cm path length cell in the thermostatted cell compartment of the SP 800 instrument

* For details of Supplementary Publications see Notice to Authors No. 7 in *J.C.S. Perkin II*, 1975, Index issue.

and the spectrum measured; this was repeated for different pH values. The pK_a was estimated from the absorption change at the wavelength for maximum absorption change using a method reported by one of us⁸ using Basic Language and the University's 'On-line' system.

RESULTS

The phosphate esters studied here were hydrolysed in base and spectral scanning throughout the reactions revealed excellent isosbestic wavelengths consistent with a clean 1:1 stoichiometry. In the case of the 4-nitrophenyl esters assay of the 4-nitrophenol produced also indicated a 1:1 stoichiometry.

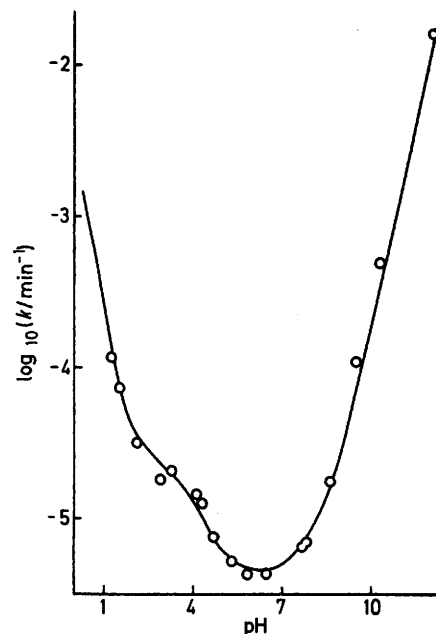


FIGURE 1 The hydrolysis of *O*-(4-nitrophenyl) 2-pyridylphosphonate (V) over a pH range at 60°, 0.1M ionic strength; line is theoretical from parameters collected in Table 1; results extrapolated to zero buffer concentration

Rate constants for phenol release were pseudo-first order up to *ca.* 90% of the total reaction where the reactivity allowed us to measure the reaction to completion. Buffer catalysis was also observed and its effect eliminated by use of extrapolation to zero buffer concentration from results for two or more concentrations. The resultant pH dependences involved an acid and base limb and one or more plateau regions in the neutral pH range. These are illustrated in Figures 1 and 2 and the results are summarised in Table 1. Supplementary Tables 1–9 record the raw data for these reactions and may be found in Supplementary Publication No. SUP 21921 (11 pp., 1 microfiche).*

Preparation of Non-protonic Models.—We were able to prepare non-protonic models of most of the systems so that we could be sure that in the hydrolysis of these compounds ambiguities did not arise through proton migration. The attempted quaternisation of esters (VII) and (X), however, failed even after refluxing the esters with methyl iodide for 48 h in methanol. We judge this absence of reaction as due to both steric hindrance in the 2-position and to the electron-

⁷ G. L. Lewis and C. P. Smyth, *J. Chem. Phys.*, 1939, **7**, 1085.

⁸ A. Williams, 'An Introduction to the Chemistry of Enzyme Action,' McGraw-Hill, New York, 1969, p. 123.

withdrawing effect of the phosphonate group (we shall see later that the pK_a of the pyridines is *ca.* 1). The absence of reaction with methyl iodide is consistent with the observation of Brown and Cahn⁹ and Brown and Kanner¹⁰ that 2-*t*-butylpyridine is only *ca.* 1/4 000-fold as reactive as pyridine to methyl iodide and that 2,6-di-*t*-butylpyridine cannot be alkylated. Moreover, Gautier and Renault¹¹ found that pyridine-2-sulphonamide also cannot be alkylated.

Buffer Catalysis.—Buffer catalysis was studied for the phosphonate monoester (VI) using a series of substituted pyridines. The effect of increasing buffer concentration at a set fraction of base species is shown in SUP 21921 where the rate constant suffers an increase of two-fold on changing buffer concentration from 0 to 1M. This effect is not due to a change in medium because changing the dioxan content of the medium in acetate buffers has little effect outside the error limits of the measurements (at pH 4.70, 5, 10, 15, and 20% dioxan has rate constants 5.36, 6.10, 5.66, and $5.76 \times 10^{-6} \text{ s}^{-1}$ respectively). The kinetics were analysed by plotting the slope of the individual plots *versus* the fraction of

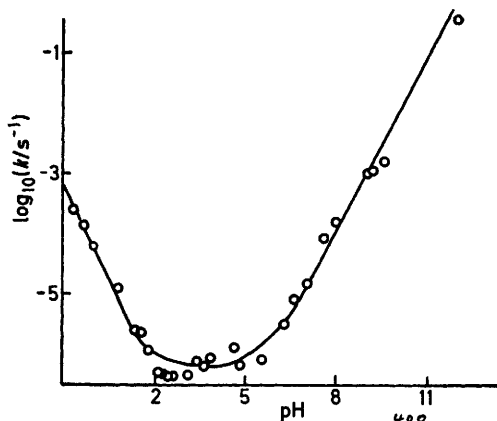


FIGURE 2 The hydrolysis of *O*-(4-nitrophenyl) (*N*-methyl-2-pyridinio)phosphonate (VI) over a pH range at 60°, 0.1M ionic strength, and zero buffer concentration; line is theoretical from parameters in Table 1

base (SUP 21921); the intercepts at $\text{frB} = 0$ and 1 are k_a and k_b respectively. In all cases the acid term was zero within the limits of the method. Data for the buffer effects are recorded in Table 2 and the raw data in SUP 21921. The Brønsted type plot of $\log_{10}k_b$ *versus* the pK_a of the pyridinium ion is illustrated in Figure 3.

TABLE 2

Catalytic effect of substituted pyridines on the hydrolysis of *O*-(4-nitrophenyl) *N*-methyl-2-pyridinio)phosphonate^a

Pyridine	pK_a	$10^5 k_b / \text{l mol}^{-1} \text{ s}^{-1}$ ^b
Unsubstituted (Pyr)	5.17	0.80
3-Methyl (3-Pic)	5.68	1.7
2-Methyl (2-Pic)	5.97	0.31
3,5-Dimethyl (3,5-Lut)	6.14	1.9
2,6-Dimethyl (2,6-Lut)	6.77	<0.1

^a 60°, 1M ionic strength made up with NaCl. ^b Errors of these values are indicated in Figure 3.

Metal Ion Catalysis.—Catalysis of the release of 4-nitrophenol from (V) was observed in the presence of metal ions at 60° in Tris (trishydroxymethylaminomethane)

⁹ H. C. Brown and A. Cahn, *J. Amer. Chem. Soc.*, 1955, **77**, 1715.

buffer. The hydrolysis is first order in substrate and the results are shown in Figure 4; substrate concentration has

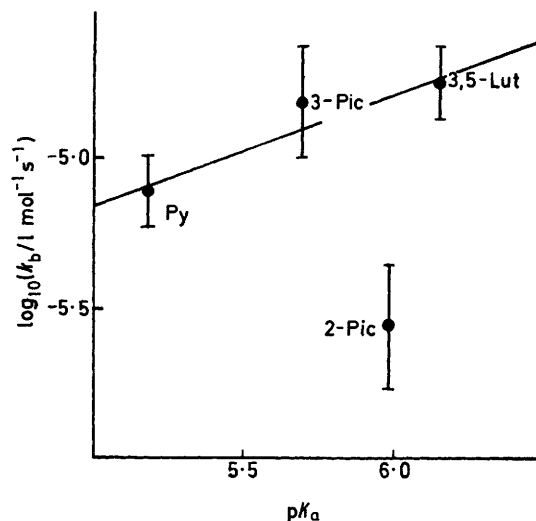


FIGURE 3 Brønsted type relationship between k_b and the pK_a of the conjugate acid for pyridine-catalysed hydrolysis of *O*-(4-nitrophenyl) (*N*-methyl-2-pyridinio)phosphonate (VI). Error bars are derived from maximum and minimum lines in the estimation of k_b (see Figure 5 for example). Abbreviations are as in Table 2 and the line has an arbitrary slope of 0.37

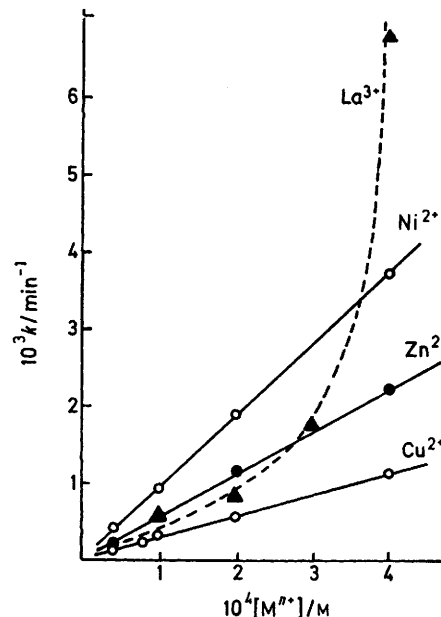


FIGURE 4 Effect of metal ion concentration on the hydrolysis of *O*-(4-nitrophenyl) 2-pyridylphosphonate (10^{-4}M) in 0.1M-Tris at pH 7.37, ionic strength 0.1M, 60°

no effect on the first-order rate constant at a given metal ion concentration.

In the absence of buffer at a pH maintained by a pH-stat (Radiometer, Copenhagen) the formation of an insoluble complex prevented monitoring the reaction. This complex formed over the pH range 3–9 and hydroxide gels appeared near pH 8. Even in the presence of 'non-liganding' type

¹⁰ H. C. Brown and B. Kanner, *J. Amer. Chem. Soc.*, 1953, **75**, 3865.

¹¹ J.-A. Gautier and J. Renault, *Compt. Rend.*, 1953, **237**, 733.

buffers (e.g. triethylenediamine) at pH 8.25 and 60° nickel at 10^{-3}M formed a hydroxide gel. At lower concentrations (ca. 10^{-4}M) of metal ion where no precipitate formed the kinetics were complicated and involved an initial rapid liberation of 4-nitrophenol followed by a slower reaction. Owing to metal hydroxide precipitation even with 'chelating' buffers the effect of pH on the nickel catalysis could not be followed above pH 8 (see Figure 5).

O-(4-Nitrophenyl) phenylphosphonate (VIII) showed no detectable metal ion catalysis (Cu^{2+} , Ni^{2+} , and Zn^{2+} at 1mM pH 7.37; 60°). Lanthanum(III) did catalyse 4-nitrophenol release (at La^{3+} , $4 \times 10^{-4}\text{M}$, $k = 1.67 \times 10^{-5}\text{ s}^{-1}$); in the absence of metal ions $k = 1.7 \times 10^{-7}\text{ s}^{-1}$ (see Table 1). Similar effects were observed by Blewett and Watts for *O*-(4-nitrophenyl) methylphosphonate hydrolyses.¹²

Determination of the pK_a values for the pyridinium groups in esters (VII) and (X) proved impossible. By

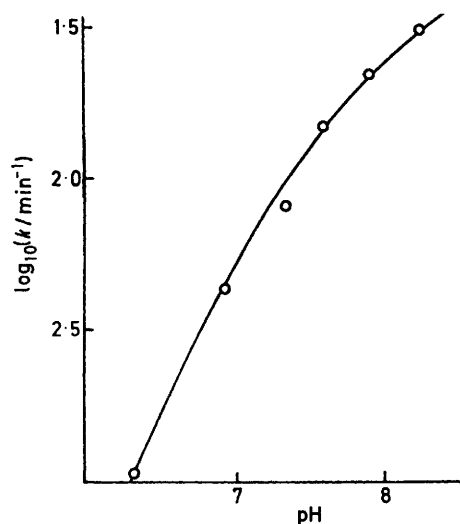


FIGURE 5 pH Dependence of the hydrolysis of *O*-(4-nitrophenyl) 2-pyridylphosphonate (V) (10^{-4}M) in the presence of Ni^{2+} (10^{-3}M) at 60°, ionic strength 0.1M, and Tris buffer

comparison with the pK_a of the pyridinium group in *OO*-diethyl 2-pyridylphosphonate (1.15 at 60°; 1M ionic strength; *via* spectral titration at 265 nm) titration with a pH meter is not feasible for these esters and the absence of a sufficiently large spectral change makes spectral titration impossible. Ester (V) gave an optical density change of ca. 0.1 units (at 300 nm) in a background absorbance of 0.8 units which is only just capable of yielding a pK_a of reasonable accuracy (4.45 at 60°).

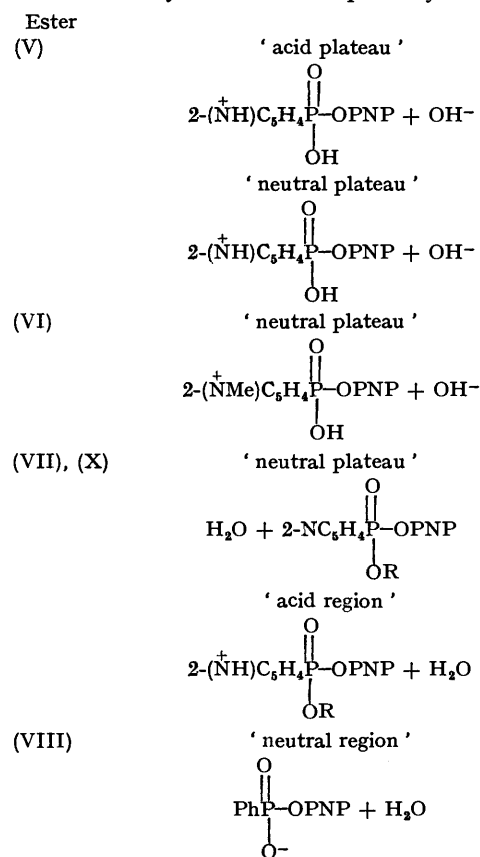
DISCUSSION

Buffer Independent Hydrolysis.—The pH dependences of the hydrolyses of the esters illustrated in Table 1 could each arise from a number of equivalent mechanisms and Table 3 illustrates those pathways which carry the majority of the reaction flux in the ranges indicated. The detailed arguments leading to these mechanisms are given later.

It is interesting that the hydrolysis of the benzene-phosphonate monoester (VIII) involves water attack on the phosphorus bearing an oxyanion whereas the other phosphonates (V) and (VI) are hydrolysed *via* hydroxide

attack on 'uncharged' phosphorus or on 'anionic' phosphorus (see Table 3). Catalysis by the pyridine

TABLE 3
Summary of mechanistic pathways



nitrogen as a general base or electrophile seems to be of minor importance except insofar as these groups affect the electron demand at the phosphorus by inductive effects.

The absence of an enhancement in the 'neutral' hydrolysis of the 2-pyridylphosphonate diesters (VII) and (X) is probably due to the very low basicity of the pyridine nitrogen (see later) for these compounds; there seems to be no steric reason for the absence of intramolecular general base catalysis as hydrolyses (for example of pyrrole-2-carboxylates by hydroxide ion) where the atomic configuration is similar¹³ do involve some participation.

Hydroxide Ion Catalysis.—The reactivity of hydroxide ion to the *O*-(4-nitrophenyl)phenylphosphonate ester is close to that expected from literature values for similar compounds.^{2c} The higher reactivity of the pyridine-2-ester (V) is expected because of the electron withdrawing power of the heterocyclic nitrogen. The enhancement observed [(V)/(VIII), (X)/(XI), and (VII)/(IX) = 4.5, 39, and 14.7 respectively] agree with that for the alkaline hydrolysis of ethyl pyridine-2-carboxylate over ethyl

¹² F. McC. Blewett and P. Watts, *J. Chem. Soc. (B)*, 1971, 881.

¹³ A. Williams and G. Salvadori, *J.C.S. Perkin II*, 1972, 883.

benzoate (19).^{14,15a} The rather low value for the ratio (V)/(VIII) appears to have no satisfactory explanation. *N*-Methylpyridinium esters (VI) and (XIII) react faster, as expected, than the corresponding pyridine compounds (V) and (XII) with an enhancement of *ca.* 1 000-fold (respectively 1 600 and 560).

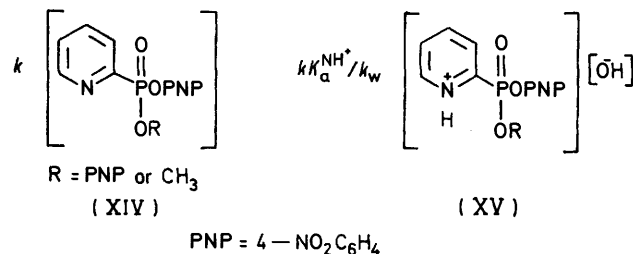
Hydronium Ion Catalysis.—The absence of inflections in the region of pH 1 in the pH dependences of the phosphonate monoester hydrolyses indicates that the hydrolysis of the neutral esters in water is negligible and in this region acid catalysed attack on the neutral ester predominates. In the case of *O*-(4-nitrophenyl) 2-pyridylphosphonate (V) acid catalysed attack on the cation carries the major part of the reaction flux and the similarity in the acid catalysed terms for this ester and *O*-(4-nitrophenyl) (*N*-methyl-2-pyridinio)phosphonate (VI) is in accord with this. Acid attack on *O*-(4-nitrophenyl) phenylphosphonate (VIII) and *O*-methyl *O*-(4-nitrophenyl) phenylphosphonate (IX) is similar indicating that OH and OCH₃ have relatively the same effect and confirming that the acid hydrolysis of the neutral species carries the reaction flux.

The diesters *O*-methyl *O*-(4-nitrophenyl) 2-pyridylphosphonate (VII) and *OO*-(bis-4-nitrophenyl) 2-pyridylphosphonate (X) have acid rate constants larger than the corresponding phenylphosphonate esters (IX) and (XI) respectively and this is not consistent with acid attack on the protonated, cationic form of the pyridine esters which should be *less* reactive than the benzene esters. We ascribe this high acid term to water attack on the pyridinium species which should be *ca.* 1 000-fold more reactive than water attack on the neutral ester (see earlier). Although a maximum is not reached (possibly because the *pK_a* of the pyridinium species may be close to zero) the largest rate constants do not exceed the 'neutral' plateau values by more than 1 000-fold.

Neutral Hydrolysis of *O*-(4-Nitrophenyl) Phenylphosphonate (VIII).—The hydrolysis of this ester possesses a pH independent rate constant from pH 4 to 8 and this reaction could involve water attack on the anion, as has been tacitly assumed in the past for similar reactions,^{2b,c} unimolecular decomposition of the anion, or hydroxide attack on the neutral species. If the latter carried the reaction flux its rate constant would be given by $k_{OH} = k_{plateau} K^{POH}/K_w$ (where K^{POH} , the ionisation of the phosphonate is taken to be 0.1 and the K_w to be $10^{-13.02}$ at 60°). This value ($1.7 \times 10^{-7} \times 0.1/10^{-13.02} \sim 1.7 \times 10^5$ l mol⁻¹ s⁻¹) is *ca.* 10 000-fold larger than that for hydroxide ion attack on *O*-methyl *O*-(4-nitrophenyl) phenylphosphonate (17 l mol⁻¹ s⁻¹) and we can therefore eliminate this mechanism. Kirby and Younas^{2b} showed that for this type of reaction the bimolecular possibility, namely water attack on the anion, is the preferred pathway.

Neutral Hydrolysis of 2-Pyridylphosphonate Diesters (VII) and (X).—The hydrolysis of the 2-pyridylphosphonate diesters possesses pH dependences with plateaux from pH 3 to 7. We were not able to measure the *pK_a* of the POH group and we assume a value of 1 in accord

with the reported parameters for other phosphonates and phosphates;^{15b} the *pK_a* of the pyridinium moiety by analogy with that for *OO*-diethyl 2-pyridylphosphonate is <1 and possible inflections in the acid region of the pH dependences of the 2-pyridylphosphonate diester hydrolyses [(X) and (VII)] indicate a



value closer to zero. A value for *pK_a* lower than that for the diethyl ester would be in order on account of the greater electron-withdrawing power of the 4-nitrophenyl group. The hydrolysis of the plateau region could involve two equivalent mechanisms [(XIV) and (XV)] where the rate constants are related to the observed one by the functions indicated. In this and the following cases the rate constant *k* is that for the 'simplest' kinetic rate law and this is usually the first order decomposition of the substrate.

It was not possible to synthesise the *N*-methylpyridinium analogue to test mechanism (XV) for reasons given earlier but we are able to estimate a rate constant for hydroxide attack on the pyridinium ester assuming it reacts 1 000-fold faster with hydroxide ion than the corresponding uncharged pyridine derivative. The estimated rate constants are 1.1×10^7 and 2.5×10^5 l mol⁻¹ s⁻¹ [from (X) and (VII) respectively] which are orders of magnitude lower than those observed for the reaction if it proceeded *via* hydroxide attack on the cation [3×10^{10} and 4.4×10^8 l mol⁻¹ s⁻¹ for (XV) derived from (X) and (VII) respectively]. Moreover one of these values comes close to the diffusion controlled rate constant at *ca.* 10^{10} l mol⁻¹ s⁻¹^{15c} thus eliminating mechanism (XV).

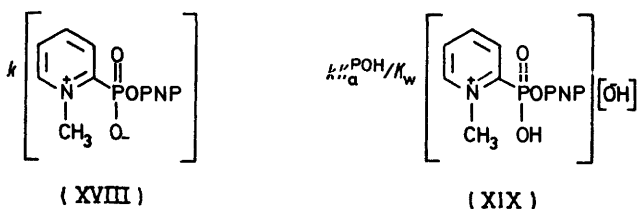
Although the 'plateau' rates for both pyridine diesters (X) and (VII) are *ca.* 100-fold in excess of those for the corresponding phenylphosphonates (XI) and (IX) this enhancement is not caused by intramolecular assistance because this increase is roughly the same as that predicted from the corresponding hydroxide rates.

Neutral Hydrolysis of (*N*-Methyl-2-pyridinio)phosphonates.—The 4-nitrophenyl ester (VI) possesses a simple pH dependence for hydrolysis (Figure 2) and the plateau reaction has two equivalent mechanisms with rate constants related to the observed one by the equations indicated. Attack of hydroxide on the cationic species (XIX) has the rate constant $6.5 \times$

¹⁴ P. R. Faulkner and D. Harrison, *J. Chem. Soc.*, 1960, 1171.

¹⁵ (a) C. C. Price and E. A. Dudley, *J. Amer. Chem. Soc.*, 1956, 78, 68; (b) W. E. Jencks and J. Regenstein in 'Handbook of Biochemistry,' Section J-187, ed. H. A. Sober, Chemical Rubber Company, Cleveland, 1970, 2nd edn.; (c) M. Eigen, *Angew. Chem. Internat. Edn.*, 1964, 1, 1.

$10^5 \text{ l mol}^{-1} \text{ s}^{-1}$ which is close to that estimated from hydroxide attack on *O*-methyl *O*-(4-nitrophenyl) 2-pyridylphosphonate (VII) ($2.5 \times 10^2 \times 1000 \text{ l mol}^{-1} \text{ s}^{-1}$); pyridinium esters as previously discussed are *ca.*



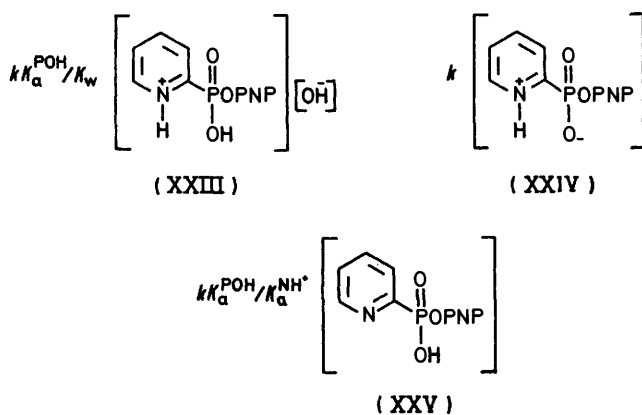
1 000-fold more reactive than the neutral species. We therefore conclude that (XIX) carries a significant part of the reaction flux.

The value of the rate constant for the zwitterion (XVIII), $6.5 \times 10^{-7} \text{ s}^{-1}$, is only four-fold larger than the rate constant for attack at phenylphosphonate (VIII) in neutral solution; we might expect a value of *ca.* $1.3 \times 10^{-4} \text{ s}^{-1}$ by comparing the hydroxide attack on (VI) and on (VIII) (a ratio of *ca.* 7 000-fold) but this ratio is probably too high for water because it is a neutral nucleophile whereas hydroxide bears a negative charge. We are not able to say how much effect this difference will make to the reactivity of water with the zwitterion (XVIII); since the rate constant calculated for (XIX) is close to the observed value it is likely that the rate law (XVIII) does not represent a significant contribution to the reaction flux.

Hydrolysis of 2-Pyridylphosphonate Monoesters.—The hydrolysis of the 4-nitrophenyl ester possesses a pH dependence with acid and base limbs and two plateau regions associated with pyridinium and pyridine moieties (acid and neutral regions respectively see Figure 1). The neutral plateau region could involve three equivalent mechanisms. Attack of hydroxide ion on the zwitterion (XXI) is the most probable mechanism but the rate constant ($63 \text{ l mol}^{-1} \text{ s}^{-1}$) is *ca.* 10-fold larger than the estimated one [from attack of hydroxide ion in the *N*-methylpyridinium species (VI), $7.1 \text{ l mol}^{-1} \text{ s}^{-1}$]; this could be ascribed to steric hindrance caused by the *N*-methyl group in the model or to a vestigial assistance by 'built-in' solvation of the oxyanion developing in the transition state for hydroxide attack. A recent study⁴ has shown that intramolecular electrophilic assistance occurs in the solvolysis of phosphonate diesters by amide NH.

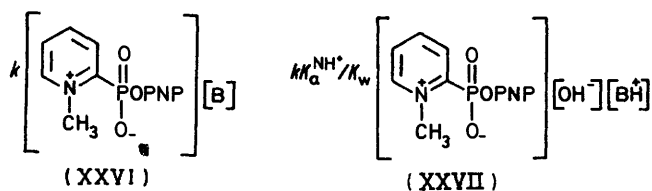
We may eliminate the attack of hydroxide ion on the neutral ester (XXII) since the rate constant (6.3×10^4) is *ca.* 300-fold larger than the attack of hydroxide ion on *O*-methyl *O*-(4-nitrophenyl) 2-pyridylphosphonate (VII) ($250 \text{ l mol}^{-1} \text{ s}^{-1}$). Also simple water attack on the anion (XX) ($6.3 \times 10^{-8} \text{ s}^{-1}$) is *ca.* two-fold less reactive than the decomposition of *O*-(4-nitrophenyl) phenylphosphonate anion (VIII) (1.7×10^{-7}) whereas it should be greater by *ca.* 15–30-fold by comparison with the ratio of hydroxide attack on (X) and (XI) and on (VII) and (IX).

The plateau region corresponding to the zwitterion could also result from three equivalent mechanisms. Attack of hydroxide ion on the cation (XXIII) has a rate constant ($3.2 \times 10^5 \text{ l mol}^{-1} \text{ s}^{-1}$) which is close to the rate constant estimated from attack of alkali on *O*-methyl *O*-(4-nitrophenyl) 2-pyridylphosphonate (VII) ($2.5 \times 10^2 \text{ l mol}^{-1} \text{ s}^{-1}$) using the factor of 1 000-fold for pyridinium *versus* pyridine. Zwitterion decomposition (XXIV) has a rate constant ($3.2 \times 10^{-7} \text{ s}^{-1}$) not much more than the hydrolysis of *O*-(4-nitrophenyl) phenylphosphonate (VIII) and an enhancement greater than 7 000-fold might be expected from a comparison of the hydroxide attack on (VIII) and (VI). We proposed earlier that this ratio is probably much too high for water attack on the same pair because of charge differences; the similarity between observed and calculated rate constants for mechanism (XXIII) suggests a minor role for zwitterion decomposition (XXIV). Reaction of water with the neutral species (XXV) has a rate constant (3.2×10^{-4}



s^{-1}) *ca.* 20-fold in excess of that for reaction of *O*-methyl *O*-(4-nitrophenyl) 2-pyridylphosphonate (IX) with water.

Buffer Catalysis of the Hydrolysis of *O*-(4-Nitrophenyl) (*N*-Methyl-2-pyridinio)phosphonate (VI).—The hydrolysis of most of the esters possessed contributions due to the buffer and it was necessary to eliminate these effects. A full study of buffer effects was carried out on the hydrolysis of *O*-(4-nitrophenyl) (*N*-methyl-2-pyridinio)phosphate (VI) (Figure 3 and Table 2); the absence of a term in the acid buffer species indicates a rate law with the base species and the phosphonate zwitterion and equivalent mechanisms for this are illustrated (XXVI)



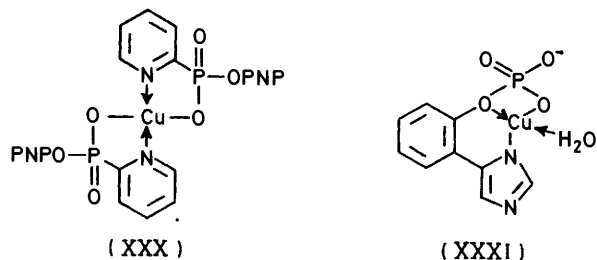
and (XXVII). The latter mechanism is excluded on the grounds of its involving an unlikely termolecular collision and the former involves either general-base catalysis by the base B or nucleophilic catalysis. Nucleophilic catalysis is consistent with the highly pronounced steric effect

observed in catalysis by substituted pyridines (Table 2, Figure 3). Previous workers have observed nucleophilic catalysis of the hydrolysis of phosphodi- and -mono-esters bearing good leaving groups.² The slope of the Brønsted type plot for the relatively unhindered pyridines (Figure 3, $\beta_{\text{nuc}} +0.37$) compares well with that found for *O*-(4-nitrophenyl) methylphosphonate (+0.29)^{2e} and bis-2,4-dinitrophenyl phosphate (+0.31)^{2a} for reaction with nucleophiles. These values are relatively high compared with those for attack of



amines on monophosphates (4-nitrophenyl and 2,4-dinitrophenyl phosphates, +0.13¹⁶ and 0^{17a} respectively) and on phosphoramidates (+0.22).^{17b,c} The mono-ester monoanion reactions presumably involve more bond formation in the transition state of the rate-limiting step (XXVIII) than those of the monophosphates (XXIX); structures (XXVIII) and (XXIX) represent the structures of the transition states and the apparent charge on the nitrogen is a measure of the bond formation. The nature of the phosphodiester hydrolysis has been proposed by Kirby^{2b} to involve addition-elimination timing rather than the elimination-addition timing of the monophosphate reaction and we suggest that part of the driving force of the latter comes from the presence of two negatively charged oxygens of relatively high basicity; phosphonate monoesters and phosphate diesters possess an oxyanion with very low basicity consistent with poor 'internal nucleophilicity'.

Metal Ion Catalysis of the Hydrolysis of *O*-(4-Nitrophenyl) 2-Pyridylphosphonate (V).—The presence of the pyridine group in the phosphonate ester is ideally suited for chelation with a metal atom and the copper complex presumably involves a square planar *trans*-configuration by analogy with, for example, the structures of bis-(amino-acidato)Cu^{II} complexes.¹⁸ Figure 4 illustrates the effect of metal ions on the hydrolysis of the above



ester. All except the lanthanum ions do not affect the hydrolysis of *O*-(4-nitrophenyl) phenylphosphonate indi-

¹⁶ A. J. Kirby and W. P. Jencks, *J. Amer. Chem. Soc.*, 1965, **87**, 3209.

¹⁷ (a) A. J. Kirby and A. G. Varvoglis, *J. Chem. Soc. (B)*, 1968, 135; (b) G. W. Jameson and J. M. Lawler, *ibid.*, 1970, 53; (c) W. P. Jencks and M. Gilchrist, *J. Amer. Chem. Soc.*, 1965, **87**, 3199.

¹⁸ R. D. Gillard and S. H. Laurie, *Chem. Comm.*, 1969, 489.

cating that the abnormal effect of the latter ions is not due to similar catalysis. The pH dependence of the metal ion catalysed hydrolysis may not be followed above pH 8 for reasons already stated and it appears that the reaction depends on an apparent ionisation constant with pK -ca. 8—9.

The metal ion catalysed hydrolysis of *O*-(4-nitrophenyl) methylphosphonate has been studied by several workers^{2c,12,19,20} Rare earth metal ions such as La^{III} and Y^{III} are very effective catalysts whereas Al^{III}, Mg^{II}, Cu^{II}, Fe^{II}, and Fe^{III} have no observable effect. The catalytically active species of Y^{III} is probably a polymeric hydrate which acts bifunctionally.¹³

An estimate of the rate enhancement brought about by having a pyridine ligand on the phosphonate ester can be obtained by comparing the rate constant for metal ion catalysed hydrolysis with that of *O*-(4-nitrophenyl) phenylphosphonate under identical reaction conditions.

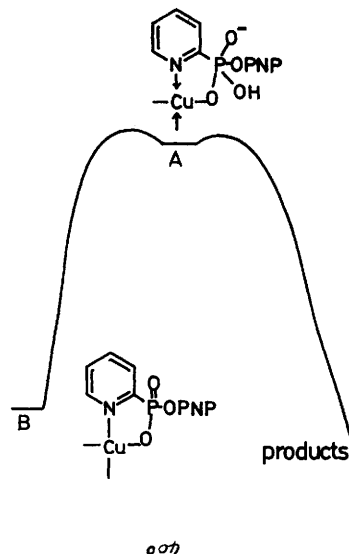


FIGURE 6 Two dimensional reaction co-ordinate for the Cu^{II} catalysed hydrolysis of *O*-(4-nitrophenyl) 2-pyridylphosphonate (V); see text for details

No rate was measurable for the latter ester in the presence of Ni^{II} and the highest possible value ($1.7 \times 10^{-8} \text{ s}^{-1}$) represents the error in the measurement. From the rate constant for the pyridine ester we estimate a rate enhancement >930. Such a rate enhancement can be explained by the inability of the analogue to form a strong complex with the metal and the formation of five-membered chelates is especially favourable. The most likely complex would be similar to that shown [(XXX)]. Such a chelate would result in neutralisation of the anionic oxygen rendering the substrate analogous to an uncharged ester and therefore more susceptible to nucleophilic attack by for example hydroxide ion. Some of the energy released on chelate formation might well result in angle strain at the phosphorus which when

¹⁹ R. J. Withey, *Canad. J. Chem.*, 1969, **47**, 4383.

²⁰ S. J. Benkovic and L. K. Dunikowski, *J. Amer. Chem. Soc.*, 1971, **93**, 1526.

constrained in a five-membered ring results in further activation to attack.²¹

In the Cu^{II} catalysed hydrolysis of 2-(imidazol-4-yl)-phenyl phosphate²⁰ it is suggested that the metal ion acts as an electrophilic catalyst reducing the p*K*_a of the leaving group and hence activating it. This may not be the origin of the catalytic activity in the case of ester (V) since the anion is clearly the ligand of choice and the ground-state structure is as in Figure 6. If the Hammond postulate holds²² then the potential energy surface connecting the two most stable levels (A and B in Figure 6) will be the lowest and therefore carry most of the reaction.

It would be interesting to compare catalytic rates with the stability constants of the metal ion complexes but these are not known. However, comparison with the stability constants for 1:1 complexes of metal with pyridine-2-carboxylic acid indicates no simple relationship (Table 4). Since some of the binding energy could be converted to strain energy it is not surprising that there is little relationship between catalytic activity and chelating power.

The importance of Tris is clear; when metal ion and pyridine ester are mixed an insoluble complex forms

²¹ R. F. Hudson and C. Brown, *Accounts Chem. Res.*, 1972, 5, 204.

TABLE 4

Comparison of catalytic rate constants for metal ions and *O*-(4-nitrophenyl) 2-pyridylphosphonate with stability constants

Metal ion	log ₁₀ <i>K</i> ^a	10 <i>k</i> ^b
Cu ²⁺	8.6	5.2
Ni ²⁺	6.4	15.5
Zn ²⁺	5.12	8.9

^a Taken from ref. 23 (0.1M-KNO₃, 25°). ^b First-order rate constants, 0.1M-Tris, pH 7.37, ionic strength 0.1M, 60°, metal ion concentration = 0.1 mmol

but in the presence of Tris the complex is soluble. It is probable that a complex is formed between metal and ester and the remaining ligand binding sites are taken by Tris or by Tris and water. In the presence of triethylenediamine buffers insoluble complexes are also formed presumably due to the inability of triethylenediamine to compete with a second molecule of ester for the binding sites on the metal.

We are grateful to the Ministry of Defence for financial support (R. A. N. and J. S. L.) and to the Royal Society and the S.R.C. for grants to purchase equipment.

[6/907 Received, 12th May, 1976]

²² G. S. Hammond, *J. Amer. Chem. Soc.*, 1955, 77, 334.

²³ 'Stability Constants of Metal-ion Complexes,' Special Publication No. 17, The Chemical Society, London, 1964.