Solvolysis of Organic Phosphates. Part IX.† Structure–Reactivity Correlations for the Hydrolysis of Organic Orthophosphate Monoesters

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Three structural parameters have been examined from the viewpoints of reliability and predictability for the linear free energy relationship study of phosphate hydrolysis: (i) stretching vibrational frequencies of P–O–C(alkyl or aromatic) and P=O bonds; (ii) the acid dissociation constant for the last dissociating proton of the phosphate (pK_{HA}); and (iii) the n.m.r. chemical shift for the alcoholic or phenolic proton (δ_{OH}) of the leaving group. Among them pK_{HA} and δ_{OH} were found to be good parameters of high sensitivity with respect to the change in structure of the leaving groups. The extent and nature of anchimeric assistance or intramolecular catalysis in the hydrolysis of organic orthophosphate monoesters have been discussed with reference to the linear free energy relationships.

THE syntheses and the reactions, particularly hydrolyses and group transfer reactions, of organic phosphates have attracted much attention from biochemists and organic chemists. An understanding of the mechanisms involved in phosphate ester hydrolyses is obviously of biochemical significance. Accumulation of rate data on the hydrolyses of various kinds of synthetic and/or natural phosphates leads to the establishment of structure–reactivity relationships and to the generalization of mechanistic criteria. Structure–reactivity correlations for phosphate and sulphate hydrolyses have been extensively studied. For example, Bunton and his co-workers,[1] and Kirby and Varvoglis [2] have reported on the reactivity of the substituted phenyl phosphates. Similarly, Fendler and Fendler have established the linear free energy relationship (l.f.e.r.) for aryl sulphate hydrolyses.[3] The esters used in their l.f.e.r. studies, however, were almost always aromatic, for which either Hammett σ or pK_a values of the leaving groups were usually adopted as the structural parameter. Certainly, the pK_a value of the leaving group is an effective and reasonable parameter for evaluation of reactivity in ester hydrolyses where P–O or S–O bond cleavage is involved as the rate-determining step. If the discussion on structure–reactivity correlations is extended from aryl to alkyl esters, one meets with several problems. First, the sensitivity of the substituent effects on alkyl ester hydrolyses is generally lower than that on aryl ester hydrolyses. Secondly, it is rather difficult to obtain reliable pK_a values for alcohols by the usual techniques because pK_a values for alcohols are generally very large,[4a] even those for aryl alcohols,[4b,c] relative to those for ordinary phenols. In addition, alkyl phosphates generally have low reactivity and consequently the kinetics must be studied at relatively high temperatures (80—100°). Thus, pK_a values determined at higher temperatures are required as the structural parameter for l.f.e.r. studies of alkyl phosphate hydrolyses. In the cases of hydrolysis of aryl phosphates, on the other hand, it is possible to adopt pK_a values determined at, for example, 25 °C as the structural parameter for l.f.e.r. studies since a kinetic study of the hydrolysis of aryl phosphates can be carried out at relatively low temperatures (<50 °C).

Bunton summarized all the rate data previously obtained for the hydrolysis of phosphate monoanions involving P–O bond fission in the transition state and suggested that the reactions involved the release of the hypothetical metaphosphate ion, which was preceded by a preliminary and partially rate-limiting proton transfer.[5] This process refers to the transfer of a proton from the phosphate group to the alkyl or aryl ester oxygen atom. However, the reaction mechanism and the involvement of anchimeric assistance still contain some ambiguities. Thus, accumulation of more rate data on alkyl phosphate hydrolyses is needed. Independently, we have prepared a variety of ring substituted pyridylalkyl phosphates and studied their spontaneous hydrolyses through kinetic measurements with particular attention to the reaction mechanism.[6-11] In these studies, we have found some unique aspects of anchimeric assistance or intramolecular catalysis. Consequently, evaluation of the extent of participation of neighbouring groups in the rate-determining process as well as characterization of the nature of the transition state is needed.

In this work, we have established the structure–reactivity correlations for the hydrolyses of organic phosphates with particular attention to alkyl phosphates having a heteroaromatic substituent. Moreover, evidence for intramolecular catalysis or anchimeric assistance in the hydrolyses was obtained from the l.f.e.r. established.

Structural Parameters for the L.f.e.r. Study.—Many investigators have suggested that organic orthophosphate monoesters usually undergo rate-determining P–O

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† Part VIII, ref. 11.

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bond cleavage at pH 3—8, where the phosphates exist predominantly in their monoanionic forms.[12] Therefore, the P–O bond energy may be the most effective parameter for evaluating the reactivity if its magnitude could be obtained directly by some experimental method. We examined three physical quantities as alternative structural parameters for the l.f.e.r. studies of the hydrolysis of organic orthophosphates: (i) stretching vibrational frequencies for the P–O–C and P=O bonds of the phosphates, $\nu_{\text{P–O–C(alkyl or aromatic)}}$ and $\nu_{\text{P=O}}$; (ii) the acid dissociation constant for the last dissociating proton of the phosphate group, pK_{HA}; and (iii) the n.m.r. chemical shift for the hydroxy-proton of either the alcohol or phenol, δ_{OH}.

TABLE 1

P=O and P–O–C frequencies for organic phosphates [a]

Phosphate	$\nu_{\text{P=O}}$/cm^{-1}	$\nu_{\text{P–O–C}}$/cm^{-1}
2-Pyridylpropyl	1292, 1175, 1157	1077, 1041, 919
2-Pyridylethyl	1254, 1219, 1156	1075, 1050, 935
2-Pyridylmethyl	1230, 1180, 1153	1060, 925
3-Pyridylmethyl	1235, 1180	1065, 1000, 941
4-Pyridylmethyl	1274, 1265, 1138	1055, 935
6-Methyl-2-pyridylmethyl	1270, 1183, 1165	1060, 950, 909
3-Hydroxy-2-pyridylmethyl	1314, 1288, 1249, 1235, 1175	1077, 922
2-Chloro-3-pyridylmethyl	1287	1054, 975
2-Amino-3-pyridylmethyl	1247, 1150, 1130	1020, 946
Trichloroethyl	1280, 1250, 1125	1036, 963, 945
Phenyl	1224, 1160	1030
Salicyl	1295, 1205	1020, 975
3-Pyridyl	1279, 1190	1047, 947
8-Quinolyl	1250, 1192, 1163, 1100	1053, 1030, 955, 933

[a] All spectra were measured by the KBr disc method.

TABLE 3

Specific rate constants for the hydrolysis of aryl phosphate monoanions at 39 °C

Phosphate	10^5k_{HA}/s^{-1}	log k_{HA}	μ/M [a]	Ref.
3-Pyridyl	2·30	−6·638	0·1	7
8-Quinolyl	0·077	−8·111	0·1	7
Phenyl	0·955	−7·020	0·1	1, 2, 6
o-Nitrophenyl	8·95	−6·048	1·0	1, 2
m-Nitrophenyl	1·61	−6·793	1·0	1, 2
p-Nitrophenyl	10·69	−5·971	1·0	1, 2
p-Methylphenyl	0·851	−7·070		1, 2
2,6-Dimethylphenyl	0·589	−7·230		1, 2

[a] Ionic strength.

(i) *Stretching vibrational frequencies for* P–O–C *and* P=O *bonds of phosphates.* In the i.r. spectra of organic phosphates the stretching vibrational frequency of P–O–C is generally observed at 900—1000 cm^{-1}, while that of P=O is around 1200 cm^{-1}; both are of high intensity. The P–O–C and P=O frequencies for the organic phosphates prepared in our laboratories are summarized in Table 1. The specific first-order rate constants for the hydrolysis of the zwitterion and monoanion species of the alkyl phosphates and for that of the monoanion species of the aryl phosphates are listed in Tables 2 and 3, respectively. These constants are for 90 and 39 °C for the alkyl and aryl phosphates, respectively, by extrapolation using the corresponding activation energies if necessary.

Thomas and Chittenden suggested that the frequencies of the P=O and P–O stretching vibrations were linearly related to the electronegativity of the substituents on the phosphorus atom.[13] Since their investigations excluded data for orthophosphate monoesters we could not adopt their relationships to our present work. Nevertheless, according to the Thomas–Chittenden postulate, one may expect that the $\nu_{\text{P=O}}$ and/or $\nu_{\text{P–O–C}}$ values may provide a good measure for the electronegativity of the leaving groups of phosphates. The P=O and P–O–C frequencies were plotted against the logarithms of the rate constants for monoanion hydrolyses. However, we could not obtain satisfactory and reliable linear relationships between these values for all the present cases. Hooidonk and Ginjaar [14] studied the

TABLE 2

Specific rate constants for the hydrolysis of alkyl phosphate zwitterions and monoanions at 90 °C [a]

Phosphate	$10^5k_{\text{H}_2\text{A}}$/s^{-1}	log $k_{\text{H}_2\text{A}}$	10^5k_{HA}/s^{-1}	log k_{HA}	μ/M [b]	Ref.
2-Pyridylpropyl	0·374	−5·427			0·1	9
2-Pyridylethyl	0·640	−5·194			0·1	9
2-Pyridylmethyl	2·33	−4·633	0·414	−5·38	0·1	6, 7, 9
3-Pyridylmethyl	0·969	−5·006	0·431	−5·37	0·1	6
4-Pyridylmethyl	0·986	−5·013	0·475	−5·32	0·1	6
6-Methyl-2-pyridylmethyl	2·74	−4·565	0·563	−5·25	0·1	9
3-Hydroxy-2-pyridylmethyl	15·5	−3·812	51·3	−3·286	0·1	8
Trichloroethyl			2·18	−4·66	0·1	10
Ethanolamine *O*-	0·933	−5·032				*c*
Ethyl			0·186	−5·73		*d*
Methyl			0·251	−5·60		25
Isopropyl			0·288	−5·54		23
Glucose 1-			0·372	−5·43		22
Glucose 6-			0·646	−5·19		20, 21
Benzyl			2·82	−4·65	1·0	27

[a] $k_{\text{H}_2\text{A}}$ and k_{HA} stand for the specific first-order rate constants of the neutral-zwitterionic and monoanionic forms, respectively. [b] Ionic strength. [c] P. W. C. Barnard, C. A. Bunton, D. Kellerman, M. M. Mahla, B. Silver, C. A. Vernon, and V. A. Welch, *J. Chem. Soc.* (*B*), 1966, 227. [d] A. Desjobert, *Bull. Soc. chim. France*, 1947, 809.

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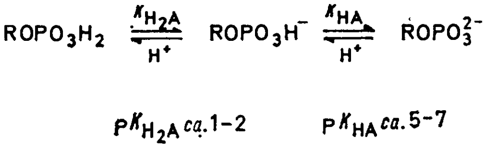
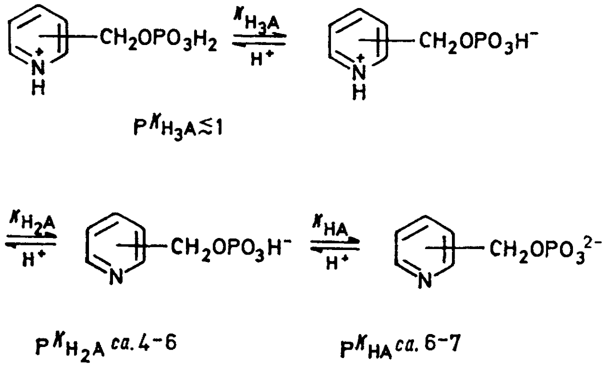
l.f.e.r. for the alkaline hydrolysis of a number of diethyl phenyl phosphates and claimed that a correlation existed between the P–O–C(aromatic) frequency and the logarithm of the first-order rate constant. However, the linearity of this relationship was rather poor. In addition, they mistook the P=O frequency for the P–O–C in assignments. Anyhow it is difficult to assign exactly these absorption bands, and also the extent of the contribution of the P=O and/or the P–O–C vibrational modes to these bands appears to be uncertain. Judging from these results, we were forced to abandon the adoption of P=O and/or P–O–C frequencies as structural parameters for our l.f.e.r. study.

(ii) *Acid dissociation constant of the second phosphate proton.* The hydrolysis of organic phosphates, which involves P–O bond fission, is assisted by an electron-attracting substituent. The pK_a value is an effective structural parameter for l.f.e.r. studies of ester hydrolyses. However, reliable pK_a values for alcohols are hard to obtain, especially at elevated temperatures, because of their weak acidity.[4]

For simple alkyl and aryl phosphate monoesters in general, three ionic species have to be considered as indicated in Scheme 1, with pK_{H_2A} *ca.* 1—2 and pK_{HA} *ca.* 5—7. For a phosphate having another basic heteroatom in the leaving group, additional ionic species must be considered, as shown in Scheme 2. Among these ionic species the most reactive is usually the monoanion with respect to the phosphate group except for the cases of phosphates having a good leaving group such as dinitrophenyl.[2] In the course of studies on the hydrolysis of a variety of pyridylalkyl phosphates,[6–11] we found that the pK_{HA} value was sensitive to the electronegativity of the leaving group. If this is the case, the pK_{HA} value may reflect the charge density on the phosphorous and/or the ester oxygen atom and consequently this thermodynamic constant can be adopted as a structural parameter for the l.f.e.r. studies instead of the pK_a value of the alcohol. Also, this parameter may reflect the P–O bond strength in the transition state. The pK_{HA} values of heteroaromatic phosphates are listed in Tables 4 and 5.



SCHEME 1



SCHEME 2

TABLE 4

Acid dissociation constants for alkyl phosphates

Phosphate	pK_{H_2A} 25 °C	pK_{H_2A} 80 °C	pK_{HA} 25 °C	pK_{HA} 80 °C	μ/M [h]	Ref.
2-Pyridylpropyl	5·60	5·09	6·90	6·75	0·1	9
2-Pyridylethyl	5·31	4·84	6·83	6·79	0·1	9
2-Pyridylmethyl	4·42	4·15	6·29	6·54	0·1	6, 19
		(4·03) [g]		(6·46) [g]	0·1	7
3-Pyridylmethyl	4·86	4·43	6·23	6·48	0·1	6, 19
4-Pyridylmethyl	5·14	4·73	6·25	6·42	0·1	6, 19
6-Methyl-2-pyridylmethyl	4·74	4·50	6·64	6·36	0·1	9, 28
		(4·43) [g]		(6·08) [g]	0·1	9
3-Hydroxy-2-pyridylmethyl	4·54	(3·80) [g]	5·75	(5·55) [g]	0·1	8
2-Chloro-3-pyridylmethyl	2·17	1·8	5·97	6·3	0·1	11, 29
2-Amino-3-pyridylmethyl	5·42	5·11 [a]	7·00	7·40 [a]	0·1	29
Trichloroethyl			5·83	6·14	0·1	10
				(5·95) [g]	0·1	10
Ethanolamine *O*-			5·57 [i]	5·7 ± 0·1 [j]		18
Ethyl				6·8 ± 0·1 [c]		*l*
Methyl			6·59 [b]	6·71 [k]		25
Isopropyl			7·02 [d]	7·35 [c]		23
Glucose 1-				6·72 [e]		22
Glucose 6-				6·35 [c]		20
Benzyl				6·12 [f]	1·0	27

[a] At 70·0 °C. [b] At 34·2 °C. [c] At 100·0 °C. [d] At 22·2 °C. [e] At 82 °C. At 75·6 °C. [g] Values in parentheses were evaluated by kinetic method. [h] Ionic strength. [i] For the last phosphate proton, the amino nitrogen atom being protonated. [j] Estimated by adopting the temperature dependency factor generally observed for an ordinary alkyl phosphate. [k] At 74·5 °C. [l] A. Desjobert. *Bull. Soc. chim. France*, 1947, 809.

On correlating these pK_{HA} values with the rate data listed in Tables 2 and 3, three linear relationships can be established as illustrated in Figures 1—3 for the monoanion and neutral-zwitterion hydrolyses. In these Figures the appropriate straight lines were drawn through the points for phosphates which hydrolyse without the aid of anchimeric assistance or intramolecular

TABLE 5

Acid dissociation constants for aryl phosphates and phenols at 25 °C

Phosphate	pK_{HA}	μ/M [d]	Ref.	Phenol	pK_a	μ/M	Ref.
3-Pyridyl	5·64	0·1	7, 28	3-Pyridinol	8·54	0·1	28
8-Quinolyl	6·42	0·1	7, 28	8-Quinolinol	9·66	0·1	*c*
Phenyl	5·88 [a]	0·1	6	Phenol	9·99		1, 2
o-Nitrophenyl	5·60 [b]		1, 2	*o*-Nitrophenol	7·23		1, 2
m-Nitrophenyl	5·50 [b]		1, 2	*m*-Nitrophenol	8·35		1, 2
p-Nitrophenyl	5·3 ± 0·1		*e*	*p*-Nitrophenol	7·14		1, 2
p-Methylphenyl	6·0 ± 0·1		*e*	*p*-Methylphenol	10·11		2
2,6-Dimethylphenyl	6·12		1	2,6-Dimethylphenol	10·58		1

[a] At 26 °C. [b] At 32 °C. [c] L. G. Sillén and A. E. Martell, ' Stability Constants of Metal-Ion Complexes,' Special Publication No. 17, The Chemical Society, London, 1964. [d] Ionic strength. [e] P. W. C. Barnard, C. A. Bunton, D. Kellerman, M. M. Mahla. B. Silver. C. A. Vernon, and V. A. Welch, *J. Chem. Soc.* (*B*), 1966, 227.

catalysis. The linear correlations are given by equations (1)—(3).

For zwitterion hydrolyses of the pyridylalkyl phosphates:

$$\log k_{\mathrm{H,A}}/\mathrm{s}^{-1}\ (\text{at } 90\ ^{\circ}\mathrm{C}) = 3{\cdot}69 - 1{\cdot}35\ \mathrm{p}K_{\mathrm{HA}}\ (\text{at } 80\ ^{\circ}\mathrm{C}) \quad (1)$$

For monoanion hydrolyses of the alkyl phosphates:

$$\log k_{\mathrm{HA}}/\mathrm{s}^{-1}\ (\text{at } 90\ ^{\circ}\mathrm{C}) = 2{\cdot}64 - 1{\cdot}23\ \mathrm{p}K_{\mathrm{HA}}\ (\text{at } 80\ ^{\circ}\mathrm{C}) \quad (2)$$

For monoanion hydrolyses of the aryl phosphates:

$$\log k_{\mathrm{HA}}/\mathrm{s}^{-1}\ (\text{at } 39\ ^{\circ}\mathrm{C}) = 3{\cdot}65 - 1{\cdot}82\ \mathrm{p}K_{\mathrm{HA}}\ (\text{at } 25\ ^{\circ}\mathrm{C}) \quad (3)$$

Bunton and his co-workers obtained an l.f.e.r. between log k_{HA} for the hydrolysis of monoalkyl or mono-

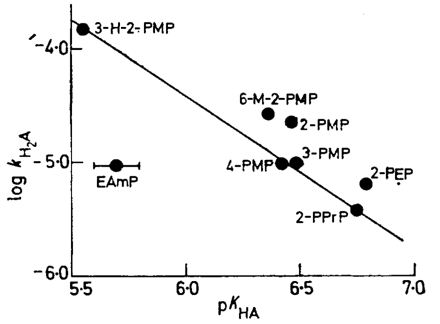


FIGURE 1 Correlation between logarithms of first-order rate constants ($k_{H,A}$/s^{-1} at 90 °C) for zwitterion hydrolysis of alkyl phosphates and acid dissociation constants for the last dissociating proton (pK_{HA} at 80 °C). Abbreviations: 3-H-2-PMP, 3-hydroxy-2-pyridylmethyl phosphate; EAmP, ethanolamine *O*-phosphate; 6-M-2-PMP, 6-methyl-2-pyridylmethyl phosphate; 2-PMP, 2-pyridylmethyl phosphate; 4-PMP, 4-pyridylmethyl phosphate; 3-PMP, 3-pyridylmethyl phosphate; 2-PEP, 2-pyridylethyl phosphate; 2-PPrP, 2-pyridylpropyl phosphate

aryl phosphates (at 100 °C) and the pK_a of the corresponding alcohols or phenols (at 25 °C) with a slope of —0·32.[1] Independently, Kirby and Varvoglis[2] have also reported the l.f.e.r. for the hydrolysis of the substituted phenyl phosphates at 100 °C using the same structural parameter as that used by Bunton [equation (4)].

$$\log k_{\mathrm{HA}}/\mathrm{min}^{-1}\ (\text{at } 100\ ^{\circ}\mathrm{C}) = 0{\cdot}91 - 0{\cdot}27\ \mathrm{p}K_{\mathrm{a}}\ (\text{at } 25\ ^{\circ}\mathrm{C}) \quad (4)$$

Through comparison of previous results with the present ones, it becomes clear that the pK_{HA} value of the phosphate is the better structural parameter than the pK_a value of the corresponding alcohol or phenol since the former shows 4—6 fold higher sensitivity than the latter. In addition, the disadvantage involved in the

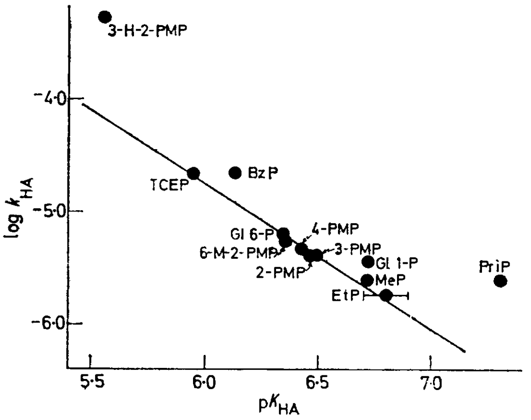


FIGURE 2 Correlation between logarithms of first-order rate constants (k_{HA}/s^{-1} at 90 °C) for monoanion hydrolysis of alkyl phosphates and acid dissociation constants for the last dissociating proton (*p*K_{HA} at 80 °C). Abbreviations: TCEP, trichloroethyl phosphate; BzP, benzyl phosphate; Gl 6-P, glucose 6-phosphate; Gl 1-P, glucose 1-phosphate; MeP, methyl phosphate; EtP, ethyl phosphate; PriP, isopropyl phosphate; others as Figure 1

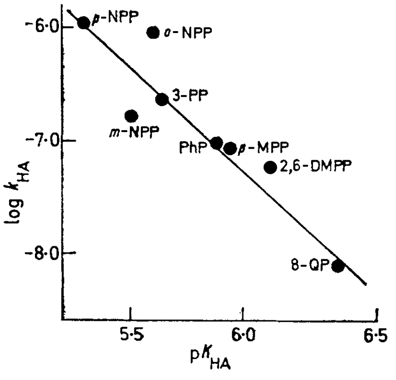
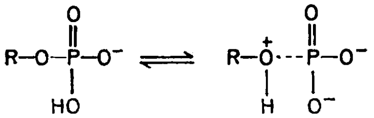


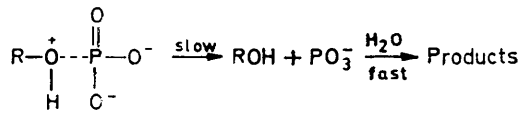
FIGURE 3 Correlation between logarithms of first-order rate constants (k_{HA}/s^{-1} at 39 °C) for monoanion hydrolysis of aryl phosphates and acid dissociation constants for the last dissociating proton (pK_{HA} at 25 °C). Abbreviations: *p*-NPP, *p*-nitrophenyl phosphate; *o*-NPP, *o*-nitrophenyl phosphate; *m*-NPP, *m*-nitrophenyl phosphate; 3-PP, 3-pyridyl phosphate; PhP, phenyl phosphate; *p*-MPP, *p*-methylphenyl phosphate; 2,6-DMPP, 2,6-dimethylphenyl phosphate; 8-QP, 8-quinolyl phosphate

latter case[1,2] is that the pK_a value obtained at 25 was used for the reaction at 100 °C in spite of evidence that the acid dissociation constant varies as a function of temperature.

The relatively low sensitivity of the pK_a value as a structural parameter for the l.f.e.r. study of monoanion hydrolyses has been rationalized by invoking opposing substituent effects along the reaction pathway.[15] Intramolecular proton transfer (5) at the pre-equilibrium stage from the phosphate group to the ester oxygen atom is suppressed by an electron-withdrawing substituent while the P–O bond fission in the transition state (6) is accelerated by an electron-withdrawing substituent.



$$\mathrm{R{-}O{-}\underset{HO}{\overset{O}{P}}{-}O^{-}} \rightleftharpoons \mathrm{R{-}\underset{H}{\overset{+}{O}}\cdots\underset{O^{-}}{\overset{O}{P}}{-}O^{-}} \qquad (5)$$



$$\mathrm{R{-}\underset{H}{\overset{+}{O}}\cdots\underset{O^{-}}{\overset{O}{P}}{-}O^{-}} \xrightarrow{\text{slow}} \mathrm{ROH + PO_3^{-}} \xrightarrow[\text{fast}]{\mathrm{H_2O}} \text{Products} \qquad (6)$$

However, for our l.f.e.r.s established between log k and pK_{HA}, the structural parameter exhibited moderately high sensitivity. The pK_{HA} values significantly reflect the P–O bond strength and the reaction rate is largely determined by the extent of P–O bond cleavage in the transition state. The pre-equilibrium proton transfer seems to be controlled by the acidity of the phosphate group, a general acid in intramolecular catalysis, and not by the charge density on the ester oxygen atom. As a result, both pre-equilibrium and rate-determining steps are assisted by an electron-withdrawing substituent. The relatively high sensitivity of the pK_{HA} values as a structural parameter may be the result of these combined effects. If another group of comparable acidity is placed at a geometrically suitable position, it will behave as an intramolecular general acid catalyst and bring about a significant rate enhancement.

(iii) *N.m.r. chemical shifts for alcoholic and phenolic protons.* In the preceding paper we investigated the temperature dependency of n.m.r. chemical shifts (δ_{OH}) for alcoholic and phenolic protons of various substituted phenols, pyridyl alcohols, and related compounds, and the structural effects of these alcohols and phenols on the n.m.r. spectra.[16] Through these investigations, we found that the chemical shifts for the alcoholic protons as well as for the phenolic protons, which were determined in anhydrous dimethyl or [$^2H_6$]dimethyl sulphoxide, were very sensitively correlated with the structure of the substituents, and that the δ_{OH} values provided useful information on the electronic nature of the substituent. Moreover, since the measurements of δ_{OH} values were over a wide temperature range (20—100 °C), they seemed adequate in providing necessary data for the l.f.e.r. study at higher temperatures. Good linear relationships between pK_{HA} and δ_{OH} have been observed for both alkyl and aryl phosphates.[16] The n.m.r. data are listed in Tables 1 and 2 of the previous paper for alcohols and phenols, respectively.

By plotting the δ_{OH} values against the logarithms of the specific rate constants three l.f.e.r.s are established, as illustrated in Figures 4—6. For this case the same criterion as used in establishing the correlation between pK_{HA} and log k was taken to draw straight lines. The same trends as those seen in the previous l.f.e.r.s were observed in terms of expressions (7)—(9).

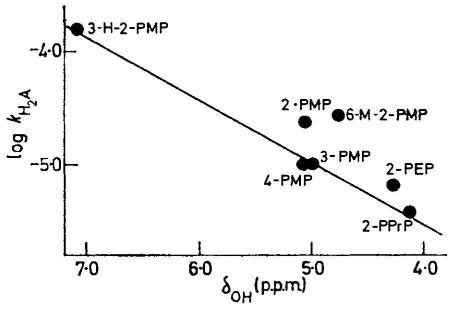


FIGURE 4 Correlation between logarithms of first-order rate constants (k_{H_2A}/s^{-1} at 90 °C) for zwitterion hydrolysis of alkyl phosphates and n.m.r. chemical shifts for alcoholic protons (δ_{OH} at 87·5 °C). Abbreviations as in Figure 1

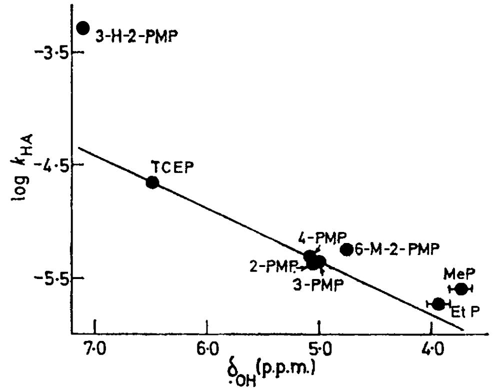


FIGURE 5 Correlation between logarithms of first-order rate constants (k_{HA}/s^{-1} at 90 °C) for monoanion hydrolysis of alkyl phosphates and n.m.r. chemical shifts for alcoholic protons (δ_{OH} at 87·5 °C). Abbreviations as in Figure 1. δ_{OH} Values for MeP and EtP have been estimated by a simple extrapolation[16]

For zwitterion hydrolyses of the alkyl phosphates:

$$\log k_{H_2A}/\mathrm{s}^{-1}\ (\text{at } 90\ ^\circ\text{C}) = -7{\cdot}72 + 0{\cdot}545\delta_{OH}\ (\text{at } 87{\cdot}5\ ^\circ\text{C}) \qquad (7)$$

For monoanion hydrolyses of the alkyl phosphates:

$$\log k_{HA}/\mathrm{s}^{-1}\ (\text{at } 90\ ^\circ\text{C}) = -7{\cdot}80 + 0{\cdot}494\delta_{OH}\ (\text{at } 87{\cdot}5\ ^\circ\text{C}) \qquad (8)$$

For monoanion hydrolyses of the aryl phosphates:

$$\log k_{HA}/\mathrm{s}^{-1}\ (\text{at } 39\ ^\circ\text{C}) = -12{\cdot}34 + 0{\cdot}582\delta_{OH}\ (\text{at } 34\ ^\circ\text{C}) \qquad (9)$$

In the l.f.e.r.s the sensitivity of the δ_{OH} value to variation of the substituent was relatively low (slopes

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[15] G. DiSabato and W. P. Jencks, *J. Amer. Chem. Soc.*, 1961, **83**, 4400.

[16] Y. Murakami and J. Sunamoto, preceding paper.

0·5—0·6). Bunton and his co-workers[1] and Kirby and Varvoglis[2] observed a similar degree of sensitivity by using the pK_a values of alcohols or phenols as the structural parameter. This may be understood from the linear relationship between the pK_a and the δ_{OH} values for substituted phenols.[16]

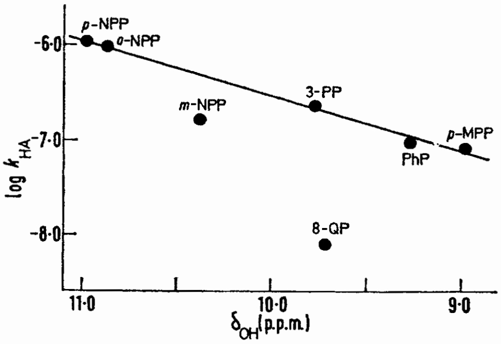
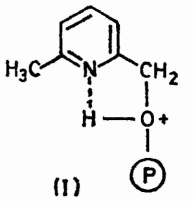
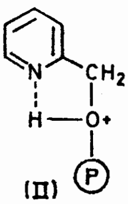


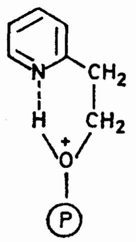
FIGURE 6 Correlation between logarithms of first-order rate constants (k_{HA}/s^{-1} at 39 °C) for monoanion hydrolysis of aryl phosphates and n.m.r. chemical shifts for phenolic protons (δ_{OH} at 34 °C). Abbreviations as in Figure 1

Deviations from the L.f.e.r.—Since there exist a few compounds which deviate, positively or negatively, from the respective l.f.e.r.s as seen in Figures 1—6 the causes need to be clarified.

(i) *Zwitterion hydrolyses of pyridylalkyl phosphates.* As shown in Figures 1 and 4, 6-methyl-2-pyridylmethyl, 2-pyridylmethyl, and 2-pyridylethyl phosphates deviated upward from the respective lines. These rate enhancements may be reasonably attributed to intramolecular general acid catalysis by the pyridinium proton [(I)—(III)],[6,7,11] which was controlled by three factors, the favourable acidity of the pyridinium relative to that of the monoanionic phosphate group, the adequate geometrical juxtaposition of the catalytic function in the reaction site, and the intramolecular mobility of the molecule toward formation of the transition state.[6,7,9]

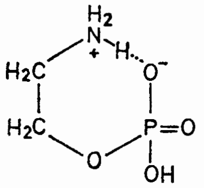

(I)


(II)


(III)

Ⓟ = PO_3H^-

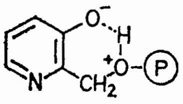
In contrast to these observations, ethanolamine *O*-phosphate (IV)[17] was far below the line (Figure 1). The local structure of phosphate (IV) around the reaction centre is very similar to that of 2-pyridylmethyl phosphate (II). Moreover, the neutral zwitterion is predominant among the three ionic species for both phosphates in the common pH range of investigation.[18] However, the basicity of the nitrogen atom of phosphate (IV) is very different from that of (II); for ethanolamine phosphate pK_N = 10·64 at 25 °C[18] and for 2-pyridylmethyl phosphate pK_N = 4·42 at 25 °C.[19] The difference in basicity between these nitrogen atoms may result in the difference in the catalytic activity. Moreover, intramolecular hydrogen bonding in structure (IV) may lead to the conformational fixing of the phosphate group,[18] which may cause the rigidity of the molecule. Unfortunately, since the discrete n.m.r. chemical shift for the alcoholic proton of ethanolamine could not be observed probably because of strong intramolecular hydrogen bonding,[16] we are unable to provide further evidence on this point.


(IV)

(ii) *Monoanion hydrolyses of alkyl phosphates.* In our investigations, a large rate enhancement was observed for the monoanion and dianion hydrolyses of 3-hydroxy-2-pyridylmethyl phosphate.[8] The positive deviation from the l.f.e.r. line is ascribed with certainty to intramolecular general acid catalysis by the 3-hydroxy-group of the phosphate (V) as previously postulated.[8]

In contrast with the result that 6-methyl-2-pyridylmethyl and 2-pyridylmethyl phosphates deviate positively from the l.f.e.r. line for zwitterion hydrolysis, both phosphates stay on the line for monoanion hydrolysis (log k_{HA} *vs.* pK_{HA}).* Consequently, both monoanionic phosphates undergo normal hydrolysis through the mechanistic pathway analogous to the cases of simple alkyl phosphates.[12]

Bunton and Chaimovich,[20] and Degani and Halmann[21] have reported independently on the hydrolysis of glucose 6-phosphate. Both groups stated that there was no anchimeric assistance by the hydroxy-groups of the sugar in monoanion hydrolysis of the phosphate. From the present l.f.e.r. study their suggestions are confirmed by the evidence that the glucose 6-phosphate monoanion is on the line. Bunton and his co-workers have suggested for the monoanion hydrolysis of glucose


(V)

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* A slight upward deviation for 6-methyl-2-pyridylmethyl phosphate in the log k_{HA}–δ_{OH} correlation (Figure 5) can be attributed to an abnormal n.m.r. effect.[16]

[17] E. Cherbuliez and J. Rabinowitz, *Helv. Chim. Acta*, 1956, **39**, 1844.

[18] S. P. Datta and A. K. Grzybowski, *J. Chem. Soc.*, 1962, 3068.

[19] Y. Murakami, M. Takagi, and H. Nishi, *Bull. Chem. Soc. Japan*, 1966, **39**, 1197.

[20] C. A. Bunton and H. Chaimovich, *J. Amer. Chem. Soc.*, 1966, **88**, 4082.

[21] Ch. Degani and M. Halmann, *J. Amer. Chem. Soc.*, 1966, **88**, 4075.

1-phosphate that the mechanistic pathway was very similar to those found for other monoalkyl phosphates.[22] From our present l.f.e.r. investigation, the observed hydrolysis rate of glucose 1-phosphate monoanion is *ca.* 1·7 times larger than expected from equation (2). Anchimeric assistance by the neighbouring group may take place to some extent in this case.

Isopropyl phosphate also deviates positively from the line (Figure 2). The mechanistic behaviour in the hydrolysis of isopropyl [23] and t-butyl phosphate monoanions [24] seems to be somehow different from that in the hydrolysis of simple primary alkyl phosphates.[25] With unimolecular P–O bond fission in the transition state in mind, the extreme rate enhancement for the branched alkyl phosphate ester must be ascribed to decreasing solvation in the transition state owing to steric hindrance around the reaction centre, as postulated in the case of 6-methyl-2-pyridylmethyl phosphate.[9] In the acid catalysed hydrolyses of ethyl and isopropyl phosphates, the marked increase in entropy of activation, from $-6{\cdot}0$ to $+8{\cdot}2$ cal mol^{-1} K^{-1}, was also attributed to a relative decrease in the number of bound water molecules in the transition state.[23] Similarly, a large rate enhancement caused by a branched bulky alkyl group has been observed by Fife and Milstein in the hydrolysis of *S*-(2-isopropyl) phosphorothioate.[26]

For the hydrolysis of benzyl phosphate monoanion the positive deviation observed in Figure 2 may be interpreted in terms of a mechanistic change associated with some mixing of the C–O bond fission pathway.[27]

(iii) *Monoanion hydrolyses of aryl phosphates.* Among the aryl phosphate monoanions, a positive deviation from the l.f.e.r. line were observed with *o*-nitrophenyl and 2,6-dimethylphenyl phosphates (Figure 3) and it could be caused either by an usual *ortho*-effect or by desolvation. On the other hand, *m*-nitrophenyl phosphate deviated negatively.

EXPERIMENTAL

All data for the rate constants and the thermodynamic constants utilized in this work have been cited from previous papers and other investigations.

Materials.—The synthesis and identification of 3-pyridyl, 8-quinolyl, phenyl, trichloroethyl phosphates, and the various pyridylalkyl phosphates have been described separately.[19, 28, 29]

I.r. Spectra.—I.r. spectra were measured on a JASCO Model DG-403 grating spectrophotometer by the KBr disc method as well as by the Nujol mull technique. No significant difference in spectra was obtained using either technique.

N.m.r. Spectra.—N.m.r. chemical shifts of the alcoholic and phenolic protons were measured in anhydrous dimethyl or [$^2H_6$]dimethyl sulphoxide at various temperatures on a Varian A-60 spectrometer. Procedures for n.m.r. measurements and characteristic features of the spectra observed for these compounds are in the preceding paper.[16]

[2/2801 *Received, 12th December, 1972*]

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[24] A. Lapidot, D. Samuel, and M. W. Broaday, *J. Chem. Soc.*, 1964, 637.

[25] C. A. Bunton, D. R. Llewellyn, K. G. Oldham, and C. A. Vernon, *J. Chem. Soc.*, 1958, 3574.

[26] T. H. Fife and S. Milstein, *J. Org. Chem.*, 1969, **34**, 4007.

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[29] Y. Murakami, J. Sunamoto, S. Kinuwaki, and H. Honda, *Bull. Chem. Soc. Japan*, in the press.