Intramolecular Catalysis of Phosphate Triester Hydrolysis. Nucleophilic Catalysis by the Neighbouring Carboxy-group of the Hydrolysis of Diaryl 2-Carboxyphenyl Phosphates

By **R. H. Bromilow, S. A. Khan,** and **A. J. Kirby,*** University Chemical Laboratory, Cambridge CB2 1EW

2-Carboxyphenyl diphenyl phosphate is rapidly hydrolysed to salicylic acid and diphenyl phosphate, in a reaction subject to highly efficient catalysis by the ionised carboxy-group. A rate enhancement of the order of 10^8 is observed, and there is convincing evidence that the reaction involves intramolecular nucleophilic catalysis. The stereochemistry of this non-linear displacement at phosphorus is in striking contrast to the corresponding reaction of the monophenyl ester, in which selective exocyclic displacement occurs, but is consistent with Westheimer's rules for pseudorotation. Kinetic and product studies with five aryl 2,3-dicarboxyphenyl phenyl phosphates support the proposed mechanism, and show that intramolecular displacements on these phosphate triesters depend exclusively on the basicity of the leaving group, and not at all on geometry. Linear free-energy relationships show that the sensitivity to the basicity of the leaving group is the largest yet measured for a displacement reaction, and allow order-of-magnitude calculations of rate constants for the breakdown of pentacovalent intermediates.

We have shown [1] that the hydrolysis of 2-carboxyphenyl phenyl phosphate (1) involves intramolecular nucleophilic catalysis by the ionised carboxy-group. Exocyclic displacement of phenoxide accounts for over 99% of the reaction, although this is the poorer of the two possible leaving groups. The hydrolysis of dialkyl 2-carboxyphenyl phosphates (2) also involves intramolecular nucleophilic catalysis by the carboxylate group,[2] but in this case displacement is exclusively endocyclic, and the products are salicylic acid and the dialkyl phosphate.

We consider [1] that displacement is stereospecific in the first case because reaction proceeds by way of a quinquecovalent intermediate (3), which does not undergo pseudorotation [3] because it has two negatively charged oxygen atoms in equatorial positions. The corresponding intermediate (4) from a triester, on the other hand, has only one O^-, which can remain equatorial on pseudorotation. Consequently, the potential-energy barrier is greatly reduced, and the salicylate oxygen atom can depart from the apical position of the pseudorotamer (5).

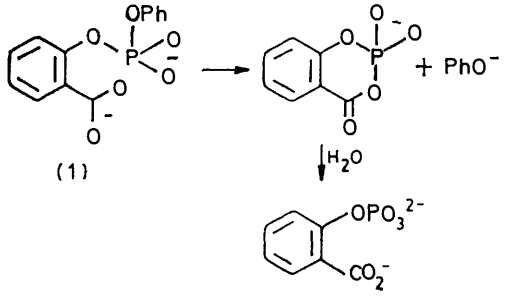
The question now arises, is the energy barrier to pseudorotation so small in a reaction of this type that it

[1] S. A. Khan, A. J. Kirby, M. Wakselman, D. P. Horning, and J M. Lawlor, *J. Chem. Soc.* (*B*), 1970, 1182.

[2] R. H. Bromilow, S. A. Khan, and A. J. Kirby, *J. Chem. Soc.* (*B*), 1971, 1091.

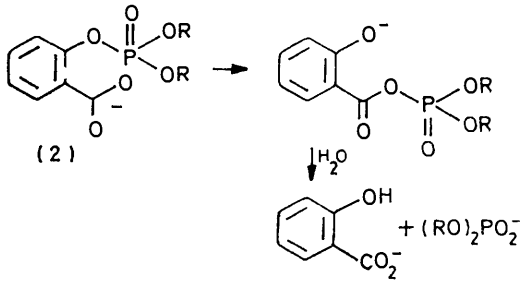
[3] F. H. Westheimer, *Accounts Chem. Res.*, 1968, **1**, 70.

can be neglected entirely? If so, intramolecular nucleophilic displacements at the phosphorus centre of triesters should depend not at all on geometry, but solely



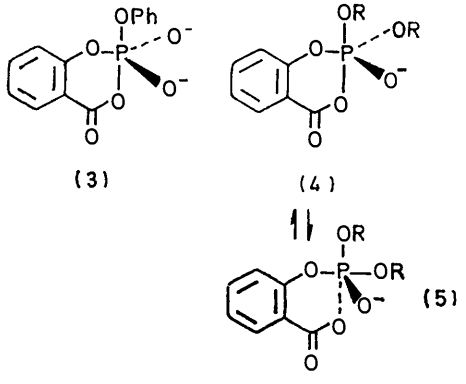
(1)

on leaving group capability. The results obtained with the dialkyl 2-carboxyphenyl phosphates (2) do not help



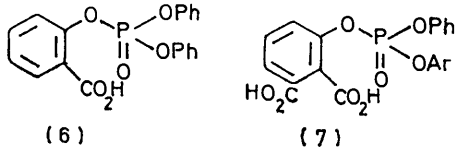
(2)

to decide this question because the carboxylate group is too weakly basic to displace an alkoxide anion, and the



(3) (4) (5)

observed reaction is the only one possible. So we have prepared several diaryl 2-carboxyphenyl (6) and 2,3-di-



(6) (7)

a; Ar = Ph
b; Ar = 3-ClC_6H_4
c; Ar = 4-ClC_6H_4
d; Ar = 3-$NO_2C_6H_4$
e; Ar = 4-$NO_2C_6H_4$

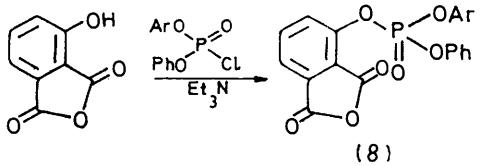
carboxyphenyl (7) phosphates, to investigate the balance between endocyclic and exocyclic displacement in cases where electronic effects are less decisive.

EXPERIMENTAL

Petrol refers to light petroleum.

2-Carboxyphenyl Diphenyl Phosphate (6).—This was prepared from diphenyl phosphorochloridate and benzyl-*o*-hydroxybenzoate. Attempts to prepare this and substituted phenyl esters from unprotected salicylic acid failed. Diphenyl phosphorochloridate (0·1 mol) was added slowly to the sodium salt of benzyl *o*-hydroxybenzoate (0·1 mol) in dry benzene in the cold. The mixture was stirred a further 30 min at room temperature, then the sodium chloride was filtered off and the solvent was removed under reduced pressure. The crude product was dissolved in ethanol and hydrogenolysed over 5% palladised charcoal at room temperature. Filtration and removal of the solvent gave solid *2-carboxyphenyl diphenyl phosphate*, m.p. 80° (from ether–petrol) (Found: C, 61·3; H, 4·45; P, 8·65. $C_{19}H_{15}O_6P$ requires C, 61·6; H, 4·05; P, 8·35%).

This procedure is not suitable for the preparation of nitroaryl derivatives, because the nitro-groups are reduced in the hydrogenolysis step. This problem was circumvented, after it was found that the introduction of a second carboxyl-group, to give 2,3-dicarboxyphenyl diphenyl phosphate, does not affect the mechanism of hydrolysis. Sufficient protection for both carboxy-groups was readily provided by linking them as the phthalic anhydride.



(8)

a; Ar = Ph
b; Ar = 3-ClC_6H_4
c; Ar = 4-ClC_6H_4
d; Ar = 3-NO_2·C_6H_4
e; Ar = 4-NO_2·C_6H_4

4-Nitrophenyl Phenyl Phosphorochloridate.—To a suspension of sodium *p*-nitrophenoxide (16·1 g, 0·1 mol) in dry benzene (400 ml) was added phenyl phosphorodichloridate (28 g, 0·13 mol) and the mixture was stirred under reflux for 4 h. Sodium chloride was filtered off and the solvent was removed by evaporation to give a yellow oil. Distillation gave a fraction, b.p. 182—185° at 0·4 mmHg (lit.,[4] 203—209° at 1 mmHg), which solidified, m.p. 78—79° (from ether–petrol) (lit.,[4] 78—80°).

3-Nitrophenyl Phenyl Phosphorochloridate.—This was prepared in the same way, b.p. 173—175° at 0·3 mmHg, and was used without further purification.

4-Chlorophenyl Phenyl Phosphorochloridate.—4-Chlorophenol (12·9 g, 0·10 mol) and monophenyl phosphorodichloridate (25 g, 0·11 mol) were heated together with lithium chloride catalyst (100 mg) at 150° for 6 h, by which time evolution of hydrogen chloride gas had ceased. The product was distilled and a fraction, b.p. 164—168° at 0·8 mmHg, was collected. This was then redistilled through a short vacuum-jacketed Vigreux column to give the product (12·4 g), b.p. 160—164° at 0·5 mmHg, which was used without further purification.

3-Chlorophenyl Phenyl Phosphorochloridate.—This was prepared similarly. The product (13·9 g), b.p. 157—161° at 0·5 mmHg, was used without further purification.

2,3-Oxydicarbonylphenyl Diphenyl Phosphate (8a).—To a

[4] I. Dilaris and G. Eliopoulos, *J. Org. Chem.*, 1965, **30**, 686.

suspension of 3-hydroxyphthalic anhydride [5] in dry benzene were added equivalent amounts of diphenylphosphorochloridate and triethylamine. The mixture was stirred, with exclusion of moisture, for 4 h at room temperature, as triethylamine hydrochloride was gradually precipitated. This was filtered off, and the solvent was removed by evaporation to give a yellow oil, which slowly crystallised. This crude product was dissolved in a small amount of acetone, and careful addition of ice-cold water gave the crude triester as a white amorphous solid. Recrystallisation from acetone–ether gave *needles*, m.p. 106—108° (Found: C, 60·65; H, 3·35; P, 8·0. $C_{20}H_{13}O_7P$ requires C, 60·6; H, 3·3; P, 7·85%).

The following anhydrides of diaryl 2,3-dicarboxyphenyl phosphate were prepared by the same method, from 3-hydroxyphthalic anhydride and the corresponding diaryl phosphorochloridates.

3-*Chlorophenyl* 2,3-*Oxydicarbonylphenyl Phenyl Phosphate* (8b).—This could be recrystallised from solvents such as chloroform–petrol, but only with a certain amount of decomposition. The most satisfactory sample was obtained by precipitation from acetone with ice-cold water, and had m.p. 63—65° (Found: C, 54·8; H, 3·05. $C_{20}H_{12}ClO_7P$ requires C, 55·8; H, 2·8%).

4-*Chlorophenyl* 2,3-*Oxydicarbonylphenyl Phenyl Phosphate* (8c).—This would not crystallise, and attempted purification by chromatography led to decomposition. The crude oil, exhaustively vacuum dried, was used in the kinetic experiments (Found: C, 54·85; H, 3·05%).

Clearly the two chloro-compounds contain some unsubstituted ester (8a). The basicity of the phenyl and chlorophenyl groups is so similar that no method of synthesis can give a well-defined single product. The results obtained with these two esters were considered useful, since three other well-characterised members of the series were available, but detailed measurements were not made.

3-*Nitrophenyl* 2,3-*Oxydicarbonylphenyl Phenyl Phosphate* (8d).—This was precipitated from acetone with cold water, followed by recrystallisation from chloroform–petrol to give pale pink *microcrystals*, m.p. 107—109°. The compound was stored in the dark as it rapidly darkened on exposure to light (Found: C, 54·35; H, 2·7; N, 2·95; P, 6·9. $C_{20}H_{12}NO_9P$ requires C, 54·5; H, 2·7; N, 3·2; P, 7·05%).

4-*Nitrophenyl* 2,3-*Oxydicarbonylphenyl Phenyl Phosphate* (8e).—This was precipitated from acetone with cold water, followed by recrystallisation from chloroform–petrol giving *microcrystals*, m.p. 140—140·5° (Found: C, 54·3; H, 3·0; N, 3·0; P, 6·95%).

RESULTS

Conditions and methods were generally as described previously,[2] with measurements made at 39° and ionic strength 1·0 (KCl).

2-*Carboxyphenyl Diphenyl Phosphate*.—Hydrolysis was followed by measuring the increase in absorbance due to the salicylic acid released at 298·5 nm. Excellent first-order kinetics were observed at all pH values, but the final absorbance, which was constant for runs between pH 5·8 and 12, fell sharply below pH *ca.* 3.

Similar behaviour was observed previously [2] in the hydrolysis of dialkyl 2-carboxyphenyl phosphates, and is a result of a change in the products of hydrolysis. Salicylic acid and diphenyl phosphate are formed almost exclusively above pH 3—4, but salicylic acid is only a minor product at low pH. Product ratios were estimated (*a*) spectrophotometrically, using the absorption due to salicylic acid at 310 nm, where phenol absorbs only very weakly and (*b*) by measuring the concentration of phenol produced. For this measurement the modified [6] Ettinger [7] procedure was employed. Results obtained independently by the two methods were in good agreement. Kinetic data and results of the product analyses for the hydrolysis of 2-carboxyphenyl diphenyl phosphate are given in Table 1.

The acyl phosphate expected to be an intermediate in this hydrolysis could be trapped as the hydroxamic acid, by carrying out the hydrolysis in the presence of a high concentration of hydroxylamine, as described previously for the reaction of a dialkyl ester.[1] Every hydroxamic acid test was positive and in this case also the rate of formation (0·58 min^{-1}) was very close to the rate of the hydrolysis (0·70 min^{-1}) at the same pH (5·90). In the acid region the hydroxylamine trapping procedure cannot be used. 2-Carboxyphenyl diphenyl phosphate was hydrolysed in 50% aqueous methanol (1M in HCl) and the solution was extracted with ether after 10 half-lives. Methyl salicylate was readily detected in the product by (t.l.c.) comparison with an authentic sample. Thus an acylating agent is present in solution during the hydrolysis of the acid form of the ester also, and this can only reasonably be an acyl phosphate.

TABLE 1

Rate constants for the hydrolysis of 2-carboxyphenyl diphenyl phosphate, at 39° and ionic strength 1·0

Conditions	pH	Salicylic [a] acid (%)	Phenol (%) [b]	k_{hyd}/ min^{-1}
1M-HCl		11·1	87·2	0·0290
0·1M-HCl		18·1	82·0	0·0301
0·04M-HCl	1·4	25·0		
0·01M-HCl	2	48·0	49·2	0·0489
0·05M-Formate buffer	3·10	82·4	16·5	0·205
0·05M-Formate buffer	3·80	87·9	11·1	
0·05M-Acetate buffer	4·08			0·532
0·05M-Acetate buffer	4·14	92·0		
0·05M-Acetate buffer	5·0			0·693
0·05M-Acetate buffer	5·31	96·1		
0·05M-Phosphate buffer	6·5			0·693
0·05M-Phosphate buffer	6·69	96·1	4·0	
0·05M-TRIS buffer [c]	8·1			0·708
0·05M-TRIS buffer [c]				0·704
0·05M-Carbonate buffer	9·6	96·0	4·3, 5·3 [d]	0·702
0·10M-Carbonate buffer	9·6			0·702
0·05M-Carbonate at 25°	9·6			0·189
0·05M-Carbonate at 32°	9·6			0·378
0·01M-NaOH	12			0·735

At pH 9·6 $\Delta H^{\ddagger}_{av} = 16·7 \pm 0·5$ kcal mol^{-1} and $\Delta S^{\ddagger}_{39} = -5 \pm 2$ cal mol^{-1} K^{-1}.

[a] Estimated spectrophotometrically (see text). [b] Estimated independently (see text). [c] Two otherwise identical runs using 0·05M-TRIS, 50% free base, in H_2O and D_2O. TRIS = tris-(2-hydroxyethyl)amine. [d] Two separate runs.

Aryl 2,3-*Dicarboxyphenyl Phenyl Phosphates*.—The free diacids were generated by incubating the phthalic anhydride (8) in 50% aqueous dioxan (1M in HCl) for 30 min at 39°. [The half-life of the anhydride of the diphenyl ester (8a) is 2·8 min under these conditions, while the subsequent

[5] E. L. Eliel, A. W. Burgstahler, D. E. Rivard, and L. Haefele, *J. Amer. Chem. Soc.*, 1955, **77**, 5092.

[6] 'Organic Reagents for Metals,' ed. W. C. Johnson, Hopkin and Williams, Chadwell Heath, 1955, 5th edn., p. 8.

[7] M. B. Ettinger, C. C. Ruchhoft, and R. J. Lishka, *Analyt. Chem.*, 1951, **23**, 1783.

hydrolysis of the triester diacids is many times slower.] A small amount of the acid solution was diluted with a large excess (at least 100-fold) of buffer to initiate the phosphate hydrolysis. The pH of each solution was measured at the end of the reaction.

The initial product of hydrolysis of the diphenyl phosphate ester (8a) is 3-hydroxyphthalic anhydride. Hydrolysis of the ester in phosphate buffer (pH 6·18) showed a rapid initial increase in absorbance at 397 nm, an absorption maximum of 3-hydroxyphthalic anhydride.[8] This absorption reached maximum intensity after *ca.* 5 min, and its disappearance followed good first-order kinetics after *ca.* 20 min of reaction. The rate constant for this disappearance was 0·154 min^{-1} (39°; pH 6·18), identical with that measured for the hydrolysis of 3-hydroxyphthalic anhydride (0·157 min^{-1} at 39° and pH 6·22).

In order to isolate the hydrolysis of the phosphate group the hydrolysis of 2,3-dicarboxyphenyl diphenyl phosphate was followed at the isosbestic point for the hydrolysis of 3-hydroxyphthalic anhydride at the pH of the particular buffer used.[8] As found previously,[8] isosbestic points could not be obtained between pH 5—8, and accurate measurements could not therefore be made in this region.

Above pH 5 3-hydroxyphthalic acid is the almost exclusive final product of hydrolysis, but at lower pH increasing amounts of phenol are produced. 3-Hydroxyphthalic acid was estimated spectrophotometrically, at 310 nm, in the same way as salicylic acid from 2-carboxyphenyl diphenyl phosphate. The phenol released was estimated independently, as before. The results were closely similar to those obtained for 2-carboxyphenyl diphenyl phosphate for the anion reactions, but the percentage of phenol produced from the phthalic acid derivative did not rise above 50% in the acid region. Results are given in Table 2.

TABLE 2

Rate constants for the hydrolysis of 2,3-dicarboxyphenyl diphenyl phosphate, at 39° and ionic strength 1·0

Conditions	pH	3-Hydroxyphthalate produced (%)	k_{hyd}/min^{-1}
1M-HCl		46·8	$2·45 \times 10^{-3}$
0·1M-HCl		48·2	$2·22 \times 10^{-3}$
0·01M-HCl	2	81·2	$6·30 \times 10^{-3}$
0·05M-Formate buffer	2·96	91·5	$2·89 \times 10^{-2}$
0·05M-Acetate buffer	4·10	95·0	$9·20 \times 10^{-2}$
0·05M-Acetate buffer	4·68		0·169
0·05M-TRIS buffer	8·24	97·1	
0·05M-TRIS buffer	8·89		0·217
0·05M-Carbonate buffer	9·45	96·0	0·215
0·05M-Carbonate buffer	9·94		0·220
0·01M-NaOH		87·6	0·233

Similar methods were used to measure the product ratios from the *m*- and *p*-chlorophenyl esters (7b) and (7c) in the pH-independent region. The method of phenol estimation used does not distinguish between phenol and a chlorophenol, and the yield of the latter was obtained by assuming that k_{exo}/k_{endo} *for the release of phenol* is constant for the three esters (7a—c). The yield of chlorophenol can thus be obtained by difference (Table 3).

3-Nitrophenyl 2,3-Dicarboxyphenyl Phenyl Phosphate (7d).—In this case comparable amounts of 3-nitrophenol and 3-hydroxyphthalic acid are produced across the whole pH range. 3-Hydroxyphthalic acid is formed by way of the anhydride, at least above pH 5, as the following experiment shows. When the solution of starting material was brought to pH 8·7 a rapid initial increase of absorbance was observed

TABLE 3

Rate constants and product distributions for the hydrolysis of aryl 2,3-dicarboxyphenyl phenyl phosphate dianion (11) [a]

Ester	pK_a of ArOH	k_{hyd}/min^{-1}	Exocyclic displacement (%) (k_{exo})	Endocyclic displacement (%) (k_{endo})
(7a)	9·95	0·216	3·5 ± 1 ($7·55 \times 10^{-3}$)	96 ± 2 (0·207)
(7b)	9·02	0·625	17 ± 2 [b] (0·106)	81·5 ± 3 (0·510)
(7c)	9·38	0·416	3·8 ± 1 [b] ($1·68 \times 10^{-2}$)	94·5 ± 2 (0·392)
(7d)	8·35	4·18	68 ± 2 (2·84)	32 ± 2 (1·34)
(7e)	7·14	59·9	98 ± 2 (58·6)	2 ± 1 (1·20)

[a] Rates in the pH-independent region between pH 5 and 11 at 39° and ionic strength 1·0. Product ratios [and rate constants for the chloro-compounds (8b) and (8c)] measured at pH *ca.* 10. [b] For displacement of chlorophenol. 1·5% (7b) and 1·7% (7c) of phenol also displaced (see text).

at 395 nm. This absorbance reached a maximum after 25 s, then decreased almost as rapidly to a lower value which remained constant after 2—3 min. This final absorbance was due to the 3-nitrophenolate ion [$\lambda_{max.}$ 395 nm ($\varepsilon_{max.}$ 1480)], but the initial products evidently included the more strongly absorbing 3-hydroxyphthalic anhydride anion [$\lambda_{max.}$ 397 nm ($\varepsilon_{max.}$ 6000 [8])] which is rapidly formed and only slightly less rapidly hydrolysed under these conditions.

The rate of the initial fast reaction of the phosphate (7d) was therefore measured at the isosbestic point for 3-hydroxyphthalic anhydride and its hydrolysis products at each pH used. The results appear in Table 4. The product ratio was estimated spectrophotometrically, using the absorption maximum of 3-nitrophenolate at 395 nm. The final

TABLE 4

Rate constants for the hydrolysis of 2,3-dicarboxyphenyl 3-nitrophenyl phenyl phosphate (7b), at 39° and ionic strength 1·0

Conditions	pH	k_{hyd}/min^{-1}
1M-HCl		$1·94 \times 10^{-2}$
0·1M-HCl		$2·34 \times 10^{-2}$
0·01-HCl	2	$9·90 \times 10^{-2}$
0·05M-Formate buffer	3·08	0·429
0·05M-Formate buffer	3·72	1·28
0·05M-Acetate buffer	4·05	2·11
0·05M-Acetate buffer	4·79	4·04
0·05M-Acetate buffer	5·26	4·24
0·05M-TRIS buffer	7·92	4·20
0·05M-TRIS buffer	8·70	4·12
0·05M-Carbonate buffer	9·54	4·08
0·05M-Carbonate buffer	10·20	4·16

absorbance obtained on hydrolysis was measured in 0·4M-NaOH, and was compared with the final absorbance expected if 3-nitrophenolate was the only product. Only 3-nitrophenolate of the final hydrolysis products absorbs at 395 nm. 3-Nitrophenyl phenyl phosphate, the second product from the reaction leading to 3-hydroxyphthalate, is quite stable except in strong alkali. When the alkaline solution of hydrolysis products was heated under nitrogen in a seale tubed for 20 h at 100° the final absorbance at 395 nm rose to the calculated value. This procedure gave a

[8] A. R. Fersht and A. J. Kirby, *J. Amer. Chem. Soc.*, 1968, **90**, 5833.

figure of 68 ± 3% of the theoretical yield of *m*-nitrophenol (mean of two runs in carbonate buffers at pH 9·6 and 10·2).

4-Nitrophenyl 2,3-Dicarboxyphenyl Phenyl Phosphate (7e). —In this case almost exclusive exocyclic displacement occurs, and the hydrolysis was followed by measuring the release of 4-nitrophenol, at 325 nm below pH 7, and at 400 nm for the anion. The reaction was too fast to measure by conventional techniques at 39° so the pH–rate profile was obtained at 17°. The plateau at 39° was measured directly using a stopped-flow apparatus attached to a Gilford spectrophotometer (by courtesy of Dr. A. R. Fersht), and the pH-jump technique. Results appear in Table 5.

TABLE 5

Rate constants for the hydrolysis of 2,3-dicarboxyphenyl 4-nitrophenyl phenyl phosphate, at ionic strength 1·0

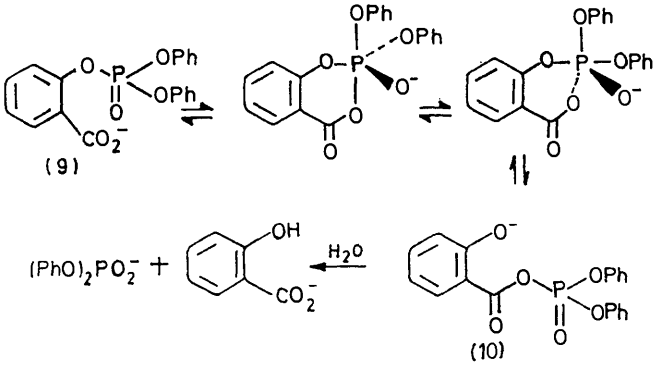
Conditions	pH at 39°	k_{hyd}/min^{-1}
1M-HCl		$3·52 \times 10^{-2}$
0·1M-HCl		$8·56 \times 10^{-2}$
0·01M-HCl	2	0·66
0·05M-Formate buffer	3·02	5·01
0·05M-Carbonate buffer	9·6	60·3 [a]
0·05M-Carbonate buffer	10·2	59·4 [a]
	At 17°	
0·1M-HCl		$1·11 \times 10^{-2}$
0·01M-HCl	2	$7·22 \times 10^{-2}$
0·05M-Formate buffer	3·12	0·628
0·05M-Formate buffer	3·54	1·84
0·05M-Acetate buffer	4·05	3·52
0·05M-Acetate buffer	5·01	8·83
0·05M-Acetate buffer	5·67	11·2
0·05M-Phosphate buffer	6·55	11·2
0·05M-TRIS buffer	8·89	10·9
0·05M-Carbonate buffer	9·60	10·8
0·05M-Carbonate buffer	10·30	10·8

[a] Measured using a stopped-flow apparatus (see text).

DISCUSSION

The hydrolysis of 2-carboxyphenyl diphenyl phosphate (6) resembles that of the dialkyl esters (2) in almost every particular. Hydrolysis is very much faster than expected for the compound lacking the carboxy-group (by a factor in the region of 10^8 in the case of the anion). Salicylic acid is produced almost quantitatively (96%) from the anion (9), but is only a minor product (10%) from the hydrolysis of the acid form (6). An intermediate, which is an acylating agent, and presumably the acyl phosphate (10) (or its conjugate acid) is formed in each case: this can be trapped as methyl salicylate when the acid form is solvolysed in 50% aqueous methanol, or as the hydroxamic acid when the anion is hydrolysed in the presence of a high concentration of hydroxylamine. The rate of formation of this hydroxamic acid can be measured, and is close to that of the hydrolysis in the absence of hydroxylamine, as expected if the formation, rather than the hydrolysis, of the intermediate acyl phosphate is rate determining. Kinetic parameters, such as the solvent deuterium isotope effect (k_H/k_D = 1·0) and the low negative entropy of activation (−5 ± 2 cal mol^{-1} K^{-1} the anion reaction), are similar.

There seems no reason to doubt, therefore, that the mechanism of hydrolysis is the same in the two cases, and that it involves intramolecular nucleophilic catalysis by the carboxy-group. (Scheme 1 outlines this mechanism for the reaction of the anion.)



SCHEME 1

Significant differences of detail are that the hydrolysis of the diphenyl ester (6) is faster than that of the dialkyl esters (by factors of *ca.* 10 for the acids and 100 for the anions) and that exocyclic displacement of phenoxide does occur to a small but measurable extent. The proportionately greater increase in the rate of hydrolysis of the anion is reflected in a much steeper change in the pH–rate profile (Figure 1) in the region of the pK_a value

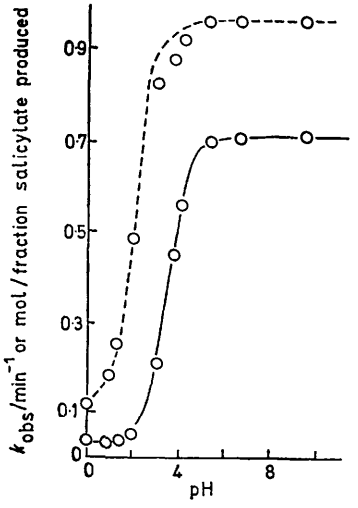


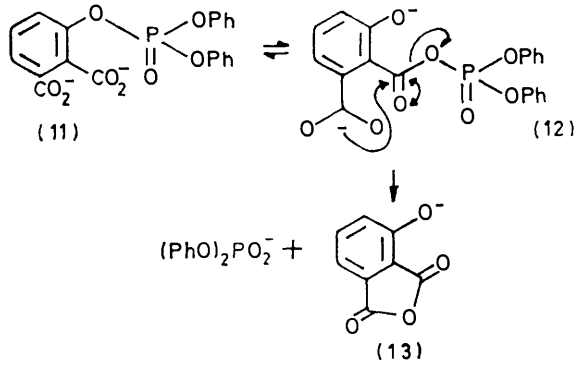
FIGURE 1 pH–Rate and –product (broken line) profiles for the hydrolysis of 2-carboxyphenyl diphenyl phosphate, at 39° and ionic strength 1·0. The curves are calculated from the measured product ratios and pH-independent rates, and are based on a pK_a value of 3·5.

of the carboxy-group of (6) [the (kinetic) pK_{app} is 3·5, as expected for (6), but the compound is too reactive for its pK_a value to be measured by conventional methods]. It also results in a sigmoid pH–product profile (Figure 1) with an apparent pK_a (2·1) considerably lower than the true pK_a.

Particularly striking is the comparison between the reactions of 2-carboxyphenyl diphenyl phosphate (6) and the diester, 2-carboxyphenyl phenyl phosphate [1] (1). In each case the carboxylate group can displace either

phenoxide or the oxygen of the salicylic acid residue. In the case of the triester, endocyclic displacement of the latter group gives a near-quantitative yield of salicylic acid, as expected, since phenoxide is the poorer leaving group. Yet phenoxide is displaced exclusively from the diester. Assuming that 1% of endocyclic displacement might not have been detected in the diester work (almost certainly an over-estimate) and that the sensitivity to the leaving group is similar for the diester and triester (which is true, as we show below), we can calculate that the additional free energy barrier to endocyclic displacement in the reaction of the diester is at least 5 kcal mol^{-1}. This barrier is presumably that associated with pseudorotation, and since the entropies of activation differ only slightly for the diester and triester reactions (that for the triester reaction, which includes a pseudorotation, is actually slightly more favourable), we can conclude that the *enthalpy* of activation for the pseudorotation process of the quinquecovalent dianion (3) is greater than 5 kcal mol^{-1}.

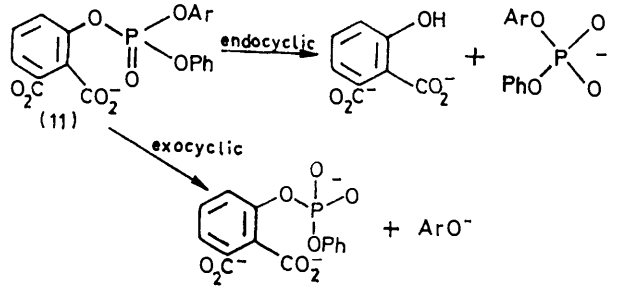
We now take up the question of whether there is a detectable pseudrotation barrier in the quinquecovalent intermediate (monoanion) derived from a triester (Scheme 1). We made 2,3-dicarboxyphenyl diphenyl phosphate originally to test our conclusion that the rate determining step in the hydrolysis of 2-carboxyphenyl diphenyl phosphate (Scheme 1) is some step in the sequence leading to the acyl phosphate intermediate (10), rather than in its hydrolysis. If the hydrolysis of the acyl phosphate were rate determining, the reaction would be expected to be accelerated by a second carboxy-group as in (12) (*cf.* the hydrolysis of the corresponding acetate ester, 3-acetoxyphthalate [8]). The anion (12) of



3-hydroxyphthalic anhydride in fact is the initial product from the hydrolysis of the dianion (11) (see Experimental section), but its rate of formation is actually 3—4 times *slower* than the hydrolysis of 2-carboxyphenyl diphenyl phosphate under the same conditions. This is consistent with our conclusion that the *formation* of the acyl phosphate is rate determining: the second carboxy-group evidently accelerates the hydrolysis of the acyl phosphate, as expected, but without affecting the rate of the overall reaction.

The hydrolysis of the phthalic acid derivative (11) thus differs very little from that of 2-carboxyphenyl diphenyl phosphate. It is a few times slower, and the acid form (7a) gives a higher proportion of endocyclic displacement product [*ca.* 50% of 3-hydroxyphthalic anhydride, compared with 10% salicylic acid from the acid form of 2-carboxyphenyl diphenyl phosphate]. This difference probably results from catalysis by the second carboxy-group of the hydrolysis of the fully protonated form of the acyl phosphate (12), which would favour the endocyclic displacement route: but is in any case observed only in the acid region. The dianion gives 96% of endocyclic displacement, exactly the same figure as that observed for the anion of 2-carboxyphenyl diphenyl phosphate.

At this stage it became clear that diaryl 2-carboxyphenyl phosphates, especially those derived from nitrophenols, would be difficult to prepare, because of the need to protect the carboxy-group of salicylic acid.



a; Ar = Ph
b; Ar = 3-ClC_6H_4
c; Ar = 4-ClC_6H_4
d; Ar = 3-$NO_2C_6H_4$
e; Ar = 4-$NO_2C_6H_4$

SCHEME 2

Since the carboxy-groups of 3-hydroxyphthalic acid are sufficiently protected as the anhydride, we used diaryl phosphates (7) of this phenol to examine the effect of varying the leaving group on the balance between endocyclic and exocyclic displacement at phosphorus by the carboxylate group.

Five compounds were compared; the diphenyl ester (7a) described above, and the *m*- and *p*-chloro- and -nitro-phenyl phenyl esters (7b—e). pH-Rate profiles for hydrolysis were measured for each compound, and product ratios determined for hydrolysis in the pH-independent region at pH *ca.* 10, using spectrophotometric assays for both the phenol and the 3-hydroxyphthalate produced. The relative importance of the two pathways (Scheme 2) changed as expected with changes in the basicity of the leaving group ArO^-. Whereas displacement of phenoxide represents only 4% of the reaction of the diphenyl ester (7a), exocyclic displacement accounts for *ca.* 98% of the reaction of the *p*-nitrophenyl ester (7e). The rates of endocyclic and exocyclic displacement are comparable for the *m*-nitrophenyl ester (7d). Full results are given in Table 3.

If the potential energy barrier to pseudorotation is significant in this reaction, it should be reflected in the relative proportions of endocyclic and exocyclic displacement, since pseudorotation is necessary for exocyclic

displacement only. Figure 2 is a logarithmic plot of this ratio, which is the ratio of k_{endo}/k_{exo} for the breakdown to products of the pentacovalent intermediate (Scheme 1), against the pK_a value of the conjugate acid of the exocyclic leaving group ArO^-. The free energy relationship

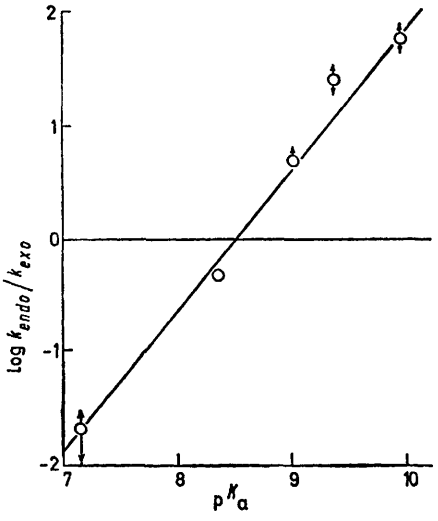


FIGURE 2 Linear free-energy relationship between the product ratio, k_{endo}/k_{exo}, for the hydrolysis of the five esters (7a—e), and the pK_a value of the conjugate acid of the exocyclic leaving group ArO^-. The arrows represent the limits of experimental error

is linear, and intercepts the x-axis at pK_a 8·52. Thus the leaving group capability of the salicylate oxygen is equal to that of an exocyclic leaving group ArO^- derived from a phenol of pK_a 8·52. Since this figure is in the region of our best estimates of the effective basicity of the salicylate oxygen (see below), we conclude that the partitioning of the quinquecovalent intermediate depends exclusively on the basicity of the leaving group, and that the pseudorotation barrier is not significant.

The acyl phosphate (10) (Scheme 1) formed in the endocyclic displacement is a highly reactive species, and the pK_a value of its conjugate acid can only be estimated. It should be a slightly stronger acid than the phenolic group of a salicylate ester. But the pK_a value of ethyl salicylate, for example, is affected by hydrogen bonding between the hydroxy and ester groups in the acid form.[9] The extra stabilisation of the anion by the *ortho*-ethoxycarbonyl group is counterbalanced by an extra stabilisation of the neutral form by hydrogen bonding, so that the pK_a (9·92 [9]) is not significantly less than that of phenol. Only the stabilisation of the anion is relevant to its performance as a leaving group and this can be estimated from available data in two ways. Scheraga and his co-workers [9] calculated the strength of the hydrogen bond of ethyl salicylate as 1·7 kcal mol^{-1}, so that in its absence the pK_a value would be expected to fall by some 1·3 units to 8·6. Alternatively, the pK_a value of ethyl *p*-hydroxybenzoate might [10] give an indication of the effective basicity of the salicylate oxygen atom in the absence of an intramolecular hydrogen bond. The pK_a value of this ester is 8·5.[11]

The data collected in Table 3 allow a unique comparison of the sensitivities of an S_N2(P) reaction to substitution both in the leaving group and in a group not displaced. Using the product ratios discussed before the observed rates of hydrolysis can be dissected to give separate rate constants for the endocyclic and exocyclic displacement reactions. These constants are plotted logarithmically in Figure 3 against the pK_a of the leaving group for the five esters (7a—e). In each case four points define an acceptable linear free-energy relationship, while the fifth diverges unaccountably from the best line by an amount well above experimental error. As would be expected, the exocyclic displacement of ArO^-, which actually bears the substituent, is more sensitive to its effects, but there is a substantial effect on the endocyclic process also.

The observed sensitivities are remarkably large. For the displacement of ArO^- from a series of dialkyl aryl phosphates by acetate ion the same plot (of log k_2 *vs.* pK_a of ArOH) has a slope of −0·88.[12] The slope of the plot of Figure 3 for the exocyclic displacement of ArO^- from the esters (7a—e) has the very large value of −1·44 ± 0·18 greater than the expected [12] maximum for

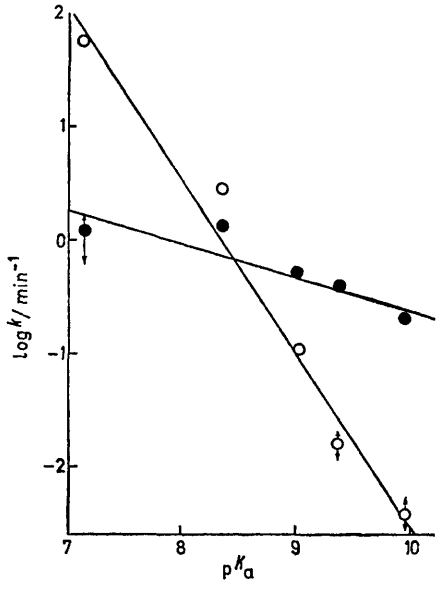


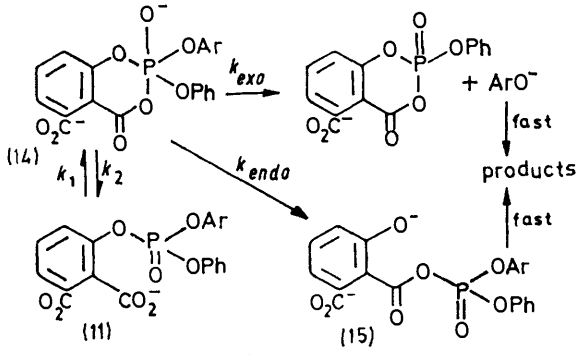
FIGURE 3 Linear free-energy relationships between the rate constants for exocyclic (open circles) and endocyclic (closed circles) displacement against the pK_a value of ArOH, the conjugate acid of the exocyclic leaving group, for the esters (7a—e)

an S_N2(P) reaction of a triester, and the highest sensitivity to substitution in the leaving group yet measured. A remarkably high sensitivity to substitution in the

[9] J. Hermans, S. J. Leach, and H. A. Scheraga, *J. Amer. Chem. Soc.*, 1963, **85**, 1392.
[10] M. Charton, *J. Amer. Chem. Soc.*, 1969, **91**, 6649.
[11] W. P. Jencks and J. Regenstein, 'Handbook of Biochemistry,' Chemical Rubber Co., Cleveland, 1968, p. J-158.
[12] S. A. Khan and A. J. Kirby, *J. Chem. Soc.* (*B*), 1970, 1172.

leaving group is a characteristic of the aryl 2-carboxyphenyl phosphate diesters also.[1] For endocyclic displacement the slope is $-0{\cdot}30 \pm 0{\cdot}08$.

The broader implications of these linear free-energy relationships will not be discussed here. But one application is directly relevant to the reaction under discussion. Since it is established that the mode of breakdown of the quinquecovalent intermediate depends only on the relative basicities of the possible leaving groups, the linear free-energy relationship illustrated in Figure 2 should apply to any set of rate constants for this reaction. Consider the simplified reaction scheme below (Scheme 3).



SCHEME 3

The quinquecovalent intermediate (14) is shown without a definite configuration, since pseudorotation is fast. And the breakdown of the acyl phosphate (15) is assumed not to be reversible, since it is catalysed by the second carboxylate group. Now the relative rates of the three modes of breakdown of (14) should be related by equation (1) since the slope of the plot of Figure 2 is

$$\log k_a - \log k_b = 1{\cdot}25\Delta pK_{ab} \qquad (1)$$

1·25. Making the steady state assumption for the concentration of (14), the observed rate constant is given by equation (2). Thus for the diphenyl ester

$$k_{obs} = k_1(k_{exo} + k_{endo})/(k_2 + k_{exo} + k_{endo}) \qquad (2)$$

(7a), for example, for which $k_{exo}/k_{endo} = 3{\cdot}5/96$ (Table 2), $k_2/k_{endo} = 10^5 \times 10^{1{\cdot}25} = 1{\cdot}8 \times 10^6$, since the pK_a values of the carboxy and phenol group of the salicylic acid residue are *ca.* 3·5 and 8·5 respectively (see above). Thus $k_{obs} = 0{\cdot}216\ min^{-1} = k_1\,(0{\cdot}04\ k_{endo} + k_{endo})/(1{\cdot}8 \times 10^6\ k_{endo})$ so that $k_1 = 3{\cdot}7 \times 10^5\ min^{-1}$. The equilibrium constant for the transfer of a phosphate diester group from one oxygen anion to another depends on the relative basicity of the groups concerned in the same way, with a slope of 1·2,[2] so that $k_1/k_2 \simeq 10^{-6}$ giving a value for k_2 of *ca.* $3{\cdot}7 \times 10^{11}\ min^{-1}$. The remaining rate constants are then simply calculated from the equations given. Similar calculations can be made for all the esters used in this work, and results for the two compounds of lowest and highest reactivity are shown in Table 6. No great precision is claimed for some of these figures: the values of k_1 and k_2 should be accurate within *ca.* 10%, but the values of k_{exo} and k_{endo} depend on a linear free energy relationship for phosphate transfer,[2] which is based on a limited amount of data. Nevertheless the extrapolations involved are not large, and the figures given for k_{exo} and k_{endo} can be taken to be meaningful within an order of magnitude.

TABLE 6

Rate constants for the individual steps of the reaction (Scheme 3)

	Diphenyl ester (7a)	*p*-Nitrophenyl phenyl ester (7e)
k_1/min^{-1}	$3{\cdot}7 \times 10^5$	$2{\cdot}1 \times 10^6$
k_2/min^{-1}	$3{\cdot}7 \times 10^{11}$	$2{\cdot}1 \times 10^{12}$
k_{exo}/min^{-1}	$7{\cdot}5 \times 10^3$	6×10^7
k_{endo}/min^{-1}	$2{\cdot}1 \times 10^5$	$1{\cdot}2 \times 10^6$

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