The Mechanism of Acyl Phosphonate Reactions. Part I. The Kinetics of the Solvolyses of Benzoyl and *p*-Toluoyl Phenylphosphonates in Aqueous Dioxan

By **Robert M. Laird** * and **Michael J. Spence**, Department of Chemistry, Newcastle upon Tyne Polytechnic, Ellison Place, Newcastle upon Tyne NE1 8ST

Rate constants have been determined for the neutral hydrolysis of benzoyl phenylphosphonate in 5, 20, and 40% aqueous dioxan and *p*-toluoyl phenylphosphonate in 20% dioxan. Acid catalysis, salt effects, and the addition of nucleophiles have been investigated in 20% dioxan at 295·5 K. It is concluded that the mechanism of hydrolysis is bimolecular addition to the acyl carbon atom to form a tetrahedral intermediate prior to phosphonate ion elimination.

ALTHOUGH the kinetics of reactions of acyl phosphates[1] and their esters,[2] have been investigated, no work has been done on the related acyl phosphonates. These compounds were of interest to us as model compounds in our studies of the related compounds formed from commercial cross-linked polystyrene–phosphonic acid.[3]

EXPERIMENTAL

Materials.—The solvents and aniline were prepared as before.[4,5] Buffer solutions were prepared from AnalaR chemicals.

Benzoyl Phenylphosphonate.—Aqueous sodium hydrogen phenylphosphonate was treated with silver nitrate (one equiv., saturated aqueous solution) and the precipitated silver hydrogen phenylphosphonate was collected, washed with water, and dried. The silver salt (1·63 g) was stirred into dry acetonitrile (10 ml) and treated with redistilled benzoyl chloride (1·21 g). The mixture was stirred for 4 h at room temperature in the dark, then filtered, and the precipitate was washed with sodium-dry ether (10 ml). Evaporation of the filtrate to small volume gave the *phosphonate* in 80% yield, m.p. 350—351 K (from ether) (Found: C, 59·6; H, 4·2. $C_{13}H_{11}O_4P$ requires C, 59·5; H, 4·2%), $\nu_{max.}$ (KBr disc) 2650w, 2570w (POH), 1750s, 1736sh (C=O), 1443m (PC), 1298m (CO), 1254s (P=O), 1238m, 1130m, and 1002m (PC, PO) cm^{-1}.

p-*Toluoyl Phenylphosphonate*.—This was obtained from *p*-toluoyl chloride by the method used for the benzoyl compound and had m.p. 389—390 K (Found: C, 61·1; H, 4·7. $C_{14}H_{13}O_4P$ requires C, 60·9; H, 4·7%), $\nu_{max.}$ (KBr disc) 2660w, 2550w (POH), 1747s, 1737sh (C=O), 1445m (PC), 1302m (CO), 1259s (P=O), 1131m, and 1002m (PC, PO) cm^{-1}.

Rate Measurements.—Neutral solvolyses were followed conductimetrically as before.[4] Reactions in perchloric acid and buffer solutions were followed spectrophotometrically by the decrease in absorbance at 260 and 265 nm for the benzoyl and *p*-toluoyl compounds respectively, as before.[5]

Product Analyses.—Reactions were conducted under the same conditions as used for kinetic studies. The analyses were done as before.[5]

RESULTS

Rate constants for the solvolyses of the anhydrides are in Table 1 and Arrhenius parameters and interpolated rate constants at 298·2 K are in Table 2. Rate constants for the reactions of the phosphonates in acid and buffer solutions are in Table 3. The products of reactions with aniline solutions are in Table 4.

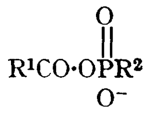
It is estimated that rate constants in Table 1 are accurate to ±2% or better, in agreement with the standard deviations obtained for the Arrhenius parameters (Table 2) by the method of unweighted least squares. The remaining rate constants are estimated to be accurate to ±3% excepting those in alkaline solutions which may be no better than ±5%.

TABLE 1

Measured rate constants for the solvolysis of aroyl phenylphosphonates in aqueous dioxan

Benzoyl phenylphosphonate						
5% Dioxan						
T/K	291·16	292·16	294·36	298·16	302·56	
10^3k/s^{-1}	3·59	3·84	4·95	6·63	9·42	
20% Dioxan						
T/K	292·16	298·16	299·36	302·16	311·36	317·76
10^3k/s^{-1}	1·20	1·74	1·92	2·33	4·15	6·20
40% Dioxan						
T/K	302·16	307·16	317·16	322·96		
10^3k/s^{-1}	0·485	0·663	1·26	1·88		
p-Toluoyl phenylphosphonate						
20% Dioxan						
T/K	289·16	291·06	295·56	306·26	313·96	
10^3k/s^{-1}	0·593	0·743	1·17	2·94	5·94	

DISCUSSION



$$R^1CO{\cdot}O\overset{\displaystyle O \atop \|}{\underset{\displaystyle O^-}{P}}R^2$$

(I)

a; R^1 = Ph, R^2 = Ph
b; R^1 = Me, R^2 = OPh
c; R^1 = Ph, R^2 = OPh

The hydrolysis of benzoyl phenylphosphonate (Ia) (Table 3) shows with change in pH a division into an

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[1] F. Lipmann and L. C. Tuttle, *Arch. Biochem. Biophys.*, 1947, **13**, 373; F. Lynen, *Ber.*, 1940, **73**, 367; D. E. Koshland, jun., *J. Amer. Chem. Soc.*, 1951, **73**, 4103; 1952, **74**, 2286.

[2] (*a*) G. DiSabato and W. P. Jenks, *J. Amer. Chem. Soc.*, 1961, **83**, 4393; (*b*) *ibid.*, p. 4400; (*c*) M. L. Bender and J. M. Lawlor, *ibid.*, 1963, **85**, 3010; (*d*) H. Chantrelle, *Biochem. Biophys. Acta*, 1948, **2**, 286; (*e*) S. A. Khan, A. J. Kirby, M. Wakselman, D. P. Horning, and J. M. Lawlor, *J. Chem. Soc.* (*B*), 1970, 1182.

[3] M. J. Spence, Ph.D. Thesis, Newcastle upon Tyne Polytechnic, 1970.

[4] R. M. Laird and M. J. Spence, *J. Chem. Soc.* (*B*), 1970, 388.

[5] R. M. Laird and M. J. Spence, *J. Chem. Soc.* (*B*), 1971, 1435.

TABLE 2

Arrhenius parameters and rate constants interpolated to 298·2 K

Phenylphosphonate	% Dioxan	E/kJ mol^{-1}	log (A/s^{-1})	10^3k/s^{-1}
Benzoyl	5	62·3 ± 2·4	8·7 ± 0·36	6·54
	20	49·8 ± 0·6	6·0 ± 0·10	1·76
	40	52·4 ± 0·96	5·7 ± 0·16	0·364
p-Toluoyl	20	69·1 ± 0·8	9·3 ± 0·14	1·46

TABLE 3

Measured rate constants for anhydride solvolyses in 20% aqueous dioxan solutions

T/K	[Salt] or [Buffer]/M	pH [a]	μ	10^3k/s^{-1}
Benzoyl benzenephosphonate				
295·5	2·62 $HClO_4$	−0·75 [b]	2·62 [c]	1·45
295·5	1·96 $HClO_4$	−0·37 [b]	2·62 [c]	1·22
295·5	1·31 $HClO_4$	0·05 [b]	2·62 [c]	0·95$_6$
295·5	0·65 $HClO_4$	0·60 [b]	2·62 [c]	0·64$_6$
295·5	2·62 $LiClO_4$		2·62 [c]	0·86$_2$
295·5	0·0573 HCl	1·33	0·0573	1·56
295·5	0·0115 HCl	2·02	0·0526 [d]	1·65
295·5	Acetate	3·92	0·0075 [d]	1·44
295·5	Acetate	4·97	0·0317 [d]	2·21
295·5	Phosphate	6·00	0·0480 [d]	2·20
295·5	Phosphate	7·00	0·0505 [d]	2·77
295·2	Borax	9·18	0·050 [d]	17
295·2	Chloroacetate [e]	2·20	0·01	1·39
295·2	Chloroacetate [e]	2·60	0·01	1·33
295·2	Chloroacetate [e]	3·00	0·01	1·29
295·4	Formate [e]	3·60	0·01	1·88
295·4	Formate [e]	4·00	0·01	2·01
295·4	Formate [e]	4·20	0·01	2·06
295·4	Formate [e]	4·40	0·01	2·23
295·5	Acetate [e]	4·40	0·01	1·99
295·5	Acetate [e]	4·60	0·01	2·08
295·5	Acetate [e]	4·80	0·01	2·07
295·5	Acetate [e]	5·00	0·01	2·14
295·5	Acetate [e]	5·20	0·01	2·12
295·5	Acetate [e]	5·20	0·02	2·63
295·4	Acetate [e]	5·20	0·05	3·35
295·5	Acetate [e]	5·20	0·1	5·85
295·5	Succinate [e]	3·60	0·01	1·70
295·5	Succinate [e]	4·00	0·01	1·76
295·5	Succinate [e]	4·50	0·01	1·82
295·4	Succinate [e]	5·50	0·01	1·70
295·5	Succinate [e]	5·80	0·01	1·68
295·5	Succinate [e]	6·10	0·01	1·72
295·5	Phosphate [e]	6·40	0·01	1·61
295·5	Phosphate [e]	6·70	0·01	1·62
295·4	Phosphate [e]	7·30	0·01	1·62
295·4	Phosphate [e]	7·70	0·01	1·60
295·3	Borate [e]	8·50	0·01	1·85
295·3	Borate [e]	8·80	0·01	1·99
295·3	Borate [e]	9·20	0·01	2·02
295·4	Carbonate [e]	9·60	0·01	4·3
295·3	Carbonate [e]	9·60	0·02	28
295·3	Carbonate [e]	10·0	0·01	14
p-Toluoyl phenylphosphonate				
295·5	0·0573 HCl	1·33	0·0573	1·41
295·5	0·0115 HCl	2·02	0·0526 [d]	1·31
295·5	Acetate	3·92	0·0075 [d]	1·37
295·5	Acetate	4·97	0·0317 [d]	1·89
295·5	Phosphate	6·00	0·0480 [d]	1·92
295·5	Phosphate	7·00	0·0505 [d]	2·62
295·5	Borax	9·18	0·050 [d]	10

[a] pH is that for 100% aqueous solution. [b] H_0 Values (C. A. Bunton, J. B. Ley, A. J. Rhind-Tutt, and C. A. Vernon, *J. Chem. Soc.*, 1957, 2327; V. Gold and J. Hilton, *ibid.*, 1955, 838, 843). [c] With $LiClO_4$. [d] Total solute molarity 0·05M [e] D. D. Perrin, *Austral. J. Chem.*, 1963, **16**, 572.

TABLE 4

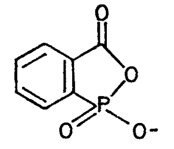
Products of the reaction of benzoyl phenylphosphonate with aniline [a] in aqueous or aqueous buffer [b] solutions

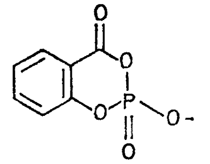
Solvent	pH	10_3 [Aniline]/M	% Anilide	$\frac{k_{\text{hydrolysis}}/\text{s}^{-1}}{k_{\text{aminolysis}}/\text{l mol}^{-1}\text{s}^{-1}}$	k_{OH^-}/l mol^{-1} s^{-1} [c]
1% Dioxan	11·22 [d]	109·7	91	0·0109	80
	10·72 [d]	10·97	86	0·0017$_9$	42
	9·22 [d]	1·097	80	0·00027$_4$	71
				$\frac{k_{\text{aminolysis}}/\text{l mol}^{-1}\,\text{s}^{-1}}{k_{\text{hydrolysis}}/\text{s}^{-1}}$	
2% Dioxan	2·02	0·009	55	1·3 × 10^5	
	3·92	0·439	80	9·1 × 10^3	
	4·97	1·552	83	3·1 × 10^3	
	7·00	2·185	93	6·1 × 10^3	
	9·18	2·194	77	1·5 × 10^3	

[a] 2·194 × 10^{-3}M total aniline in the buffers . [b] As in Table 3. [c] Assuming rate constants for aminolysis and neutral hydrolysis to be constant. [d] initial value.

acid-catalysed, a neutral (uncatalysed), and a hydroxide-promoted hydrolysis as found by DiSabato and Jenks [2b] for the related acetyl phenyl phosphate (Ib). The hydrolysis in alkaline solutions is interpreted similarly as a bimolecular reaction with the lyate ion. In neutral solutions, both the magnitude of the sensitivity of the reaction to solvent changes [6] and the log A values, corresponding to negative values of $\Delta S^{\ddagger}$ (Table 2), are [as for (Ib) [2b]] evidence [7] for a bimolecular hydrolysis.

(II)





(III)

Although attack by amines occurs only at the carbonyl group for reactions of both cyclic and acyclic types of acyl phosphonates [8] (Table 4) and acyl phenylphosphates,[2] hydrolysis has been proved to be an attack at the phosphorus atom of 1,3-dioxo-2,1-benzoxaphosphole 1-oxide (II) by Blackburn and Brown [8] and of 2,4-dioxo-4*H*-benzodioxaphosphorin 1-oxide (III) by Bender and Lawlor.[2c] The results of DiSabato and Jenks show that for (Ib) methanolysis occurs only at the carbonyl group [2b] and that the Brønsted plot is characteristic of an activated ester,[2a] and hence for related acyclic anhydrides hydrolysis at the carbonyl group seems certain.

Comparison of the rate of hydrolysis of benzoyl phenylphosphonate with those of related compounds in more aqueous solvents (Table 5), shows that acylation in (Ia) is faster than phosphorylation of the cyclic phosphonate (II) and greatly exceeds phosphorylation of the cyclic phosphate (III). As Chantrelle [2d] has indicated that acetyl phenyl phosphate (Ib) is more reactive than the benzoyl compound (Ic) it appears that

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[6] J. F. Bunnett, in 'Techniques of Organic Chemistry,' ed. A. Weissburger, Interscience, London, 1961, 2nd edn., vol. VIII, part 1, p. 242; K. B. Wiberg, 'Physical Organic Chemistry,' Wiley, London, 1964, p. 419.

[7] L. I. Schalenger and F. A. Long, *Adv. Phys. Org. Chem.*, 1963, **1**, 1.

[8] G. M. Blackburn and M. J. Brown, *J. Amer. Chem. Soc.*, 1969, **91**, 525.

an approximately 10^4-fold decrease in acylation by solvent occurs with the poorer leaving group. The preference in the cyclic compounds for phosphorylation over acylation, when for the reactions of esters [9] phosphorylation is less sensitive to electronic effects than acylation, suggests that phosphorylation in these compounds also is accelerated by ring strain.[9] Since the overall hydrolysis reaction is reduced for the cyclic compounds, an explanation of the preference for phosphorylation over acylation must be sought in not merely the facilitation of the phosphorylation reaction but also in the not less than 10^3- and 4×10^4-fold decreases in acylation rate constants for (II) and (III) respectively. As models show both the cyclic anhydride rings to be under strain, the conformation would favour a direct displacement at the carbonyl carbon atom, as found for cyclic acyl arylsulphonates.[5,10] Because a displacement at carbon requires more energy than an addition to a carbonyl group,[11] such a mechanism requires both a good leaving group and either a conformation [5] or solvent [12] unfavourable to the alternative addition. These conditions being only partially met, as phosphonate is a much poorer leaving group than either sulphonate or chloride, acylation in the cyclic compounds is suppressed for both mechanisms and only phosphorylation is observed.

TABLE 5

Comparison of rate constants for the hydrolysis of benzoyl phenylphosphonate (Ia) in 5% dioxan with those for related anhydrides

Ref.	Compound	Solvent	μ	T/K	k/s^{-1}	k(Ia)/s^{-1}
2*b*	(Ib)	H_2O	0·6	312·2	$2{\cdot}5 \times 10^{-6}$	$2{\cdot}0 \times 10^{-2}$
8	(II) [a]	H_2O	0·1	352·7	$6{\cdot}2 \times 10^{-2}$	0·52
2*c*	(III)	H_2O	1·0	298·2	$1{\cdot}5$—$1{\cdot}8 \times 10^{-5}$	$6{\cdot}5 \times 10^{-3}$
2*e*	(III)	1% Dioxan	1·0	312·2	$4{\cdot}7 \times 10^{-5}$	$2{\cdot}0 \times 10^{-2}$

Ethyl ester; parent compound reported more reactive.

Hence it follows that for the acyclic anhydrides acylation procedes *via* a tetrahedral intermediate. This is a reaction in which the electron-releasing *p*-methyl group retards the initial addition step (Table 2).

As the alkylphosphonates have pK_a values around pH 2,[13] the results for acid catalysis at $\mu = 2{\cdot}62$ refer to weak catalysis of the unionised compound. The extrapolated value for zero acid strength $0{\cdot}40 \times 10^{-3}$ s^{-1} shows the hydrolysis is slower for the neutral species than for the anion with a value of $0{\cdot}862 \times 10^{-3}$ s^{-1} at the same ionic strength. Such weak catalysis seems characteristic of the hydrolysis of acetyl phenyl phosphate [2b] and of carboxylic anhydrides in general.[14] Correlation of log k with H^0 and log c_{H^+} gave the results in Table 6. With the variance ratio, F, exceeding the 5% level, it is unwise to base any firm conclusions, but the trend in favour of the concentration correlation is in accord with a bimolecular attack.[15]

TABLE 6

Correlation of log k with H^0 and log c_{H^+} for hydrolysis of phenylphosphonates

	Correlation coefficient	Standard deviation	Gradient	F [a]
H^0	$-0{\cdot}9953$	0·01805	$-0{\cdot}2616$	
$-\log c_{H^+}$	$-0{\cdot}9998$	0·00785	$-0{\cdot}5806$	0·06

[a] G. W. Snedecor, 'Statistical Methods,' Collegiate Press, Ames, Iowa, 5th. edn., 1956.

Neglecting buffer catalysis, a value of 10 l mol^{-1} s^{-1} for the reaction with hydroxide ion at 295·2 K in 20% dioxan is obtained and from the product ratios (Table 4) a value of 64 ± 16 l mol^{-1} s^{-1} for the reaction in water. These values are comparable with the value 8·3 l mol^{-1} s^{-1} obtained for acetyl phenylphosphate at 332·2 K in water.[2b] Similarly, using the 5% dioxan hydrolysis value and the values in Table 4, the rate constant for reaction with aniline is estimated at $\geqslant 10$ l mol^{-1} s^{-1} in water at 295·2 K and may be compared with the corresponding phenylphosphate value of $5{\cdot}0 \times 10^{-3}$ l mol^{-1} s^{-1}.[2a] These results while emphasising the similarity of the two acylating agents, suggest that in this series selectivity decreases with increase in reactivity.

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[9] R. F. Hudson, 'Structure and Mechanism in Organo-phosphorus Chemistry,' Academic Press, London, 1965, p. 257; A. J. Kirby and S. G. Warren, 'Organic Chemistry of Phosphorus,' Elsevier, London, 1967, p. 311.

[10] R. M. Laird and M. J. Spence, *J. Chem. Soc.* (*B*), 1971, 454.

[11] M. L. Bender, *Chem. Rev.*, 1960, **60**, 53; S. L. Johnson, *Adv. Phys. Org. Chem.*, 1967, **5**, 237.

[12] P. Haberfield and R. B. Trattner, *Chem. Comm.*, 1971, 1481.

[13] L. Keay, *Canad. J. Chem.*, 1965, **43**, 2637; E. J. Behrman, M. J. Biallas, H. J. Brass, J. O. Edwards, and M. Isaks, *J. Org. Chem.*, 1970, **35**, 3063, 3069; *J. Amer. Chem. Soc.*, 1970, **92**, 4675.

[14] C. A. Bunton, J. H. Fendler, N. A. Fuller, S. Perry, and J. Rocek, *J. Chem. Soc.*, 1965, 6174.

[15] F. A. Long and M. A. Paul, *Chem. Rev.*, 1957, **57**, 935.