The Phosphoryl Cation as an Intermediate in the Reaction of Benzoyl Phosphates

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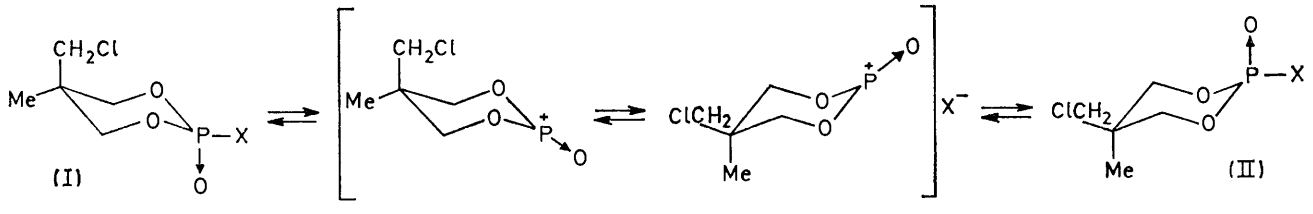
By means of a system of geometrical isomers, *cis*- and *trans*-2-benzoyloxy-5-chloromethyl-5-methyl-2-oxo-1,3,2-dioxaphosphorinans, evidence is presented which strongly suggests that benzoyl phosphate esters may ionize to phosphoryl cations. The degree of ionization which can be followed by observing a change in the isomer ratio is solvent dependent with ion pairs formed in solvents of moderate polarity. Based on the known equilibration of benzoyl phosphates to pyrophosphate, solvent-separated ions are pictured as being formed in solvents of high polarity.

THE mechanism of substitutions at phosphorus has received much attention.[1a,c] Our interests have centred primarily on those substrates which are related to the 'high energy' phosphates prevalent in biological systems. Although there is some dispute,[2] earlier work on the hydrolysis of the mono- and di-anions of acetyl and benzoyl phosphates has, based on kinetic data, indicated that they are capable of ionizing by means of a dissociative mechanism.[3a,f] It is the purpose of this paper to introduce a system by which ionization can be easily followed by observing product ratios and to establish that neutral benzoyl phosphates may also undergo ionization under the proper conditions.

In a recent publication [4] we described a new diagnostic tool which can be utilized to aid in determining the mechanism of nucleophilic substitutions at phosphorus. In expanding the usefulness of this technique we have been able to prepare and purify a number of 2-substituted *trans*- and *cis*-5-chloromethyl-5-methyl-2-oxo-1,3,2-dioxaphosphorinans (I) and (II). The geometrical isomers can be distinguished by chemical shift differences; equatorial methyl resonances are upfield from axial methyl resonances while the peaks for methylene hydrogen atoms of axial chloromethyl groups are considerably downfield from those for equatorial chloromethyl groups.

The ability of the isomers to interconvert, a phenomenon which can be followed simply by n.m.r. spectroscopy, is strongly dependent upon X and solvent polarity.[5] The isomers are stable at temperatures of over 200° [6a,b] and show no signs of isomerization when dissolved in polar solvents in those cases where X is an amino-, alkoxy-, or phenoxy-group. On the other hand, when X is phosphate as in a pyrophosphate, 4-nitrophenoxy, 2,4-dinitrophenoxy, or chlorine, isomerization proceeds at rates dependent upon solvent polarity and the effectiveness of X as a leaving group. In all cases where isomerization takes place only the two isomers are detected and isolated.

We have interpreted isomerization to be the result of ionization which allows the configuration at phosphorus to invert giving a new population distribution of isomers. At equilibrium, the isomer ratio favours the *trans*-form by *ca.* 2·5 : 1 depending upon the nature of X and solvent.



The ratio is best explained as due to ion-pair formation with the equilibrium to the left as a consequence of dipole interaction between ring oxygen atoms and the chloromethyl dipole. We have previously shown [4] that in the case of the phosphorochloridate [I; X = Cl (axial)], the presence of silver ion shifted the equilibrium to the right due to formation of a solvent-separated phosphoryl cation.

Much interest has been generated over the conformational mobility of 2-substituted 5-halogenomethyl-

[1] (*a*) T. C. Bruice and S. J. Benkovic, 'Bioorgainic Mechanisms,' Benjamin, New York, 1966, ch. 5; (*b*) A. J. Kirby and S. G. Warren, 'The Organic Chemistry of Phosphorus,' Elsevier, Amsterdam, 1967, ch. 10; (*c*) W. E. McEwen, 'Topics in Phosphorus Chemistry,' eds. M. Grayson and E. J. Griffith, Wiley, New York, vol. 2; (*d*) R. F. Hudson, 'Structure and Mechanism in Organo-Phosphorus Chemistry,' Academic Press, New York, 1965, ch. 8; (*e*) M. J. Gallagher and I. D. Jenkins, 'Topics in Stereochemistry,' eds. E. L. Eliel and N. L. Allinger, Wiley, New York, 1968, vol. 3, ch. 1.

[2] J. A. Maynard and J. M. Swan, *Austral. J. Chem.*, 1963, **16**, 596.

[3] (*a*) A. J. Kirby and W. P. Jerrcks, *J. Amer. Chem. Soc.*, 1965, **87**, 3209; (*b*) A. J. Kirby and A. C. Varvoglis, *ibid.*, 1967, **89**, 415; (*c*) *J. Chem. Soc.* (*B*), 1968, 135; (*d*) C. A. Bunton, E. J. Fendler, and J. H. Fendler, *J. Amer. Chem. Soc.*, 1967, **89**, 1221; (*e*) R. Bentley, *ibid.*, 1949, **71**, 2765; (*f*) J. H. Park and D. E. Koshland, jun., *J. Biol. Chem.*, 1958, **233**, 986.

[4] W. S. Wadsworth, jun., and H. L. Horton, *J. Amer. Chem. Soc.*, 1970, **92**, 3785.

[5] W. S. Wadsworth, jun., S. Larsen, and H. L. Horten, *J. Org. Chem.*, in the press.

[6] (*a*) W. S. Wadsworth, jun., *J. Org. Chem.* 1967, **32**, 1603; (*b*) R. S. Edmundson and E. W. Mitchell, *J. Chem. Soc.* (*C*), 1968, 3033.

5-methyl-2-oxo-1,3,2-dioxaphosphorinans with a single conformation shown to be present in the solid state in a few cases.[7] Based primarily on the chemical shifts of ring hydrogens with solvent and temperature, limited mobility has been depicted for similar isomers in solution.[8a,c] In the present case we believe the isomers to exist primarily as shown due to the preference of the substituent at phosphorus for the equatorial position. Thus, with the phenyl phosphates the change in chemical shifts of ring hydrogens with solvent or temperature are slight especially in the case of the *trans*-isomer. Thus, if

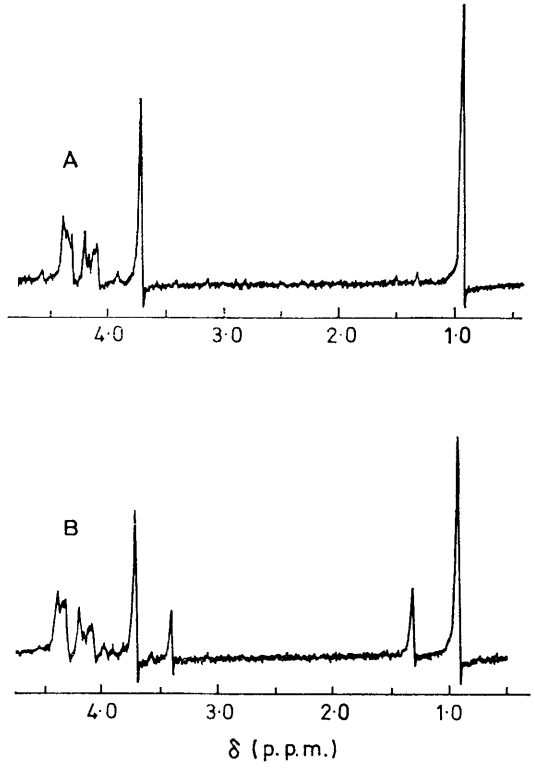


FIGURE 1 A, N.m.r. spectrum of *trans*-isomer before isomerization; B, n.m.r. spectrum of *cis*- and *trans*-mixture after equilibration at 50° in $CDCl_3$. Both spectra were taken for deuteriochloroform solutions on a Varian A-60A spectrometer with tetramethylsilane as an internal standard

conformational mobility does exist in solution, those conformations shown must predominate and in any case detection of interconversion of the isomers by n.m.r. spectroscopy is in no way hindered by conformational changes. Indeed, at elevated temperatures, peaks due to identical axial and equatorial 5-substituents in the two isomers do not tend to coalesce.[9]

The benzoyl phosphate (I; X = OBz) was prepared from benzoyl chloride and 5-chloromethyl-2-hydroxy-5-methyl-2-oxo-1,3,2-dioxaphosphorinan (I; X = OH). The isomers were separated by means of fractional crystallization from benzene and the *trans*-isomer, the least soluble, was obtained in pure form. Although upon melting isomerization took place, none was observed in a benzene solution of the pure isomer. In more polar solvents isomerization was observed (Figure 1) and could be simply followed by monitoring the conformational change at C-5. The final ratio of isomers was indicative of ion-pair formation.

Besides being dependent upon solvent polarity and temperature, isomerization was acid catalysed. Isomerization in nitrobenzene which required *ca.* 300 h at 50° to reach equilibrium was greatly accelerated by the addition of very small amounts of (I; X = OH), benzoic acid or toluene-*p*-sulphonic acid. Also, although isomerization did not occur in benzene at 50°, it proved to be rapid (*ca.* 48 h to reach equilibrium) after a small amount (<0·01 equiv.) of toluene-*p*-sulphonic acid was added. Although isomerization took place in acetonitrile, formation of the acid (I; X = OH) rendered rate data meaningless. Isomerization at 50° was also unusually rapid in chloroform which contained a small quantity of HCl as impurity.

The *cis*-benzoyl phosphate (II; X = OBz) could not be completely separated from the *trans*-isomer, although from relative n.m.r. peak intensities the benzene filtrates remaining from removal of the less soluble *trans*-isomer contained an enriched mixture (5 : 1 *cis* : *trans*). In nitrobenzene the product enriched in the *cis*-form gave, after warming at 50°, an isomer mixture identical to that obtained from the pure *trans*-form after its isomerization.

In a more polar solvent, *i.e.* dimethylformamide, following isomerization, the *trans*-benzoyl phosphate equilibrated at room temperature to pyrophosphate and benzoic anhydride, a reaction which has previously been reported for benzoyl phosphates.[10] Formation of the products which could be isolated, was followed by n.m.r. spectroscopy (Figure 2). As expected the final equilibrium mixture [reactions (1)—(3)] could also be obtained by allowing a dimethylformamide solution of pyrophosphate and benzoic anhydride to stand at room temperature.

$$\text{ion pair} \rightleftharpoons \text{solvent separated ions} \quad (1)$$

$$BzO^- + \text{benzoyl phosphate} \rightleftharpoons Bz_2O + \text{phosphate anion} \quad (2)$$

$$\text{phosphate anion} + \text{phosphoryl cation} \rightleftharpoons \text{pyrophosphate} \quad (3)$$

In a highly polar solvent separated ions would be expected. Pyrophosphate is formed from an intermediate phosphoryl cation. Indeed, the formation of

[7] T. A. Beineke, *Acta Cryst.*, 1969, **B25**, 413. We have shown by *X*-ray analysis that solid (I; X = piperidino or phenoxy) exists entirely in the conformation shown. R. E. Wagner, W. Jensen, O. Johnson, and W. S. Wadsworth, jun., Abstracts, 163rd National A.C.S. Meeting, Boston, 1972.

[8] (*a*) R. S. Edmundson and E. W. Mitchell, *J. Chem. Soc.* (*C*). 1970, 752; (*b*) A. R. Katritsky, M. R. Nesbit, J. Michalski, Z. Trelimowski, and A. Zwierzak, *J. Chem. Soc.* (*B*), 1970, 140; (*c*) D. W. White, G. K. McEwen, R. D. Bertrand and J. G. Verkade, *ibid.*, 1971, 1454.

[9] Unpublished data.

[10] K. V. Petrov and A. A. Neimysheva, *Zhur. obshchei Khim.*, 1959, **29**, 1923.

pyrophosphate is evidence for an intermediate cation for in all cases studied both charged and uncharged nucleophiles attack the starting benzoyl phosphate with C–O bond scission only. No product arising from P–O

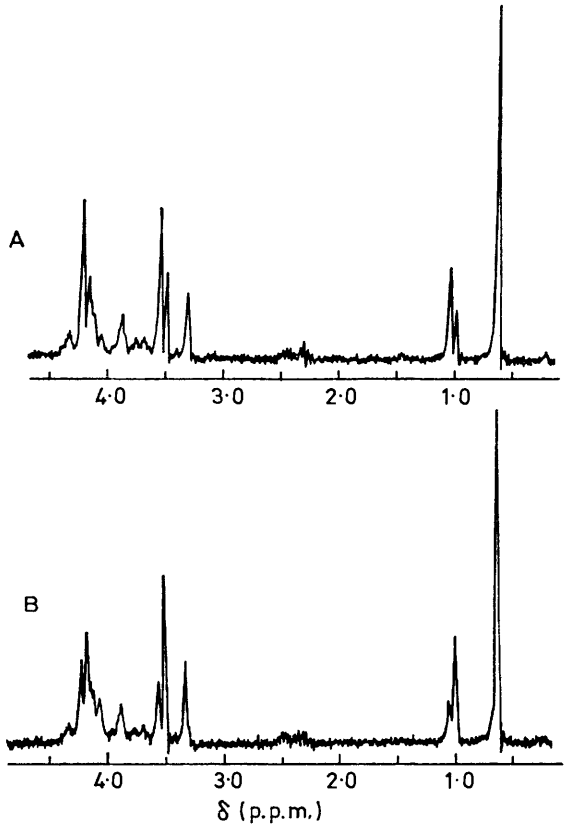


FIGURE 2 A, Spectrum of *trans*-isomer in [$^2H_7$]DMF showing stages of isomerization and equilibration taking place at room temperature. The equatorial methyl and chloromethyl hydrogen atoms of the pyrophosphate overlap those of the starting benzoyl phosphate. The peaks assigned to pyrophosphate (δ 1·0 and 3·58 p.p.m.) are identical to those found in the spectrum of an authentic sample, spectrum of final equilibrium mixture

bond scission is detected, a result recently reported for an analogous system.[11] Thus, it is unlikely that pyrophosphate results from direct nucleophilic attack at phosphorus.

For comparison purposes pyrophosphate was prepared independently by treating the sodium salt of the acid (I; X = OH) with the phosphorochloridate [I; X = Cl (axial)]. The product which could possibly contain three isomers gave an n.m.r. spectrum identical, except for the relative peak heights for hydrogen atoms on groups at C-5, to the product obtained upon equilibration of the *trans*-benzoyl phosphate.

The role of solvent in phosphoryl cation formation is at this point uncertain. The equilibration to pyrophosphate was also observed in pyridine and thus it would appear that the solvent plays a major role in stabilizing the positive charge.

Unfortunately, the isolation of pure isomers of *para*-substituted 2-benzoyloxy-5-chloromethyl-5-methyl-2-oxo-1,3,2-dioxaphosphorinans proved, because of their extreme reactivity, to be difficult. Due to acid catalysis of isomerization and facile attack by nucleophiles leading to C–O bond cleavage, chromatographic and other methods of purification were unsuccessful. Although by repeated recrystallization both *p*-chloro- and *p*-methyl-benzoyl phosphates could be slightly enriched in the *trans*-isomer, we have been unable to obtain a pure isomer from these or other *para*-substituted analogues. Nevertheless, both the partially purified *trans*-*p*-chloro- and -*p*-methyl-benzoyl phosphates underwent isomerization in nitrobenzene and gave pyrophosphate in dimethylformamide. That the *para*-substituent does have an effect on the reactivity of the benzoyl phosphates and in particular their ability to ionize was indicated by the lack of success in preparing the *p*-nitro-analogue. In all attempts, under conditions which were successful for the other phosphates, nearly quantitative yields of pyrophosphate were obtained.

EXPERIMENTAL

Analyses were performed by Galbraith Laboratories, Knoxville, Tennessee.

2-Chloro-5-chloromethyl-5-methyl-2-oxo-1,3,2-dioxaphosphorinan.— 4-Alkyl-2,6,7-trioxa-1-phosphabicyclo[2,2,2]-octane [12] (37·0 g) in carbon tetrachloride (200 ml) was added dropwise with cooling (ice-bath) and stirring to sulphuryl chloride (33·75 g) in carbon tetrachloride (200 ml). The solution was stirred for 1 h and solvent was removed under reduced pressure. The solid *product*, recrystallized from carbon tetrachloride (49 g, 91%), m.p. 69—71°, was dried and stored under anhydrous conditions. It is assumed to be stereochemically analogous to 2-bromo-5-bromomethyl-5-methyl-2-oxo-1,3,2-dioxaphosphorinan [7] [I; X = Br (axial)], δ ($CDCl_3$) 1·10 (Me) and 3·90 p.p.m. (CH_2Cl) (Found: C, 27·3; H, 4·25; P, 14·4. $C_5H_9Cl_2O_3P$ requires C, 27·45; H, 4·15; P, 14·1%).

5-Chloromethyl-2-hydroxy-5-methyl-2-oxo-1,3,2-dioxaphosphorinan.—The above phosphorochloridate (10·0 g) was added to water (25 ml) and the mixture was heated gently until homogeneous. The solution was chilled and filtered by suction and the *product* was recrystallized from acetonitrile (8·5 g, 92%), m.p. 144—146°, δ ($CDCl_3$) 1·03 (Me) and 3·80 p.p.m. (CH_2Cl) typical of equatorial and axial groups respectively. The peak position of the hydroxy-group proton is unknown (Found: C, 30·1; H, 5·15; Cl, 17·55. $C_5H_{10}ClO_4P$ requires C, 30·0; H, 5·0; Cl, 17·5%).

trans-*2-Benzoyloxy-5-chloromethyl-5-methyl-2-oxo-1,3,2-dioxaphosphorinan.*—To the above acid (4·0 g) and triethylamine (2·02 g) in acetonitrile (50 ml) was added dropwise, with stirring and cooling, benzoyl chloride (2·8 g). The mixture was stirred for 1 h and filtered by suction. Solvent was removed from the filtrate under reduced pressure and the crystalline residue was washed well with water and dried (5·4 g, 90%), *cis* : *trans* 1 : 3 (by n.m.r.), δ ($CDCl_3$) *cis*, 1·36

[11] R. S. Edmundson, C. I. Forth, and T. A. Moran, *J. Chem. Soc.* (*C*), 1971, 2452.

[12] W. S. Wadsworth, jun. and W. D. Emmons, *J. Amer. Chem. Soc.*, 1962, **84**, 610.

(Me) and 3·45 (CH_2Cl); *trans*, 0·97 (Me) and 3·75 p.p.m. (CH_2Cl) (Found: C, 47·4; H, 4·6; Cl, 11·5. Calc. for $C_{12}H_{14}ClO_5P$: C, 47·35; H, 4·6; Cl, 11·5%). The product was recrystallized three times from benzene to give the pure *trans*-form (2·15 g), m.p. 105—107°. Upon melting the *trans*-isomer reverted to a mixture, *cis* : *trans* 1 : 2·2. The benzene filtrates upon removal of solvent gave a mixture of isomers, *cis* : *trans* 5 : 1 (by n.m.r.).

Isomerization of Benzoyl Phosphate Isomers.—A sample of the *trans*-isomer was dissolved in benzene and after reflux it was recovered unchanged. A sample dissolved in nitrobenzene gave (by n.m.r.) *cis* : *trans* 1 : 2·2 after 300 h at 50° and after 35 h at 50° in the presence of toluene-*p*-sulphonic acid (0·01 equiv.). The mixture enriched in the *cis*-isomer gave in nitrobenzene after 300 h at 50° *cis* : *trans* 1 : 2·2. Likewise, isomerization of the pure *trans*-isomer in CD_3CN and $CDCl_3$, was followed by observing changes in peak ratios.

Reaction of Benzoyl Phosphate with Nucleophiles.—The n.m.r. spectrum obtained immediately upon dissolving the benzoyl phosphate in CD_3OD was identical, except in the aromatic region, to a spectrum of the acid (I; X = OH) in CD_3OD. In a separate experiment, upon addition of methanol, methyl benzoate and the acid were isolated in approximately quantitative yields. An excess of piperidine when added to the phosphate, gave upon distillation *N*-benzoylpiperidine (96%) and the piperidinium salt of the acid as residue both identical in all respects to authentic samples. In neither case, although care was taken, could a trace of the known methyl phosphate or phosphoramidate,[5] respectively, be detected.

2-p-*Chlorobenzoyloxy-* *and* 2-p-*Methylbenzoyloxy-5-chloromethyl-5-methyl-2-oxo-1,3,2-dioxaphosphorinan.*—The procedures for the preparation of these analogues were identical to that of the benzoyl phosphate. The crude *p*-chloro-analogue, *cis* : *trans* 1 : 3 (by n.m.r.), was recrystallized four times from benzene to give *cis* : *trans* 1 : 6. The crude *p*-methyl analogue was recrystallized four times from carbon tetrachloride to give *cis* : *trans* 1 : 7. Nitrobenzene solutions of both products gave *cis* : *trans* 1 : 2·5 after 300 h at 50°.

Equilibration of trans-2-*Benzoyloxy-5-chloromethyl-5-methyl-2-oxo-1,3,2-dioxaphosphorinan.*—A [$^2H_7$]dimethylformamide solution of the *trans*-isomer which indicated, by n.m.r., the presence of the single isomer gave after standing at room temperature for 2 days a spectrum which indicated *cis* : *trans* 1 : 4. After 12 days the presence of new peaks was observed. After 1 month there was no further change. At 50° equilibrium was reached after 10 days. The new peaks, δ 0·68 (Me_{ax}), 1·00 (Me_{eq}), 3·35 (CH_2Cl_{ax}), and 3·50 p.p.m. (CH_2Cl_{eq}), proved to have the same chemical shifts as those found for authentic pyrophosphate in dimethylformamide. A spectrum identical to that obtained at equilibrium was observed after a [$^2H_7$]dimethylformamide solution containing an equivalent of pyrophosphate and benzoic anhydride had stood at 50° for ten days. In a separate experiment the benzoyl phosphate (1·52 g) was dissolved in dimethylformamide (10 ml). After standing at 50° for 10 days solvent was removed under reduced pressure. The residue was extracted with ether and the insoluble portion, which proved identical to pyrophosphate, was recrystallized from carbon tetrachloride. Solvent was removed from the ether extract and the residue was recrystallized from hexane to give a crystalline solid, m.p. 43°, which was identical to authentic benzoic anhydride.

Preparation of the Pyrophosphate, Bis-(5-chloromethyl-5-methyl-2-oxo-1,3,2-dioxaphosphorinan-2-yl) Ether.—5-Chloromethyl-2-hydroxy-5-methyl-2-oxo-1,3,2-dioxaphosphorinan (4·0 g) was treated with a solution of sodium hydroxide (0·8 g in 20 ml of water). Water was removed under reduced pressure and the residue was added to 2-chloro-5-chloromethyl-5-methyl-2-oxo-1,3,2-dioxaphosphorinan (4·36 g) in acetonitrile (30 ml). The mixture was stirred at room temperature for 3 days and solvent was removed. The product was washed with cold water and dried (5·45 g, 71%). Partial separation of isomers could be achieved by fractional crystallization from carbon tetrachloride but pure isomers could not be obtained by this or by chromatographic methods, δ ($CDCl_3$) 1·03 (Me_{eq}), 1·41 (Me_{ax}), 3·42 (CH_2Cl_{eq}), and 3·77 p.p.m. (CH_2Cl_{ax}) (Found: C, 31·3; H, 4·7; Cl, 18·6; P, 16·0. Calc. for $C_{10}H_{18}Cl_2O_7P_2$: C, 31·4; H, 4·7; Cl, 18·3; P, 16·25%).

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