

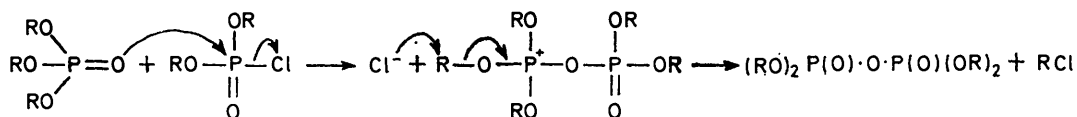
## Mechanism of the Reaction between Trialkyl Phosphates and Dialkyl Phosphorochloridates: Nucleophilic Sites in Phosphorus(v) Esters

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Reaction between the phosphate 2-methoxy-5,5-dimethyl-1,3,2-dioxaphosphorinan-2-one (Ia), labelled with  $^{18}\text{O}$  in the phosphoryl group, and the phosphorochloridate 2-chloro-5,5-dimethyl-1,3,2-dioxaphosphorinan-2-one (II), to give the labelled pyrophosphate 2,2'-oxybis-(5,5-dimethyl-1,3,2-dioxaphosphorinan-2-one) (III) shows that the reaction proceeds through nucleophilic attack on the chloridate by both the methoxy and the phosphoryl oxygen atoms of the phosphate. The former route is probably rather more important than the latter.

UNTIL recently, the reaction (thermal condensation) between trialkyl phosphates and dialkyl phosphorochloridates had been assumed to proceed exclusively *via* nucleophilic attack by the phosphate phosphoryl oxygen atom on the electrophilic phosphorus atom of the chloridate (Scheme 1).<sup>1,2</sup> In 1972, however, as a

We have allowed the phosphate (Ia) † to react with the unlabelled chloridate (II) in refluxing xylene (2 h). According to whether the alkoxy (i) or the phosphoryl (ii) oxygen of the phosphate attacks the chloridate, the label appears on a phosphoryl or the bridge oxygen, respectively, of the resultant anhydride (Scheme 3).

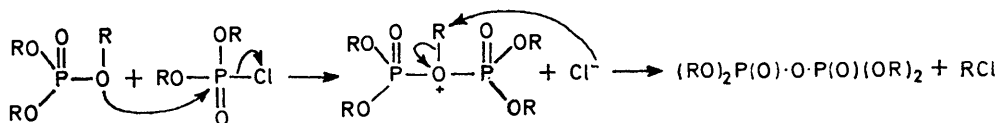


SCHEME 1

result of studies involving (a) reactions between trialkyl phosphates and dialkyl phosphorochloridates bearing a different alkyl group, and (b) reactions of tri-*O*-alkyl and of *OOS*-trialkyl phosphorothioates with dialkyl phosphorochloridates, it was suggested that attack by the phosphate alkoxy oxygen atoms was important (Scheme 2).<sup>2</sup> From the distribution of the various

If both modes of attack operate, then the relative proportions of phosphoryl-labelled (IIIa) and bridge-labelled (IIIb) pyrophosphate reflect the relative importance (rates) of the two modes.

*Synthesis of Labelled Materials.*—All labelled materials were derived from 2-chloro-5,5-dimethyl-1,3,2-dioxaphosphorinan (IV) and water containing 10-30% of

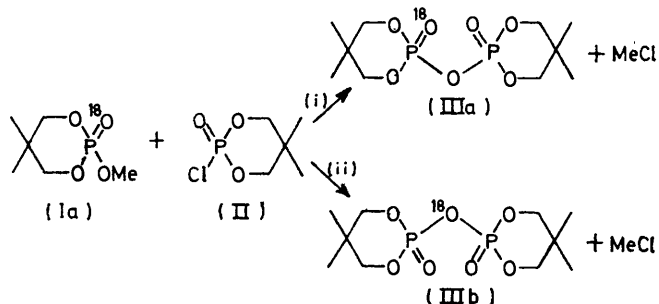


SCHEME 2

products of these reactions, strong evidence was obtained for the mechanism in Scheme 2.

By means of isotopic labelling techniques we have now obtained more direct evidence for the operation of Scheme 2 and we have derived approximate values for the relative importance of phosphoryl oxygen and alkoxy oxygen attack in the thermal condensation of the phosphate 2-methoxy-5,5-dimethyl-1,3,2-dioxaphosphorinan-2-one (I) † with the phosphorochloridate 2-chloro-5,5-dimethyl-1,3,2-dioxaphosphorinan-2-one (II).

$\text{H}_2^{18}\text{O}$ . Routes to the phosphoryl-labelled compounds (Ia)—(IIIa) are shown in Scheme 4, along with the measured enrichments ‡ of the labelled species.



SCHEME 3

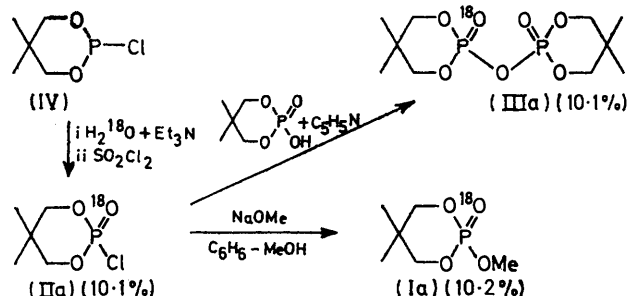
† A Roman numeral without a suffix refers either to unlabelled material or to material with the labelling unspecified. Suffix 'a' signifies P=O (phosphoryl) labelling and 'b' P-O- labelling.

‡ Enrichments were obtained from the heights of appropriate peaks in the mass spectra of samples. Natural abundances were subtracted from overall abundances. Peaks chosen were: for (I),  $(M - 15) + 2$ ; for (II),  $(M - 35) + 2$ ; and for (III),  $M + 2$ .

<sup>1</sup> G. M. Kosolapoff, 'Organophosphorus Compounds,' J. Wiley, New York, 1950, 2nd edn., p. 339.

<sup>2</sup> A. Zwierzak, *Phosphorus*, 1972, 2, 19.

*Scrambling Controls.*—There was no measurable conversion of (IIIa) into (IIIb) in refluxing xylene over 2 h, which rules out the possibility of thermal scrambling (intra- or inter-molecular) in the pyrophosphate product. Catalysis of such scrambling by the chloridate (II), or scrambling between (II) and (III), was also shown to be very small. The phosphoryl-labelled pyrophosphate (IIIa), after 2 h in refluxing xylene in the presence of 2 mol. equiv. of unlabelled phosphorochloridate (II), showed a small loss of label (9.9% enrichment reduced



SCHEME 4

to 9.4%) to the chloridate but no measurable conversion into (IIIb). Unlabelled pyrophosphate, after similar treatment with 2 mol. equiv. of labelled chloridate (IIa), was enriched by *ca.* 0.6%. This figure was too low for accurate measurement, or for practicable estimation of the ratio (IIIa):(IIIb). Further, it should be remembered that these conditions of steady, high concentrations (0.4M-pyrophosphate) are much more favourable for scrambling than those in the condensation reaction mixture (overall concentration of pyrophosphate plus phosphorochloridate = 1M) where either the pyrophosphate or the chloridate are at

*Analysis of the Pyrophosphate Products.*—The position of the label in the pyrophosphate (III), and the ratio (IIIa):(IIIb), was determined by analysis of the methyl ester (I), obtained by treating the pyrophosphate with sodium methoxide. Phosphoryl-labelled (IIIa) gives (Ia) labelled to half the extent to which the (IIIa) was labelled, while bridge-labelled (IIIb) gives only unlabelled (I), whichever pyrophosphate phosphorus atom is attacked. In confirmation of this, (IIIa) of 10.1% enrichment (see synthetic routes above) gave (Ia) of 5.1% enrichment on treatment with sodium methoxide.

Stretching frequencies for the  $\text{P}=\text{O}$  groups are readily identifiable in the i.r. spectra of labelled materials (see Experimental section). Peaks arising from  $\text{P}-^{18}\text{O}-\text{P}$  groups were not identifiable, however, in a very complex region of the spectrum.

## RESULTS AND DISCUSSION

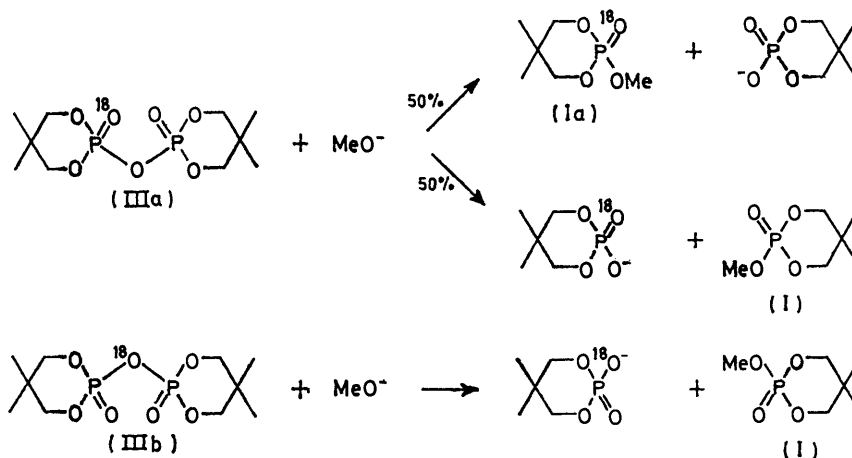
The results for the thermal condensation (two independent runs) are given in the Table. The final

## Enrichments (%) for the thermal condensation \*

Run	A	B	C	D
1	10.2	9.8	2.9	59
2	10.2	9.9	2.9	59

\* A, Enrichment (Ia) of (I) before thermal condensation. B, Total [(IIIa) and (IIIb)] enrichment of (III). C, Enrichment (Ia) of (I) from degradation of (III). D, Enrichment in (IIIa) as a percentage of total enrichment [(IIIa) + (IIIb)] of (III) ( $= \frac{2C}{B} \times 100$ ).

column gives the proportion of (IIIa) as a percentage of the total enrichment (single label) of the product pyrophosphate, effectively the rate of alkoxy-attack, relative to phosphoryl attack.



very low or zero concentrations for significant portions of the heating period. Scrambling after thermal condensation was thus taken as zero for the purposes of subsequent calculations.

Our conclusion, therefore, is that in this particular thermal condensation, attack by the phosphate alkoxy oxygen atom on the chloridate centre is an important route. As far as the production of the cyclic pyro-

phosphate is concerned, this occurs by alkoxy-attack to the extent of  $ca. 60 \pm 10\%$ .\*

Ring opening is unlikely to be very extensive in view of the known resistance to cleavage of the 1,3,2-dioxaphosphorinan ring system.<sup>3-5</sup> If this is the case, then this figure is applicable to the overall reaction and reflects the relative nucleophilicities of the phosphoryl and methoxy oxygen atoms towards the phosphorochloridate centre.

For other phosphate esters the quantitative importance of alkoxy attack would probably differ and would depend upon the ester alkyl groups. We anticipate that in the case of trimethyl phosphate, for example, alkoxy attack would be even more important because of the presence of three small, reactive, alkoxy-groups.

Further work is clearly necessary to establish accurate values for relative reactivities (P=O *vs.* P-O-R), but the importance of alkoxy attack is clearly established.

#### EXPERIMENTAL

Benzene, toluene, and xylene were dried over sodium hydride, and pyridine over phosphorus pentoxide, and each was freshly distilled immediately before use. The light petroleum used had b.p. 60–80°. <sup>18</sup>O Was obtained from <sup>18</sup>O-enriched water (10.3% enrichment) (British Oxygen Company). <sup>18</sup>O-Enrichment was calculated from appropriate peak heights in the mass spectra of labelled compounds (see footnote, p. 201). Mass spectra were obtained with the A.E.I. MS9 mass spectrometer (direct sample insertion at *ca.* 100°, 20 eV, trap-current 100 μA).

2-Chloro-5,5-dimethyl-1,3,2-dioxaphosphorinan (IV) was obtained by an established procedure.<sup>6</sup>

*2-Chloro-5,5-dimethyl-1,3,2-dioxaphosphorinan-2-one*.—*Unlabelled* (II). A mixture of water (0.54 g, 0.03 mol), triethylamine (3.03 g, 0.03 mol), and tetrahydrofuran (3.0 cm<sup>3</sup>) was added dropwise, with stirring and external cooling, to a solution of the dioxaphosphorinan (IV) (5.06 g, 0.03 mol) in benzene (50 cm<sup>3</sup>). Stirring was continued and after 1 h a solution of sulphuryl chloride (4.05 g, 0.03 mol) in benzene (10 cm<sup>3</sup>) was added over *ca.* 15 min. Stirring was continued for a further 30 min.

The temperature was maintained at 20–25° throughout. The benzene layer was then dried (MgSO<sub>4</sub>) and evaporated to give the crude phosphorochloridate (4.6 g, 84%). Recrystallisation (benzene–light petroleum) gave prisms (3.8 g, 69%), m.p. 105–106° (lit.,<sup>4</sup> 104.5–106°).

*Labelled* (IIa). The labelled compound was prepared as above from the dioxaphosphorinan (IV) (10.12 g, 0.06 mol) and <sup>18</sup>O-enriched water (1.08 g, 0.06 mol). The product (7.03 g, 64%) had m.p. 104–106° and was enriched with *2-chloro-5,5-dimethyl-1,3,2-dioxaphosphorinan-2-[<sup>18</sup>O]one* to the extent of 10.1%;  $\nu_{\max}$ . 1265 (P=<sup>18</sup>O str) and 1301 cm<sup>-1</sup> (P=O str).

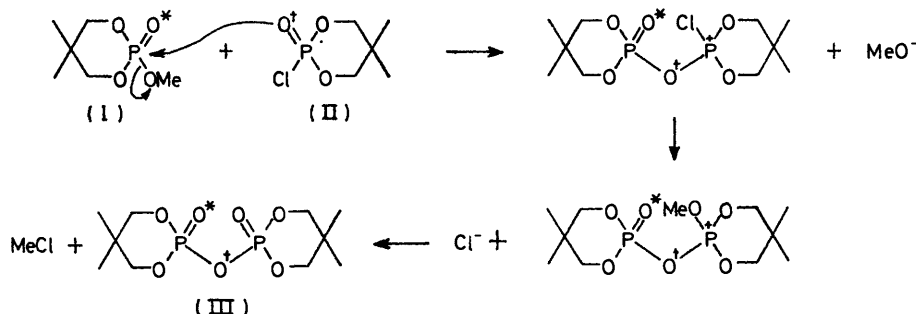
*2-Hydroxy-5,5-dimethyl-1,3,2-dioxaphosphorinan-2-one*.—This was obtained by an established hydrolysis<sup>4</sup> of the phosphorochloridate (II).

*2,2'-Oxybis-(5,5-dimethyl-1,3,2-dioxaphosphorinan-2-one)*.—*Unlabelled* (III). A mixture of the dioxaphosphorinanone (II) (1.85 g, 0.01 mol), 2-hydroxy-5,5-dimethyl-1,3,2-dioxaphosphorinan-2-one (1.66 g, 0.01 mol), and pyridine (0.79 g, 0.01 mol) in benzene (30 cm<sup>3</sup>) was stirred and refluxed gently for 2 h. The mixture was cooled, solvent was evaporated, and the residue was dissolved in chloroform (75 cm<sup>3</sup>) and washed (3 × 35 cm<sup>3</sup> water). The solution was dried (MgSO<sub>4</sub>) and evaporated to give the crude pyrophosphate (3.0 g, 96%), m.p. 184–187°. The pure material (from ethyl acetate) had m.p. 194–196° (lit.,<sup>4</sup> 193–195°).

*Labelled* (IIIa). The labelled compound was prepared as above from 2-chloro-5,5-dimethyl-1,3,2-dioxaphosphorinan-2-[<sup>18</sup>O]one (2.77 g, 0.015 mol; 10.1% enrichment) and the hydroxydioxaphosphorinanone (2.49 g, 0.015 mol). The product had m.p. 192–194° and was enriched with *2,2'-oxybis-5,5-dimethyl-1,3,2-dioxaphosphorinan-2-[<sup>18</sup>O]one* to the extent of 10.1%. The position of the label was confirmed by degradation with sodium methoxide (see below);  $\nu_{\max}$ . 1270 (P=<sup>18</sup>O str) and 1312 cm<sup>-1</sup> (P=O str).

*2-Methoxy-5,5-dimethyl-1,3,2-dioxaphosphorinan-2-[<sup>18</sup>O]one* (Ia).—Sodium (0.92 g, 0.04 mol) was dissolved in anhydrous methanol (60 cm<sup>3</sup>) and the solution was added dropwise, with stirring, to a solution of the dioxaphosphorinan-2-[<sup>18</sup>O]one (IIa) (7.38 g, 0.04 mol; 10.1% enrichment) in benzene (60 cm<sup>3</sup>). Stirring was continued for 2 h at 35–40°. The mixture was then evaporated to

\* A referee has suggested the following mechanism as an alternative to attack by methoxy oxygen upon the phosphorochloridate.



This mechanism would result in phosphoryl-labelled pyrophosphate (IIIa) when the starting phosphate was phosphoryl-labelled (\*) and would involve no attack by methoxy oxygen. However, we have carried out a condensation between the phosphoryl-labelled chloridate (IIa) and the unlabelled methyl phosphate (I). If this mechanism were operative then the pyrophosphate would be bridge-labelled (†). We observed that the pyrophosphate produced (measured enrichment 10.5%) is exclusively phosphoryl-labelled (measured enrichment of methyl ester from degradation of pyrophosphate, 5.4%). We can thus discount this alternative mechanism in favour of our proposal of attack by methoxy oxygen.

<sup>3</sup> R. L. McConnell and H. W. Coover, *J. Org. Chem.*, 1959, **24**, 630.

<sup>4</sup> R. S. Edmundson, *Tetrahedron*, 1965, **21**, 2379.

<sup>5</sup> R. S. Edmundson and A. J. Lambie, *J. Chem. Soc. (B)*, 1967, 577.

<sup>6</sup> A. Zwierzak, *Canad. J. Chem.*, 1967, **45**, 2501.

dryness, dissolved in benzene (100 cm<sup>3</sup>), filtered, and evaporated again to give the crude methyl phosphate (6.62 g, 92%). The pure ester (from benzene–light petroleum) had m.p. 96–98° (lit.,<sup>7</sup> for unlabelled material, 94°) and was enriched with 2-methoxy-5,5-dimethyl-1,3,2-dioxaphosphorinan-2-[<sup>18</sup>O]one to the extent of 10.2%;  $\nu_{\max}$  1250 (P=O str) and 1288 cm<sup>-1</sup> (P=O str).

*Degradation of the Unlabelled Cyclic Pyrophosphate (III) with Sodium Methoxide.*—Sodium (0.07 g, 0.003 mol) was dissolved in anhydrous methanol (5 cm<sup>3</sup>) and the solution was immediately added to a solution of the pyrophosphate (III) (0.94 g, 0.003 mol) in methanol (10 cm<sup>3</sup>). The resultant mixture was kept at room temperature for 1 h and then evaporated to dryness. The residue was triturated with benzene (25 cm<sup>3</sup>) and, after filtration, the solution was evaporated to yield an oil which crystallised readily upon seeding. Recrystallisation (from benzene–light petroleum, twice) gave 2-methoxy-5,5-dimethyl-1,3,2-dioxaphosphorinan-2-one (I) (0.22 g, 41%) as needles, m.p. 96–97.5°.

*Degradation of Labelled Samples of the Cyclic Pyrophosphate (IIIa).—Determination of the site of labelling.* Degradation to the methyl ester was carried out as for the unlabelled pyrophosphate above, and the  $M + 2$  enrichment of the resultant methyl ester determined. Analysis of the pyrophosphate of 10.1% enrichment, the synthesis of which is described above, gave methyl ester of 5.1% enrichment. This confirmed the position of the label in the pyrophosphate (in the phosphoryl group) and also confirmed the validity of this method of analysis. Other samples of labelled pyrophosphate were analysed in this way to establish the position(s) of the label, and the results are in the Table.

*Scrambling control in the absence of phosphorochloridate.* The cyclic pyrophosphate (IIIa) (1.00 g, 0.00318 mol; 10.1% enrichment) was refluxed in xylene (10 cm<sup>3</sup>) for 2 h. The pyrophosphate was recovered from the cooled solution

by precipitation with light petroleum (30 cm<sup>3</sup>) and the position of the label determined as above. The methyl ester obtained from the degradation was enriched to the extent of 5.1%, showing that the whole of the label had remained in the phosphoryl group.

*Scrambling control in the presence of phosphorochloridate.*

(a) A mixture of the labelled phosphorochloridate (IIa) (0.74 g, 0.004 mol; 10.1% enrichment), unlabelled pyrophosphate (III) (0.63 g, 0.002 mol), and xylene (5 cm<sup>3</sup>) was refluxed for 2 h. The pyrophosphate was recovered from the cooled solution by precipitation with light petroleum and washed with benzene (2 × 5 cm<sup>3</sup>; recovery 0.44 g). On recrystallisation (ethyl acetate) the sample had m.p. 192–195° and the  $M + 2$  enrichment was 0.61%.

(b) A mixture of the phosphorochloridate (II) (1.12 g, 0.006 mol), labelled pyrophosphate (IIIa) (0.94 g, 0.003 mol; 9.9% enrichment), and xylene (7.5 cm<sup>3</sup>) was refluxed for 2 h. Pyrophosphate recovered as above (m.p. 192–195°) had an  $M + 2$  enrichment of 9.4%, and the methyl ester from degradation of this pyrophosphate had an enrichment of 5.1%.

*Thermal Condensation of the Phosphate (Ia) with the Phosphorochloridate (II).*—A mixture of the phosphoryl-labelled methyl phosphate (Ia) (1.80 g, 0.01 mol; 10.2% enrichment), and the phosphorochloridate (II) (1.85 g, 0.01 mol) was refluxed in xylene (10 cm<sup>3</sup>) for 2 h. The mixture was then set aside in a refrigerator for 24 h, after which crystals of the pyrophosphate were collected and washed successively with benzene (3 cm<sup>3</sup>) and light petroleum (5 cm<sup>3</sup>). The crude product, m.p. 155–170° (1.28 g, 41%), was recrystallised (from ethyl acetate) to give the pure pyrophosphate, m.p. 192–195° (0.72 g). The  $M + 2$  enrichment of this product was 9.8% and that of the methyl ester (m.p. 95–97°) obtained from its degradation was 2.9%.

[4/765 Received, 17th April, 1974]

<sup>7</sup> R. S. Edmundson, *Tetrahedron*, 1964, **20**, 2781.