A Reinvestigation of the Reaction Between 2-Methoxy-5,5-dimethyl-1,3,2-dioxaphosphorinan-2-one and 2-Chloro-5,5-dimethyl-1,3,2-dioxaphosphorinan-2-one

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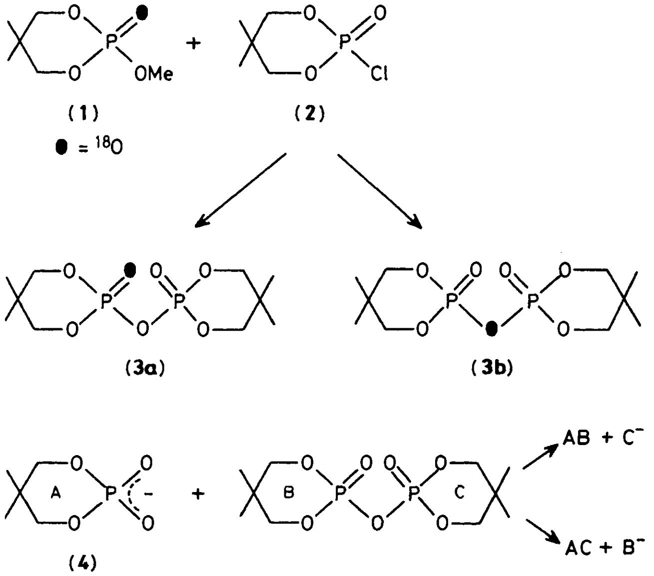
The title compounds together give pyrophosphate and methyl chloride probably *via* a cycle of reactions involving cyclic phosphate diester and hydrogen chloride as carriers; rapid formation of dioxadiphosphetanes from intermediate five-co-ordinate phosphoranes and a slower intermolecular scrambling account for the distributions of ^{18}O observed starting with various patterns of ^{18}O labelling.

Phosphoryl esters, $R^1R^2P(O)OR^3$, are weakly nucleophilic. Their nucleophilic site is usually assumed to be the phosphoryl oxygen[1] and this has been demonstrated by means of ^{18}O-labelling in the case of reaction with phosgene.[2] However, in 1975, Simpson and Zwierzak[3] treated the ^{18}O-labelled ester (**1**) with the phosphoryl chloride (**2**) and analysed the resulting pyrophosphate (**3**) by reaction with sodium methoxide and estimation of the ^{18}O content of the resulting methyl ester. One half of the ester formed from (**3a**) will contain ^{18}O whereas (**3b**) can lead only to unlabelled ester. Starting with methyl ester (**1**) containing 10.2% ^{18}O in the phosphoryl oxygen, Simpson and Zwierzak recovered ester containing 2.9% ^{18}O. They concluded that the pyrophosphate was a 60:40 mixture of (**3a**) and (**3b**) and that, whereas (**3b**) resulted from the expected nucleophilic attack of phosphoryl oxygen, (**3a**) was the result of nucleophilic attack on (**2**) by the methoxy oxygen of (**1**). We have reinvestigated this reaction with the advantages of high levels of isotopic substitution and high-field ^{31}P n.m.r. spectroscopy and provide a different interpretation of these results.

When the methyl ester (**1**) and the phosphoryl chloride (**2**),



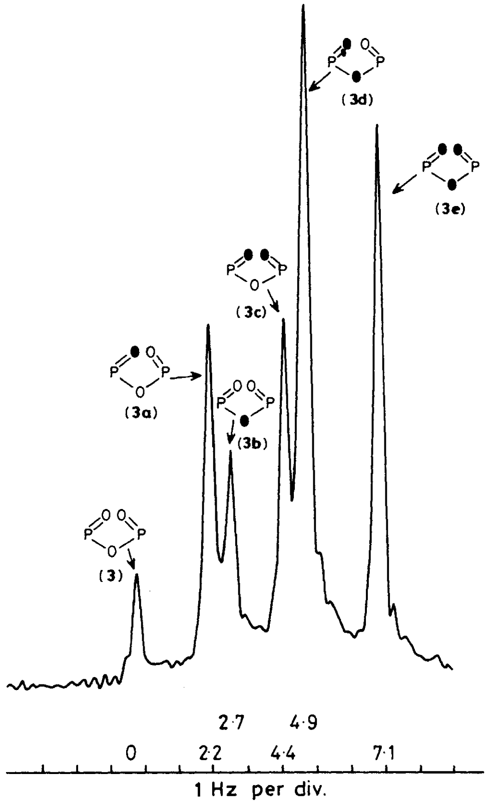
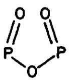
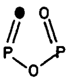
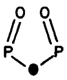
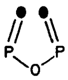
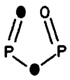
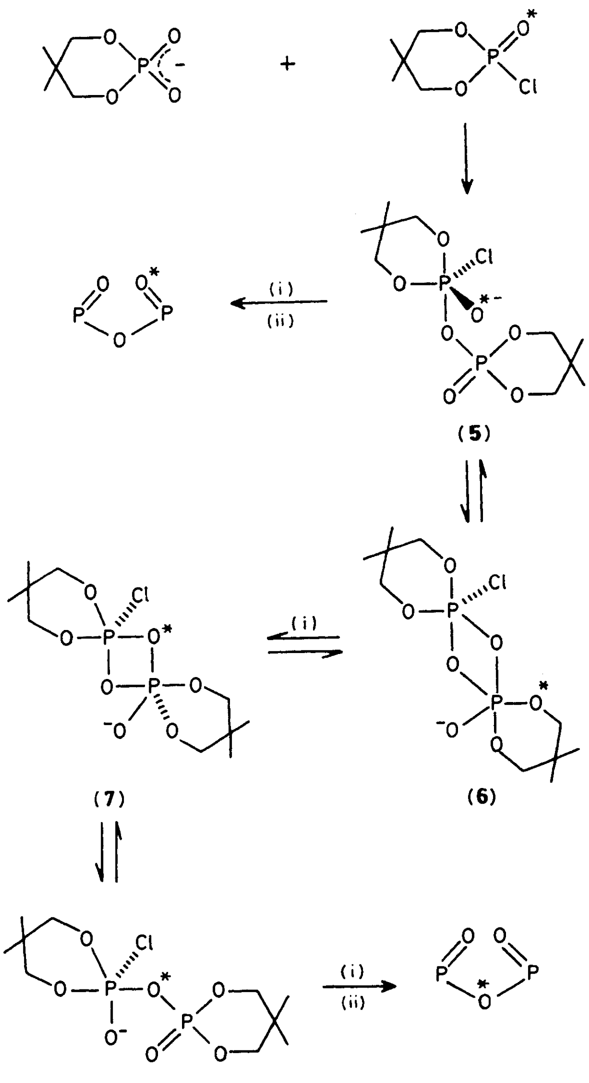


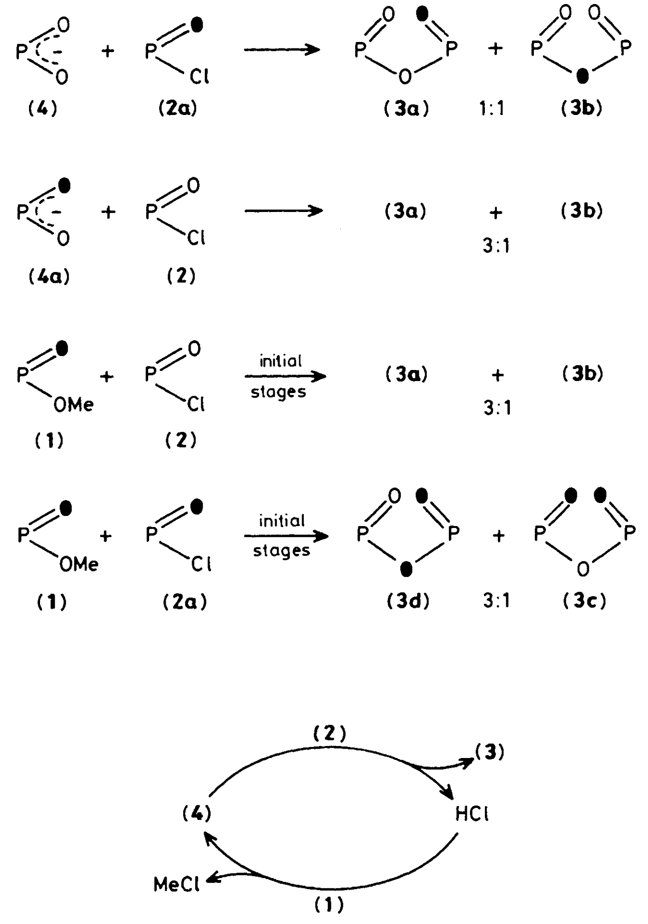
Figure 1. ^{31}P N.m.r. spectrum at 121 MHz in $CDCl_3$ of pyrophosphate formed from ester (**1**) and phosphoryl chloride (**2**), both labelled with 95% ^{18}O in their phosphoryl oxygens, in xylene at 120 °C for 24 h.

Table 1. Pyrophosphates formed from ester (**1**) and phosphoryl chloride (**2**), both labelled with 95% ^{18}O in their phosphoryl oxygens, in xylene at 120 °C.

	 (3)	 (3a)	 (3b)	 (3c)	 (3d)	 (3e)
Found(%) 24 h	4.9	15.8	9.9	15.7	28.4	24.3
Found(%) 2 h	1.8	11.4	7.7	21.8	44.2	13.0
Calc. (%) for total scrambling	4.9	17.0	8.5	14.7	29.4	25.2



Scheme 1. (i), pseudorotation; (ii) $-$ Cl$^-$.



Scheme 2

both labelled with 95% ^{18}O in the phosphoryl oxygen, were heated together in xylene at 120 °C for 24 h the ^{31}P n.m.r. spectrum of the resulting pyrophosphate (Figure 1) showed the ^{18}O to be almost completely scrambled among the three exocyclic oxygens (Table 1). In this system a P^{18}O single bond produces an upfield ^{31}P n.m.r. shift of 0.023 p.p.m. and a P^{18}O double bond a shift of 0.035 p.p.m.; the effects are additive. In unsymmetrically labelled molecules an extreme AB system leads to one apparent signal halfway between the two expected; *e.g.* the signal at 4.9 Hz to high field of unlabelled pyrophosphate is due to (**3d**) in which the two phosphorus signals would individually be at 2.7 and 7.1 Hz relative to (**3**).[4]

Under the conditions used by Simpson and Zwierzak, 2 h refluxing in xylene, scrambling was extensive but not complete (Table 1). This scrambling is most easily envisaged as involving exchange between (**3**) and traces of cyclic phosphodiester (**4**).

Attempts to prepare an authentic sample of (**3a**) by reaction of unlabelled phosphodiester anion (**4**) with ^{18}O-labelled (**2a**) in CDCl$_3$ at 30 °C revealed unexpected complexity. The reaction gave, even in its first stages, a 1 : 1 mixture of (**3a**) and (**3b**). Similarly monolabelled anion (**4a**) with unlabelled (**2**) gave (**3a**) and (**3b**) in a ratio of 3 : 1 throughout the course of the reaction. Clearly whichever oxygen of (**4**) or (**4a**) attacks the phosphoryl chloride it becomes equivalent at some stage of the reaction sequence with the phosphoryl oxygen of the phosphoryl chloride. This is probably *via* the topomeric dioxadiphosphetanes (**6**) and (**7**) formed from the initial five-co-ordinate phosphorane (**5**) which must pseudorotate before expelling chloride anion[5] (Scheme 1).

Application of a similar dioxadiphosphetane hypothesis to the Simpson–Zwierzak reactions described above, *i.e.* (a) labelled (**1**) with unlabelled (**2**) and (b) labelled (**1**) with labelled (**2a**), predicted that in their early stages, before intermolecular scrambling became important, reaction (a) would lead to a 1 : 1 ratio of (**3a**) and (**3b**) whereas reaction (b) would give entirely (**3d**). Neither prediction was correct; reaction (a) gave (**3a**) and (**3b**) in a ratio of 3 : 1 and reaction (b) gave (**3d**) and (**3c**) in a ratio of 3 : 1. These are the ratios of isomeric pyrophosphates expected from attack of cyclic phosphodiester anion (**4a**) on phosphoryl chlorides (**2a**) and (**2**) respectively!

The rate of a Simpson–Zwierzak reaction is inversely related to the purity of the starting materials and to the precautions taken to exclude moisture. We conclude that the formation of pyrophosphate is initiated by a small amount of phosphodiester (**4**). This reacts with the phosphoryl chloride (**2**) to give pyrophosphate and HCl which then reacts with methyl ester to give methyl chloride and (**4**),[6] see Scheme 2. This hypothesis, together with the formation of dioxadiphosphetanes from the intermediate five-co-ordinate phosphoranes and a slower intermolecular scrambling in the product, account for the experimental observations.

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