On the Mechanism of Reaction of Activated Phosphoryl Compounds with Phosphoryl Anions: A Reassessment of the Role of Dioxadiphosphetanes

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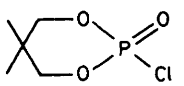
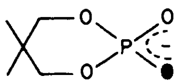
Activated phosphoryl compounds react with phosphoryl anions to give anhydrides without the intervention of dioxadiphosphetane intermediates; the mechanism has been probed using oxygen isotopes and high field ^{31}P n.m.r. spectroscopy.

As part of a study on the mechanism of the reaction between phosphate triesters and phosphorochloridate diesters it was noted that the reaction of the phosphorochloridate (**1**) with the corresponding anion (**2**) to give the symmetrical pyrophosphate (**3**) apparently proceeded *via* a dioxadiphosphetane intermediate.[1] This was proposed on the basis of assignments of the ^{31}P n.m.r. resonances to the possible isotopomeric pyrophosphate tetraesters arising when the reaction was carried out with [^{18}O]-labelled starting materials. We report here an oxygen isotope study of a range of such reactions involving activated phosphoryl compounds and phosphoryl anions and conclude that these do not involve dioxadiphosphetane intermediates. These observations have led to a reinterpretation of the data obtained in the original study.


(**1**)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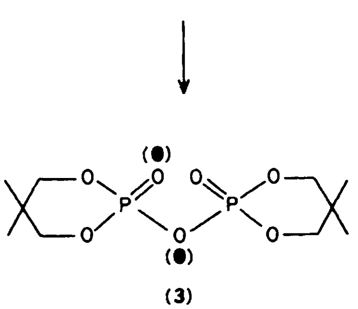
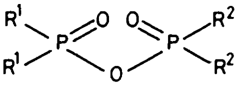
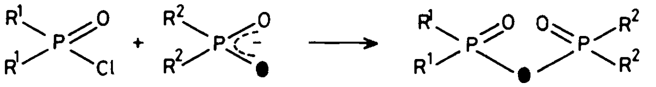

(**3**)

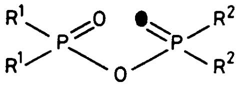
When diethyl phosphorochloridate (**4**) is reacted with diethyl [^{18}O]phosphate anion (**5**) (*ca.* 85% ^{18}O at the labelled site) in dry dichloromethane, tetraethyl pyrophosphate (**6**) is produced in quantitative yield based on ^{31}P n.m.r. spectroscopy. The high field ^{31}P n.m.r. spectrum showed a resonance at −13.1 p.p.m. due to unlabelled pyrophosphate (**6a**), and two upfield shifted resonances at −13.116 and −13.123 p.p.m. in a ratio of *ca.* 3 : 1, corresponding to singly [^{18}O]-labelled pyrophosphates. Similar results were obtained for the reaction of diphenyl phosphorochloridate with diphenyl phosphate anion. The assignment of the high field resonances depends critically upon the absolute magnitude of the ^{18}O isotope shifts.[2] For the bridge-labelled pyrophosphate (**6b**) the structure is symmetrical and therefore the ^{31}P n.m.r. spectrum will show a singlet upfield from the unlabelled pyrophosphate (**6a**) due to ^{18}O in a single bond. We have recently shown that the range for such shifts (0.015—0.036 p.p.m.) is surprisingly large and varies markedly with compound type,[3] as observed for ^{18}O-induced shifts in ^{13}C n.m.r. spectroscopy.[4] For the non-bridge-labelled pyrophosphate (**6c**), the symmetry of the non-structure is removed and the ^{31}P n.m.r. spectrum is expected to show an extreme AB system, where the difference in the chemical shifts of the two nuclei will be equal to the ^{18}O-induced upfield shift produced by isotope in a double bond, range *ca.* 0.04—0.06 p.p.m., and the ^{31}P–^{31}P coupling constant will be in the range 18—22 Hz, typical for pyrophosphates.[5] The central line of the extreme AB system is expected



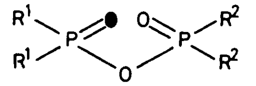
(**6a**) $R^1 = R^2 = -OEt$
(**9a**) $R^1 = -OPh$; $R^2 = -OEt$
(**15a**) $R^1 = R^2 = -Ph$



(**4**) $R^1 = -OEt$ (**5**) $R^2 = -OEt$ (**6b**) $R^1 = R^2 = -OEt$
(**7**) $R^1 = -OPh$ (**8**) $R^2 = -OPh$ (**9b**) $R^1 = -OPh$; $R^2 = -OEt$
(**13**) $R^1 = -Ph$ (**14**) $R^2 = -Ph$ (**15b**) $R^1 = R^2 = -Ph$



(**6c**) $R^1 = R^2 = -OEt$
(**9c**) $R^1 = -OPh$; $R^2 = -OEt$
(**15c**) $R^1 = R^2 = -Ph$



(**9d**) $R^1 = -OPh$; $R^2 = -OEt$

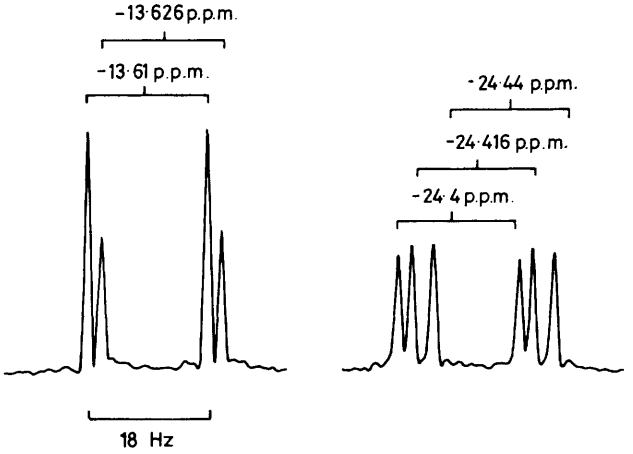


Figure 1. ^{31}P n.m.r. spectrum (Bruker AM-300, 121.5 MHz) of the mixed pyrophosphate (**9**) derived from the reaction of diethyl phosphorochloridate (**4**) with diphenyl [^{18}O]phosphate anion (**8**).

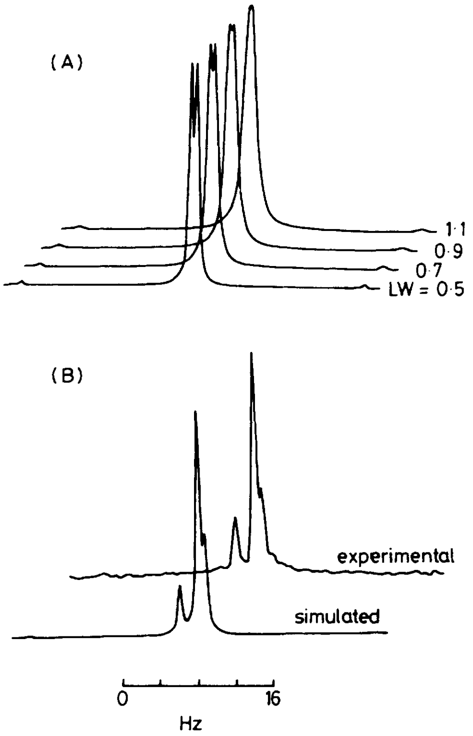


Figure 2. (A) The simulated spectra using the Bruker PANIC programme for two nuclei of spin 1/2, differing in chemical shifts by 4.8 Hz and coupling with J of 18 Hz. The various simulations illustrate the effect of the variation in the assumed line widths. (B) The full simulation of the spectrum of tetraethyl [^{18}O]pyrophosphate (**6**) derived from the reaction of diethyl phosphorochloridate (**4**) with diethyl [^{18}O]phosphate anion (**5**) assuming (**6c**) to be of the form shown in (A) with line width 0.5 Hz, and (**6b**) to be upfield from (**6a**) by 0.016 p.p.m. (1.96 Hz at 121.5 MHz); together with the experimental spectrum.

to be halfway between the shift for the unlabelled pyrophosphate (**6a**) and the true position of the P=^{18}O, *i.e.* upfield shifted from (**6a**) in the range 0.02—0.03 p.p.m. In view of the surprisingly large ranges of both single and double bond ^{18}O-induced shifts[3] we considered it essential to examine some relevant model compounds.

Reaction of diethyl phosphorochloridate (**4**) with diphenyl [^{18}O]phosphate anion (**8**) gave the mixed pyrophosphate (**9**). The ^{31}P n.m.r. spectrum can be assigned without ambiguity since the P=^{18}O labelled species appear at their true positions. The ^{31}P n.m.r. spectrum is shown in the Figure 1. The unlabelled pyrophosphate tetraester (**9a**) appears as two doublets centred at −13.61 and −24.40 p.p.m. with a coupling constant of 18 Hz, assigned to the diethoxyphosphoryl and diphenoxyphosphoryl residues respectively. In addition, there is an upfield shifted doublet centred at −13.626 p.p.m. corresponding to ^{18}O-isotope in the bridging (**9b**) site of the diethoxyphosphoryl residue, together with two upfield shifted doublets at −24.416 and −24.44 p.p.m. corresponding to the diphenoxyphosphoryl residue with ^{18}O in the bridging (**9b**) and non-bridging (**9d**) positions. Since no resonances corresponding to ^{18}O in the non-bridging site on the diethoxyphosphoryl residue (**9c**) are observed, there is no need to postulate the involvement of a dioxadiphosphetane intermediate. The same conclusion can be reached on the basis of reaction of diphenyl phosphorochloridate (**7**) with diethyl [^{18}O]phosphate anion (**5**) to give the mixed pyrophosphate (**9**) with the label in the bridging (**9b**) and non-bridging (**9c**) sites around the diethoxyphosphoryl residue [but no (**9d**)].

Using these values for the P–^{18}O and the P=^{18}O shifts together with the coupling constant taken from the mixed pyrophosphate (**9**) it is possible to analyse the spectrum obtained for the reaction of (**4**) with (**5**) to give tetraethyl pyrophosphate (**6**). We have simulated the appearance of the phosphoryl labelled pyrophosphate (**6c**) using $\Delta\delta = 0.04$ p.p.m. and a ^{31}P—^{31}P coupling constant of 18 Hz. The appearance of the central lines of the extreme AB is strongly dependent on the line-width, appearing as a broad single line if the line width approaches 1 Hz but resolving into two lines as the line width is reduced to 0.5 Hz, Figure 2A. The central features appear 0.020 p.p.m. upfield from the unlabelled pyrophosphate (**6a**). The singlet for the symmetrical bridge-labelled pyrophosphate (**6b**) is now expected to appear 0.016 p.p.m. upfield from (**6a**). Figure 2B shows the experimental spectrum together with the full simulation of the (**6a**) plus (**6b**) and (**6c**) in a ratio of 1 : 1. It can be seen that the downfield line of the central AB doublet coincides with the singlet for (**6b**) and that this results in two apparent resonances in the ratio of 3 : 1. The experimental spectrum is best simulated by addition of (**6b**) and (**6c**) in a 1 : 1 ratio which would be the result of a coupling reaction proceeding *via* a direct displacement not involving a dioxadiphosphetane intermediate.

A similar analysis of the spectrum of the pyrophosphate (**3**) derived from the reaction of (**1**) and (**2**) suggests an alternative assignment to that originally made.[1] It is likely that the unsymmetrically labelled pyrophosphates are upfield from the symmetrically labelled pyrophosphates, with the central features of the extreme AB systems appearing as well resolved doublets, one line of which overlaps with the downfield singlet of symmetrically labelled pyrophosphates. The reassignment of the n.m.r. spectrum does not significantly alter the conclusions reached concerning the mechanism of the reaction of the phosphate triester and the phosphorochloridate diester, in that the appearance of triply labelled pyrophosphates implies that *inter*molecular exchange occurs and this can best be accommodated by the cycle of reaction proposed in our previous study.

In the case of the reaction of diphenylphosphinoyl chloride (**13**) with diphenyl [^{18}O]phosphinate (**14**) the ^{31}P n.m.r. spectrum could not be assigned analogously. Upfield of the unlabelled pyrophosphinate (**15**) (+25.815 p.p.m.) was a broad single line ($\Delta\delta$ 0.024 p.p.m.) and a sharp singlet ($\Delta\delta$ 0.034 p.p.m.) with an integrated intensity ratio of 1 : 1. The most reasonable assignment in this case is that the central unresolved AB component corresponding to (**15c**) is now downfield of the bridge-labelled material (**15b**), in contrast to the pyrophosphates. This is reasonable since in phosphinate model compounds a P=^{18}O shift is less than twice the P–^{18}O, whereas in phosphates the P=^{18}O shift is greater than twice the P–^{18}O shift.[3] Phosphonates are apparently similar to phosphates in the relative magnitude of these shifts.

In conclusion, using high field ^{31}P n.m.r. spectroscopy and ^{18}O isotopically labelled starting materials we have shown that, in general, activated phosphoryl compounds react with phosphoryl anions without the intermediacy of dioxadiphosphetanes.

We thank the S.E.R.C. for financial support.

Received, 4th June 1987; Com. 760

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