Reinvestigation of the ^{31}P NMR evidence for the formation of diorganyl phosphoropyridinium intermediates

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A ^{31}P NMR study on the reactions of diphenyl and diethyl chlorophosphates/bromophosphates with pyridine showed that equilibria of these reactions are heavily shifted to the left and thus concentrations of the putative diorganyl phosphoropyridinium chlorides/bromides are usually below the detection level of this spectroscopic method. However, when diphenyl iodophosphate was subjected to reaction with pyridine, we were able for the first time to observe the formation of a diorganyl phosphoropyridinium intermediate by ^{31}P NMR spectroscopy.

Introduction

A reaction which attracts considerable attention and has been the subject of numerous mechanistic investigations, is phosphorylation of alcohols. Due to the crucial role played by nucleophilic catalysis, the quest for the intermediates involved in this reaction has a long history.[1,2] ^{31}P NMR spectroscopy is a powerful tool for studying reactions occurring at the phosphorus center,[3,4] as it often permits detection of reactive intermediates involved, and in this way can provide insight into the reaction mechanism or reaction pathway of a particular phosphorus compound. For phosphorylation of alcohols in pyridine using phosphate monoester derivatives, ^{31}P NMR spectroscopy provides strong evidence for the intermediacy of the corresponding pyridinium adduct of metaphosphate **1**.[2,5,6] In contradistinction to this, phosphoropyridinium intermediates **2** derived from phosphate diesters, although postulated on many occasions,[7,8] remained more elusive.[9] Due to lack of potential stabilisation by a betaine structure as in **1**, intermediates of type **2** are assumed to be more reactive than **1**, and thus less likely to be detected. However, recently Perich *et al.*[10] reported on ^{31}P NMR evidence for the accumulation of phosphoropyridinium intermediates of type **2** upon reaction of various chlorophosphate diesters with pyridine. The importance of this claim for mechanistic interpretations and understanding of numerous transformations of phosphorus compounds that involve intermediacy of **2**,[11] prompted the present investigation.

Results and discussion

Using ^{31}P NMR spectroscopy Perich and co-workers observed[10] that upon addition of pyridine to diphenyl chlorophosphate in tetrahydrofuran (THF; $\delta_P = -7$ ppm), a new species resonating at −25.5 ppm (*ca.* 25%) was formed. Since the same compound (*ca.* 83%) was formed also from diphenyl bromophosphate ($\delta_P = -16.8$ ppm) in the presence of pyridine, diphenyl phosphoropyridinium structure **2a** was assigned to this intermediate (Chart 1). Crucial to this assignment was the fact that the compound resonating at −25.5 ppm was not formed in THF until pyridine was added, and the amount of **2a** increased from 25 to 83%, when chlorophosphate was replaced by bromophosphate as a substrate. The last phenomenon, the authors rationalised by assuming better leaving group ability of the bromide over the chloride anion.

1
R = alkyl or aryl

2
2a, R = Ph
2b, R = Et

Chart 1

The above interpretation was then extended to the reactions of pyridine with dialkyl chlorophosphates ($\delta_P = -11.2$, -13.7, and -13.4 ppm respectively, for methyl, ethyl and benzyl derivatives), which gave compounds to which structures of type **2** were assigned.[10]

Three aspects of these observations seemed to warrant closer examination. Firstly, the resonance signals attributed to structures of type **2** were conspicuously close to those of the corresponding pyrophosphates[3] (*ca.* −25 ppm for tetraphenyl and *ca.* −11 ppm for tetraalkyl pyrophosphates). Unfortunately, the authors apparently overlooked such a possibility as no attempt was made to distinguish between species of type **2** and the corresponding tetrasubstituted pyrophosphates. Secondly, generation of the same intermediate from two different starting materials (*i.e.* from chloro- and bromophosphates) does not provide *per se* any proof for a chemical structure of the intermediate. Thirdly, although the addition of pyridine to chlorophosphates in THF triggered the formation of new intermediates, these species do not necessarily have to contain pyridine as an integral part of their structures.

To clarify these ambiguities concerning the assignments of the phosphoropyridinium structure **2** to the compounds formed upon addition of pyridine to various chlorophosphates in THF, the following experiments were carried out using diphenyl and diethyl halophosphates as model compounds.

Reaction of diphenyl chloro- and bromophosphates with pyridine

When diphenyl chlorophosphate **3a** (Chart 2) was dissolved in dry THF, ^{31}P NMR spectroscopy indicated the presence of only

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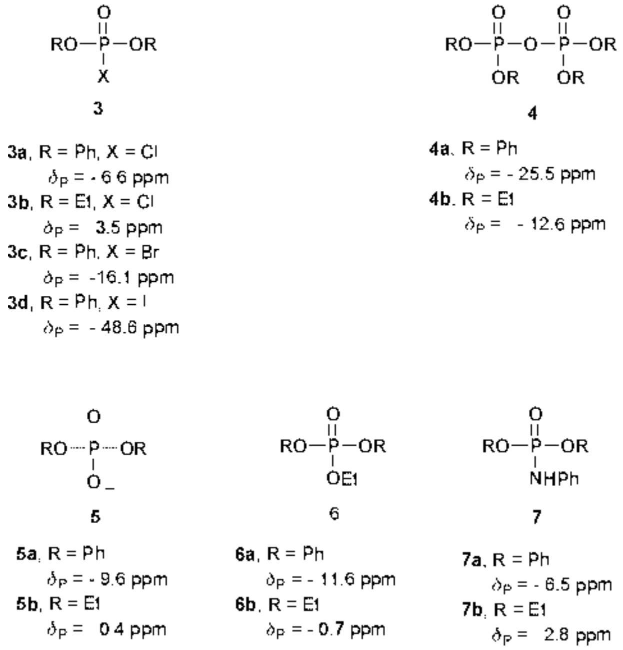


Chart 2

starting material but the addition of pyridine (10 equiv.) triggered formation of a new compound resonating at −25.5 ppm (*ca.* 20%). These, Perich *et al.* interpreted as an indication for the formation of phosphoropyridinium intermediate **2a**.

However, upon incremental addition of water (from 0.1–1 equiv.) to this reaction mixture, the signal at −25.5 ppm gradually increased in intensity to become the major one when the amount of added water reached *ca.* 0.5 equiv. Continuing the addition of water, a gradual disappearance of the signal at −25.5 ppm and formation of a new resonance at −9.6 ppm were observed. A compound resonating at −9.6 ppm was found to be the final product of this reaction and was identified as diphenyl phosphate (comparison with a genuine sample of **5a**). Spiking of the reaction mixture before addition of water with tetraphenyl pyrophosphate showed that the initially formed intermediate at −25.5 ppm had an identical chemical shift to that of pyrophosphate **4a**. These experiments were consistent with a pyrophosphate structure **4a** of the compound resonating at −25.5 ppm, and made the phosphoropyridinium structure **2a** postulated by Perich *et al.* less likely.

The formation of pyrophosphate **4a** from chlorophosphate **3a** upon addition of pyridine can be explained by the presence of adventitious water. This possibility was substantiated by separate experiments which showed that chlorophosphate **3a** did not undergo any detectable hydrolysis when dissolved in THF containing 0.5 equiv. of water. However, addition of pyridine (10 equiv.) to such a mixture resulted in an immediate formation of pyrophosphate **4a** as the major product. When more than 1 equiv. of water was present in the THF solution before addition of pyridine, the sole product of the reaction was the expected diphenyl phosphate **5a**.

Although phosphoropyridinium intermediate **2a** and tetraphenyl pyrophosphate should give a similar ^{31}P NMR spectrum (a singlet), these compounds were expected to afford different products upon reaction with alcohols or amines. For a compound with the pyrophosphate structure, formation of two products was predicted (equimolar amounts of phosphate diester **5a** and a compound of type **6** or **7**), while from a structure of type **2a**, only ester **6** or amidate **7** should be formed.

To this end, the reaction mixture resulting from addition of pyridine to the THF solution of diphenyl chlorophosphate, and consisting of **3a** (*ca.* 80%) and an intermediate resonating at −25.5 ppm (*ca.* 20%), was treated with excess of ethanol (20 equiv.) or aniline (20 equiv.). In both instances the reactions were fast (<5 min), and together with the expected ester **6a** ($\delta_P = -11.6$ ppm, *ca.* 90%, for the reaction with ethanol) or amidate **7a** ($\delta_P = -6.5$ ppm, *ca.* 90%, for the reaction with aniline), *ca.* 10% of diphenyl phosphate **5a** was formed. The amount of the latter was always proportional to the amount of an intermediate resonating at −25.5 ppm, and its formation was consistent with a pyrophosphate structure **4a** of the intermediate.

Finally, to check if pyridine was an integral part of an intermediate resonating at −25.5 ppm, we carried out a reaction of chlorophosphate **3a** in THF with triethylamine (10 equiv.). Formation of the same intermediate (*ca.* 15%) as in the reaction above indicated that pyridine was not an indispensable reactant in this transformation.

All the reactions above were repeated both in acetonitrile and with diphenyl bromophosphate **3c** as a starting material. Essentially the same results were obtained and the reaction mixtures were usually indistinguishable by ^{31}P NMR spectroscopy from those when chlorophosphate **3a** was used as a reactant.

Reaction of diethyl chlorophosphate with pyridine

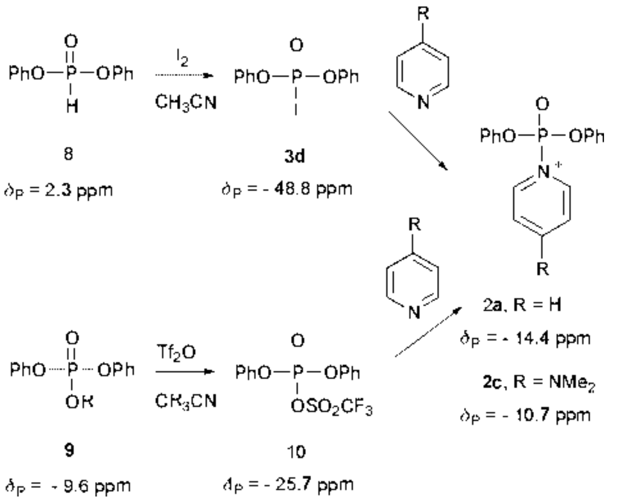
When diethyl chlorophosphate **3b** in THF or in acetonitrile was treated with pyridine (10 equiv.), formation of the same intermediate as reported by Perich *et al.* ($\delta_P = -12.6$ ppm, *ca.* 5%) was observed using ^{31}P NMR spectroscopy. Addition of water (0.5 equiv.) caused immediately the disappearance of the starting material, and the compound resonating at −12.6 ppm became the only phosphorus-containing species in the reaction mixture. This compound, however, could not have the phosphoropyridinium structure **2b** postulated by Perich *et al.*, as it was completely resistant (within a few hours) to hydrolysis, and did not react with the added ethanol (20 equiv.) or aniline (20 equiv.) to produce the expected phosphotriester **6b** or phosphoramidate **7b**. On this basis, and by comparison with a genuine sample of **4b**, we identified the compound resonating at −12.6 ppm as tetraethyl pyrophosphate. In this instance, again, adventitious water was apparently responsible for its formation in variable amounts upon addition of pyridine to chlorophosphate **3b** in THF solution.

Reaction of diphenyl iodophosphate with pyridine

The most likely reason why phosphoropyridinium intermediates of type **2** could not be detected by ^{31}P NMR spectroscopy by reacting the corresponding chloro- or bromophosphates with pyridine, was that the equilibria of these reactions, due to the high nucleophilicity of chloride and bromide anion towards the phosphorus centre, were almost entirely to the left.[12] However, this should not be the case for iodophosphate derivatives, which due to the presence of a weak P–I bond (*ca.* 44 kcal mol^{-1} *vs.* 79 kcal mol^{-1} for the P–Cl and 63 kcal mol^{-1} for the P–Br bond, respectively[13]) are significantly more reactive than the other halophosphates.

We therefore generated diphenyl iodophosphate **3d** *in situ* (Scheme 1) by reacting diphenyl H-phosphonate **8** with iodine (1.2 equiv.) in acetonitrile. The reaction was fast (<5 min) and produced iodophosphate **3d** ($\delta_P = -48.6$ ppm) as the major product (*ca.* 90%).[14] Upon addition of pyridine (50 equiv.) to this reaction mixture, the signal from **3d** almost completely disappeared (*ca.* 2%) and two new resonances at −14.4 ppm (singlet, *ca.* 65%) and −25.5 ppm (singlet, *ca.* 25%) appeared. A compound resonating at −25.5 ppm was identified as tetraphenyl pyrophosphate **4a** (*vide supra*), while the signal at −14.4 ppm belonged to a new intermediate, which we did not observe in the reactions of halophosphates **3a** and **3c** with pyridine.

As to a possible structure of this intermediate, some additional observations were pertinent. Firstly, taking into account that pyridinium adducts of type **1** resonate at *ca.* −5 ppm in



Scheme 1

^{31}P NMR spectra,[6,15] the chemical shift of −14.4 ppm could be compatible with a diester phosphoropyridinium intermediate of type **2**. Secondly, the intermediate resonating at $\delta_P = -14.4$ ppm was rather unstable and disappeared completely when the reaction mixture was left standing overnight. The only signal that could be detected by ^{31}P NMR spectroscopy was that of pyrophosphate **4a** (at −25.5 ppm). Thirdly, addition of water (50 equiv.) to the reaction mixture immediately produced only diphenyl phosphate **5a** ($\delta_P = -9.6$ ppm), while the reaction with ethanol (50 equiv.) or aniline (50 equiv.) (also rapid), afforded **6a**–**5a** and **7a**–**5a** in *ca.* 8 : 1 ratio. Fourthly, the mixed phosphoric triflic anhydride **10** ($\delta_P = -25.7$ ppm, generated *in situ* from **9** and triflic anhydride, Scheme 1; see also the Experimental section), which was expected to be easily converted into a pyridinium adduct of type **2**, afforded upon addition of pyridine the intermediate resonating at $\delta_P = -14.4$ ppm.

Thus, this line of evidence seems to indicate that the intermediate giving rise to a signal at −14.4 ppm was a highly reactive species and apparently contained a single phosphorus center. This, together with the value of its chemical shift and how it was generated, leads us to tentatively assign to this intermediate a structure of diphenyl phosphoropyridinium derivative **2a**.

To substantiate this assignment, we repeated the above experiments with a substituted pyridine, to demonstrate that the position of the resonance at $\delta_P = -14.4$ ppm was affected by the nature of the pyridine used, and hence the pyridine moiety was an integral part of the postulated intermediate **2**. To this end, 4-(dimethylamino)pyridine (DMAP, 3 equiv.) was added to the reaction mixtures containing *in situ* generated iodophosphate **3d** or phosphoric triflic mixed anhydride **10** (Scheme 1). In both instances, the formation of a new intermediate, resonating at $\delta_P = -12.6$ ppm and with reactivity analogous to that of **2a**, was observed. Since an intermediate with an identical chemical shift ($\delta_P = -12.6$ ppm) was also produced in the reaction of chlorophosphate **3a**[16] or bromophosphate **3c** in acetonitrile with DMAP (2 equiv.), we assigned to it a diphenyl phosphoryl[4-(dimethylamino)pyridinium] structure **2c**. It was gratifying to note that the resolution enhanced ^{31}P NMR spectrum of the intermediate **2c** (produced from the mixed anhydride **10** and DMAP, Scheme 1) showed the expected splitting pattern of the signal due to the presence of P–N–C–H couplings (triplet, $^3J_{PH} = 5.5$ Hz), which supported further this structural assignment.[17]

An attempted generation of diethyl phosphoropyridinium derivative **2b** failed. Although diethyl iodophosphate was cleanly produced in the reaction of diethyl H-phosphonate with iodine,[18] the subsequent addition of pyridine gave a complex mixture of products (pyridinium adduct of type **1**, pyrophosphate **4b**, and various polyphosphates; ^{31}P NMR spectroscopy), but none of them could be identified as phosphoropyridinium intermediate **2b**. Product distribution in this reaction may suggest that apparently the initially formed **2b** underwent rapid dealkylation by pyridine and iodides under the reaction conditions, giving rise to a variety of secondary products. Similar results were obtained previously when diethyl H-phosphonate was subjected to oxidation with iodine in pyridine.[8]

In conclusion, ^{31}P NMR experiments on the reactions of halophosphate diesters with pyridine showed that equilibria for these reactions are almost entirely to the left for chloro- and bromophosphates, and to the right for the corresponding iodophosphates. This explains dramatic differences in chemical reactivity between these compounds.[19] Using ^{31}P NMR spectroscopy we were able for the first time to observe the formation of diorganyl phosphoropyridinium intermediate **2a**, when diphenyl iodophosphate was subjected to the reaction with pyridine. Signals previously assigned to this type of intermediate[10] were shown to be due to the corresponding tetrasubstituted pyrophosphates.

Experimental

Reactions were carried out in 10-mm NMR tubes and spectra were recorded on a Varian 300 MHz spectrometer. For ^{31}P NMR experiments 2% H_3PO_4 in D_2O was used as an external standard (coaxial inner tube). Anhydrous solvents for the studies were prepared in the following way: pyridine (ScanLab) was distilled from CaH_2 and stored over molecular sieves 4 Å; acetonitrile (ScanLab) was made anhydrous by storing over molecular sieves 4 Å; tetrahydrofuran (Merck) was refluxed over Na–benzophenone and freshly distilled before use. Diphenyl chlorophosphate, diethyl chlorophosphate, and diphenyl H-phosphonate were commercial grades from Aldrich.

The reference compounds **4a**, **4b**, **5a**, **5b**, **6a**, **6b**, **7a** and **7b** which have been used for the identification of some of the reaction products were produced according to standard procedures.[20] Diphenyl phosphorobromidate **3c** was generated *in situ* by addition of bromine (1.2 equiv.) to diphenyl H-phosphonate in THF in the presence of triethylamine (1.2 equiv.).

A typical protocol for ^{31}P NMR experiments

A phosphorus-containing compound (*e.g.* **3a**, **3b**; 0.2 mmol) was dissolved in THF or acetonitrile (2 mL) and upon addition of the reagents as described in the text, progress of the reaction was followed using ^{31}P NMR spectroscopy.

Generation of diphenyl phosphoropyridinium intermediate 2a

Method A. Diphenyl H-phosphonate (0.2 mmol) in acetonitrile or THF (2 mL) was allowed to react with iodine (1.2 equiv.). When the formation of diphenyl iodophosphate **3d** was complete (*ca.* 5 min, ^{31}P NMR), pyridine (100 μL) was added. Progress of the reaction was followed by ^{31}P NMR spectroscopy as described in the text.

Method B. Diphenyl phosphoric acid (0.2 mmol) in acetonitrile or THF (2 mL) was allowed to react with triflic anhydride (3.0 equiv.). When the formation of the mixed diphenyl phosphoric triflic anhydride **10** was complete (*ca.* 5 min, ^{31}P NMR), pyridine (100 μL) was added. Progress of the reaction was followed by ^{31}P NMR spectroscopy as described in the text.

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