A new mechanism for nucleophilic substitution at a thiophosphoryl centre revealed by the reaction of diisopropylamine with $PSCl_3$

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The reaction of $PSCl_3$ with Pr^i_2NH at 60 °C affords the disubstitution product $(Pr^i_2N)_2P(S)Cl$ without first forming the monosubstitution product $Pr^i_2NP(S)Cl_2$; a P^{III} compound (possibly PCl_3) generated *in situ* seems to be a crucial intermediate.

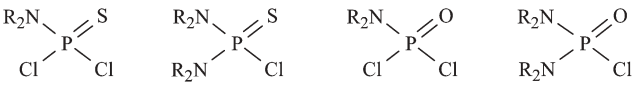
It is the quest for a more complete understanding of biologically-important phosphoryl transfer reactions that drives the continuing mechanistic study of nucleophilic substitution at P=O and P=S centres.[1] These reactions are usually associative [$S_N2(P)$] with a five-coordinate P^V transition state or intermediate, although a dissociative elimination–addition (EA) pathway may become important when the phosphorus atom bears an acidic ligand (OH, SH, NHR) so that a metaphosphate-like three-coordinate P^V intermediate can be formed.[2]

The diisopropylamino phosphorothioic dichloride **1** (R = Pr^i) is a known compound but the ways in which it has been obtained are not straightforward.[3] We hoped it could be simply prepared by the direct reaction of $PSCl_3$ with Pr^i_2NH but that proved not to be the case.† Since $S_N2(P)$ reactions at four-coordinate phosphoryl and thiophosphoryl centres are very sensitive to steric effects[4] it would not have been remarkable if $PSCl_3$ had merely failed to react with a nucleophile as bulky as Pr^i_2NH. It did react, however, albeit only reluctantly, but the product was not the expected amino dichloride **1** (R = Pr^i). The identity of the product and the possible reasons for its formation are our concern here and it is to assist our understanding that we have made a comparative study of the reactions of $PSCl_3$ and $POCl_3$ with Pr^i_2NH and Et_2NH.

When $PSCl_3$ (δ_P 31.0) was added to a solution of Et_2NH (2.5 equiv., 2.0 mol dm^{-3}) in $CDCl_3$ at room temperature it was rapidly converted into the amino dichloride **1** (R = Et)[5] (δ_P 60.7; quintet, J_{PH} 18.5), reaction being complete inside 5 min ($t_{0.5} \leqslant$ 1.25 min).‡ Addition of more Et_2NH (2.0 equiv.) caused further substitution and formation of the bis(amino) chloride **2** (R = Et)[5] (δ_P 83.0; 9 lines, J_{PH} 15) but this was at least 700 times slower ($t_{0.5} \sim$ 15 h at 25 °C).

Using $POCl_3$ as the substrate the reaction with Et_2NH (2.0 mol dm^{-3} in $CDCl_3$) to give the amino dichloride **3** (R = Et)[6] (δ_P 16.1; quintet, J_{PH} 16.5) was so fast as to be quite violent; in a competition experiment (limited Et_2NH) $POCl_3$ was found to be *ca.* 40 times as reactive as $PSCl_3$. Here too, further substitution to give the bis(amino) chloride **4** (R = Et)[7] (δ_P 26.7; 9 lines, J_{PH} 13.5) was relatively slow ($t_{0.5} \sim$ 20 min) though again some 45 times faster than the corresponding P=S transformation.

The reaction of $POCl_3$ with Pr^i_2NH (2 mol dm^{-3} in $CDCl_3$) was sluggish at room temperature ($t_{0.5} \sim$ 26 h at 25 °C) and at least 5×10^4 times slower than its reaction with Et_2NH [$t_{0.5} \leqslant$ 2 s, estimated from the rate for $PSCl_3$ with Et_2NH ($t_{0.5} \leqslant$ 1.25 min) and the 40-fold greater reactivity of $POCl_3$]. The product was the expected amino dichloride **3** (R = Pr^i)[8] (δ_P 11.5; t, J_{PH} 28.5) with no indication in the ^{31}P NMR spectrum of any of the bis(amino) compound **4** (R = Pr^i) (lit.,[9] δ_P 20).



In the case of $PSCl_3$ there was no appreciable reaction with Pr^i_2NH (2.2 equiv., 2.0 mol dm^{-3} in $CDCl_3$) after 26 days at 25 °C (^{31}P NMR: 97% of total phosphorus accounted for by $PSCl_3$; no single product > 0.6%). At 60 °C reaction did occur but it showed some unexpected features. First, there was an induction period so that the product (δ_P 68.9) was barely detectable (*ca.* 1%) after 2 days but accounted for 9% of the total phosphorus in the reaction mixture after 4 days and 50% after 8 days. Second, the reaction stopped (no free amine remained) with almost half the $PSCl_3$ still unreacted, implying that formation of the product consumes 4 equivalents of amine, not two. Third, the ^{31}P NMR signal of the product was not the triplet expected for the monoamino compound **1** (R = Pr^i) but a quintet (J_{PH} 22). Even when a large excess of $PSCl_3$ was used (solvent and reactant) the monosubstitution product **1** (R = Pr^i) could not be detected (δ_P 49.2, t, J_{PH} 29.5 for authentic sample†). These observations suggest that the mechanism of substitution is something other than conventional $S_N2(P)$ and that the product is the bis(amino) chloride **2** (R = Pr^i)[10] (M^+ 298, 300; ^1H and ^{13}C NMR signals indicative of diastereotopic methyls in the *N*-isopropyl groups). In the same way the reaction of dicyclohexylamine with $PSCl_3$ (large excess) gave the bis(amino) compound **2** (R = C_6H_{11}) (δ_P 70.4, quintet, J_{PH} 22; M^+ 458, 460).

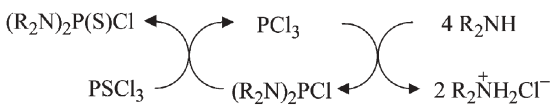
It is hard to imagine further reaction of the monosubstitution product **1** (R = Pr^i) being competitive with its formation by $S_N2(P)$ let alone so fast that it does not accumulate enough to be detected. In any case when some authentic **1** (R = Pr^i) was included in the $PSCl_3$ (neat)–Pr^i_2NH reaction mixture it remained unchanged, neither increasing nor decreasing, as the amine reacted with $PSCl_3$ to give the bis(amino) product **2** (R = Pr^i). The conclusion must be that Pr^i_2NH can convert $PSCl_3$ into the disubstitution product **2** (R = Pr^i) without passing through the monosubstitution product **1** (R = Pr^i).§

In looking for an explanation we were mindful of the high reactivity of P^{III} compounds towards nucleophiles, in particular the ready reaction of PCl_3 with Pr^i_2NH (in $CHCl_3$) to give $(Pr^i_2N)_2PCl$,[11] and of the tendency of P^{III} compounds to abstract

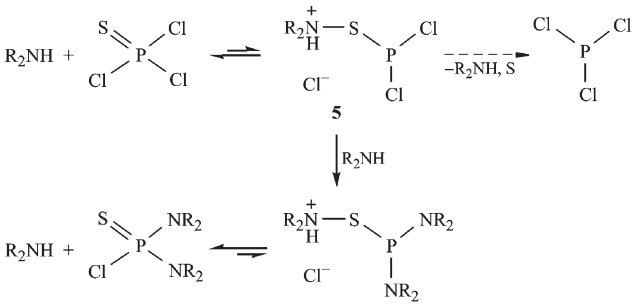
sulfur from $PSCl_3$.[12] Control experiments showed that under the conditions of our $PSCl_3$–Pr^i_2NH reactions (at 60 °C) PCl_3 is rapidly transformed into $(Pr^i_2N)_2PCl$ (δ_P 138) and that this is then gradually converted into the P=S compound **2** (R = Pr^i). They also showed that addition of a little PCl_3 (0.1 equiv.) eliminated the induction period and greatly increased the rate of the reaction of $PSCl_3$ with Pr^i_2NH to give **2** (R = Pr^i).[13] It would therefore be possible for a catalytic amount of PCl_3 to cause the reaction of $PSCl_3$ with Pr^i_2NH to give the disubstitution product **2** (R = Pr^i) without the monosubstitution product **1** (R = Pr^i) ever being formed (Scheme 1, R = Pr^i).

If PCl_3 is responsible it seems it must be generated in the reaction mixture, not only because of the induction period but also because the same behaviour was seen using $PSCl_3$ that had been washed with water to destroy (by hydrolysis) any PCl_3 impurity that might be present. We do not know how PCl_3 could be formed but perhaps Pr^i_2NH is so bulky it does not act as a nucleophile at the P atom of $PSCl_3$ but attacks at the S atom instead. There are many examples of amines and other nucleophiles attacking at a two-coordinate bivalent sulfur atom, notably in the substitution reactions of sulfenic acid derivatives.[14] Nucleophilic attack at a one-coordinate bivalent sulfur (as in $R_2C{=}S$) is much less common except with organometallic reagents (which probably react by electron transfer)[15] but it has been reported[16] for $(CF_3)_2C{=}S$ and $Cl_2C{=}S$ and seems plausible for $Cl_3P{=}S$. That being so, the crucial P^{III} species may not be PCl_3 itself but some related species such as **5** (Scheme 2, R = Pr^i).¶ The extended induction period could be due to traces of moisture in the reaction mixture so that any PCl_3 (or related P^{III} species) that is generated is at first destroyed by hydrolysis [$>P{=}Cl \rightarrow >P(O)H$]. Only when the water has been consumed can the reaction with Pr^i_2NH (Scheme 1, R = Pr^i) make substantial headway.

In principle P^{III} species could be involved in many substitution reactions of thiophosphoryl compounds but in practise they will probably be important only when nucleophilic attack at the phosphorus atom is severely hindered or the nucleophile is especially thiophilic.



Scheme 1



Scheme 2

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Notes and references

† A straightforward route to **1** (R = Pr^i) was subsequently found *viz.* addition of Pr^i_2NH (2 equiv.) to PCl_3 in ether and thiation of the crude product using a concentrated solution of sulfur in boiling toluene.

‡ Reactions were carried out in NMR tubes using distilled $PSCl_3$ or $POCl_3$ and dried amine. Values of $t_{0.5}$ are an indication of the time taken to reach 50% completion but are not true half lives as the amine was not in large excess. The products have previously been reported but in some cases with little data; they were provisionally identified in reaction mixtures by their ^1H-coupled ^{31}P NMR signals and definitively after isolation by their ^1H and ^{13}C NMR ($CDCl_3$) and mass spectra. *J* values are in Hz.

1 (R = Et), δ_H 3.50 (4H, dq, J_{PH} 18.5, J_{HH} 7) and 1.24 (6H, t, J_{HH} 7), δ_C 42.7 (d, J_{PC} 3.5) and 13.7 (d, J_{PC} 3.5), M^+ 205, 207, 209 (10%).

2 (R = Et), δ_H 3.28 (8H, dq, J_{PH} 14, J_{HH} 7) and 1.19 (12H, t, J_{HH} 7), δ_C 41.0 (d, J_{PC} 4) and 13.7 (d, J_{PC} 4), M^+ 242, 244 (50%).

3 (R = Et), δ_H 3.34 (4H, dq, J_{PH} 16.5, J_{HH} 7) and 1.23 (6H, t, J_{HH} 7), δ_C 41.2 (d, J_{PC} 4) and 13.6 (d, J_{PC} 3), M^+ 189, 191, 193 (20%).

4 (R = Et), δ_H 3.18 (8H, dq, J_{PH} 14, J_{HH} 7) and 1.17 (12H, t, J_{HH} 7), δ_C 40.3 (d, J_{PC} 4) and 13.8 (d, J_{PC} 3.5), $(M + H)^+$ (ES) 227, 229 (100%).

1 (R = Pr^i) (authentic) δ_H 3.98 (2H, d × sept, J_{PH} 29, J_{HH} 7) and 1.43 (12H, d, J_{HH} 7), δ_C 51.4 (d, J_{PC} 4.5) and 22.2 (d, J_{PC} 2), M^+ 233, 235, 237 (4%).

2 (R = Pr^i), δ_H 3.79 (4H, d × sept, J_{PH} 22, J_{HH} 7), 1.42 (12H, d, J_{HH} 7) and 1.38 (12H, d, J_{HH} 7), δ_C 48.7 (d, J_{PC} 4.5), 22.5 (d, J_{PC} 2.5) and 22.1 (d, J_{PC} 2.5), M^+ 298, 300 (8%).

3 (R = Pr^i), δ_H 3.71 (2H, d × sept, J_{PH} 29, J_{HH} 7) and 1.38 (12H, d, J_{HH} 7), δ_C 49.5 (d, J_{PC} 5) and 22.0 (d, J_{PC} 2), $(M + H)^+$ (ES) 218, 220 (100%).

§ Had $Pr^i_2NP(S)Cl_2$ proved to be more reactive than $PSCl_3$ the possibility of dissociative reaction by an $S_N1(P)$ mechanism, with a phosphorylium ion intermediate ($X_2P^+{=}S$; X = Cl or Pr^i_2N), might have merited consideration (*cf.* ref. 17).

¶ Another possibility for the reactive P^{III} species is $ClSPCl_2$ resulting from nucleophilic attack of chloride ion at the S atom of $PSCl_3$ (Scheme 2 with Cl^- in place of R_2NH).

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