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Reactions of phosphonamidic acids and phosphonamidothioic acids with alcohols: mechanistic differences revealed by differing responses to steric effects

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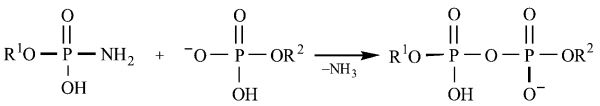
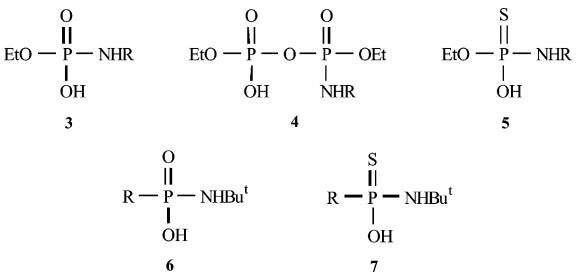
The formation of RP(X)(OH)OR′ (R = Pr^i or Bu^t, R′ = Me or Pr^i) from RP(X)(OH)NHBu^t and R′OH in $CDCl_3$ is insensitive to steric effects when X = S but not when X = O (> 10^3 times slower with R = Bu^t, R′ = Pr^i than with R = Pr^i, R′ = Me), pointing to a dissociative elimination–addition mechanism (metathiophosphonate intermediate) when X = S but an associative $S_N2(P)$ mechanism when X = O.

Phosphoramidic acid monoesters first attracted attention as phosphoryl donors for the synthesis of biologically important pyrophosphates (Scheme 1).[1] Kinetic studies pointed to a bimolecular reaction in which the donor **1**, probably as the zwitterion $R^1OP(O)(O^-)NH_3^+$, experiences direct nucleophilic attack by the acceptor **2**.[1,2] Later work by Jankowski and Quin showed that *N*-substituted phosphoramidic acid monoesters **3** will phosphorylate alcohols efficiently, at least when the substituent on the N atom is bulky (R = mesityl or adamantyl) so that competing formation of the pyrophosphate **4** (self-phosphorylation) is discouraged.[3] Kinetic analysis in this case led to the conclusion that alcohol phosphorylation is a unimolecular elimination–addition (EA) process in which the zwitterion first fragments to give a reactive metaphosphate intermediate ($EtOPO_2$).[3,4] Similar reactivity and kinetics were observed with the thiophosphoryl analogue **5** (R = 1-adamantyl), suggesting a similar unimolecular mechanism with a metathiophosphate intermediate (EtOPOS).[5]

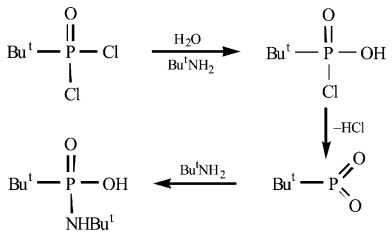


Scheme 1



The extent to which a bulky substituent on the N atom of a phosphoramidic ester (or on the ester O atom) can suppress direct attack by the nucleophile must be limited because it is two bonds removed from the phosphoryl reaction centre. The steric effect would be greater, and the suppression of direct attack more certain, if the bulky group were attached directly to the phosphorus atom. We have therefore prepared the *P*-*tert*-butyl phosphonamidic acid **6** (R = Bu^t) and its thiophosphonyl analogue **7** (R = Bu^t) and examined their reactions with alcohols, looking particularly for evidence pertaining to the role of metaphosphate-like intermediates (Bu^tPO_2 and Bu^{t}POS). To aid interpretation of the results the less hindered *P*-isopropyl compounds (R = Pr^i) were also included in the study.

The phosphonamidic acid **6** (R = Bu^t) (δ_P 42.8) was obtained from the phosphonic dichloride by reaction with water in Bu^tNH_2 (30 °C, 7 days) (Scheme 2). The same approach was used to prepare **7** (R = Bu^t) (δ_P 87.9) (70 °C, 7 days) and **7** (R = Pr^i) (δ_P 90.1) (Pr^iNH_2; 5 °C, 0.5 h) from $RP(S)Cl_2$, while **6** (R = Pr^i) (δ_P 40.3) was conveniently obtained by hydrolysis ($NaOH–H_2O$) of the known[6] phosphonamidic chloride Pr^{i}P(O)(NHBu^t)Cl. The acids were isolated as solids.† In solution they were sufficiently stable to allow characterisation by ^{1}H NMR spectroscopy and ES mass spectrometry.



Scheme 2

The reactivity of the acids was examined using dilute solutions (~0.03 mol dm^{-3}) in $CDCl_3$ containing MeOH or Pr^{i}OH (0.4 or 1.2 mol dm^{-3}). The reactions were maintained at 45 °C and were examined periodically by ^{31}P NMR spectroscopy (^{1}H decoupled).

The thiophosphonyl (P=S) reactions all gave predominantly the expected ester **9** (R = Pr^i or Bu^t, R′ = Me or Pr^i) (^{31}P singlet downfield of substrate) although with the less hindered *P*-isopropyl substrate a little of the pyrophosphonate **8** (R = Pr^i) was also formed (self-phosphonylation) (small ^{31}P doublets at higher field; ≤10% of total product integral).‡ Approximate rate constants were deduced from four spectra recorded during the first 50% of reaction.§ The results (Table 1) show that the hindered *tert*-butyl compound **7** (R = Bu^t) is as reactive as the less congested isopropyl compound (R = Pr^i), in fact 1.5–4 times more reactive. They also show that its reactivity is practically as great with Pr^{i}OH as with the more nucleophilic (less hindered) MeOH and increases when the concentration of alcohol is reduced. On all counts an associative $S_N2(P)$ mechanism seems untenable leaving as the probable alternative a dissociative elimination–addition (EA) process with a reactive

Table 1 Approximate pseudo-first-order rate constants (*k*) for reactions of RP(S)(OH)NHBu^t (**7**) and RP(O)(OH)NHBu^t (**6**) in $CDCl_3$ containing alcohols at 45 °C

	$10^5k/s^{-1}$			
Alcohol	**7** (R = Pr^i)	**7** (R = Bu^t)	**6** (R = Pr^i)	**6** (R = Bu^t)
MeOH (1.2 mol dm^{-3})	4.3	6.9	7.4	9.5×10^{-3}
MeOH (0.4 mol dm^{-3})	4.7	15	2.9	2.5×10^{-3} [a]
Pr^{i}OH (1.2 mol dm^{-3})	1.4	5.3	1.0	1.3×10^{-3} [a]
Pr^{i}OH (0.4 mol dm^{-3})	3.0	12	1.0 [b]	$< 1 \times 10^{-3}$

[a] Very approximate (≤20% complete in 120 days) [b] Product largely pyrophosphonate (self-phosphonylation)

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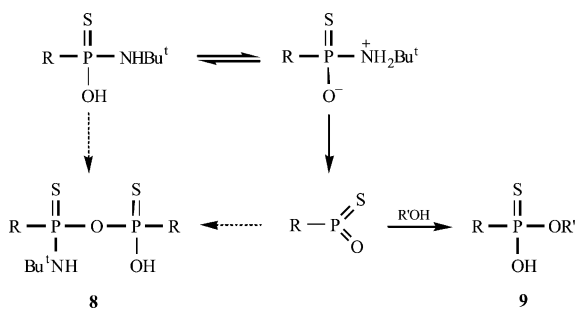
metathiophosphonate intermediate (Scheme 3). Reduced solvation (stabilisation) may be responsible for the greater reactivity observed with the more hindered substrate and a lower concentration of the alcohol. For the isopropyl compound **7** (R = Pr^i) it seems there is some contribution from S_N2(P), at least in the reaction with MeOH, since it is 4 times less reactive than the *tert*-butyl compound with Pr^{i}OH (0.4 or 1.2 mol dm^{-3}) but only 3 or 1.5 times less reactive with MeOH (0.4 or 1.2 mol dm^{-3}). A mixture of EA and S_N2(P) mechanisms for the isopropyl substrate is also suggested by the results of competition experiments using 1 : 1 MeOH–Pr^{i}OH: the OMe/OPr^i product ratio (^{31}P NMR) increases from 2.1 with 0.4 mol dm^{-3} alcohol (total) to 3.0 with 1.2 mol dm^{-3} and 4.9 with 4.8 mol dm^{-3}, in accord with an increasing contribution from a more discriminating bimolecular S_N2(P) pathway. For the *tert*-butyl substrate the OMe/OPr^i product ratio is 1.5 ± 0.1 at all alcohol concentrations.

For the P=O substrates **6** a very different picture emerges (Table 1). The reactivity of the *P*-isopropyl compound **6** (R = Pr^i) is not much different from that of its P=S counterpart **7** but with MeOH the rate of reaction does now decrease when the concentration of the alcohol is reduced, as expected for S_N2(P), while with the less nucleophilic Pr^{i}OH formation of pyrophosphonate (self-phosphonylation) (δ_P 31 and 25; both d, J_{PP} 41 Hz) is as important as reaction with the alcohol (1.2 mol dm^{-3} Pr^{i}OH) or more important (0.4 mol dm^{-3} Pr^{i}OH). There is also a fairly strong 9 : 1 preference for reaction with the less hindered alcohol in a MeOH–Pr^{i}OH competition experiment (1.2 mol dm^{-3} total alcohol). The more sterically congested *tert*-butyl compound **6** (R = Bu^t) is much less reactive, by a factor of about a thousand. Such high sensitivity to steric effects is also seen in conventional acid-catalysed P–N bond cleavage reactions, notably hydrolysis of the amides RP(O)(NH$_2$)Ph and RP(O)(NHPh)Ph (> 10^3 times slower with R = Bu^t than with R = Pr^i),[7] and is surely compelling evidence for an associative S_N2(P) mechanism. In this case, with R = Bu^t, there may be some contribution from the dissociative EA mechanism (metaphosphonate formation) but it cannot be the dominant pathway since reduction of the concentration of MeOH or replacement of MeOH by Pr^{i}OH causes a substantial reduction in rate, as it does when R = Pr^i. A contribution from EA is, however, suggested by the slightly more modest 6.5 : 1 preference for MeOH over Pr^{i}OH seen in the competition experiment (1.2 mol dm^{-3} total alcohol). Little if any pyrophosphonate is formed when R = Bu^t even though reaction with the alcohol is so slow. Self-phosphonylation must therefore be extremely slow, presumably because both the donor and the acceptor contain the bulky *tert*-butyl group.

We conclude that phosphonamidothioic (P=S) acids can react easily by elimination–addition (RPOS intermediate) so that even with an unhindered nucleophile (MeOH) it takes only moderate hindrance in the substrate (R = Pr^i) for the EA pathway to match S_N2(P) in importance. By contrast phosphonamidic (P=O) acids are reluctant to react by elimination–addition (RPO_2 intermediate) so the EA pathway becomes competitive only when S_N2(P) is greatly retarded, as with a low concentration of a hindered nucleophile (Pr^{i}OH) and a very hindered substrate (R = Bu^t). This contrasting behaviour is not a result of S_N2(P) being much easier for the P=O compounds; there is actually little difference in the reactivity of **6** and **7** when the contribution of S_N2(P) is at its greatest (R = Pr^i and MeOH nucleophile).¶ Rather is it a consequence of the difficulty the P=O compounds have in forming metaphosphate-like intermediates. They are therefore much less able to escape the impact of steric hindrance by following a dissociative EA pathway instead of S_N2(P). Note that where S_N2(P) is most disfavoured (R = Bu^t and Pr^{i}OH nucleophile at low concentration) the P=O compound **6** is at least 10^4 times less reactive than its P=S counterpart and even then it is consumed mainly by reaction with itself [probably S_N2(P)] rather than with the alcohol.

It may not seem surprising that a P=S substrate such as **7** should form a metaphosphate-like intermediate much more easily than its P=O counterpart—there are precedents[8]—but it does seem remarkable given that such intermediates are apparently formed with equal ease from the phosphoramidate **3** and its P=S counterpart **5**.[3–5] The reason for this apparent disparity is not immediately obvious.



8 **9**

Scheme 3

Notes and references

† The crude products were partitioned between aqueous NaOH and CH_2Cl_2 (or ether) and the free acids were liberated by acidification of the aqueous portion. They were generally pure by ^{31}P NMR spectroscopy and were used as obtained. The acid **7** (R = Bu^t) contained impurities (*ca*. 6%) but attempts to purify were not successful and it too was used as obtained.

‡ In the reactions Bu^{t}NH$_2$ is liberated. As reaction proceeds the substrate and product are increasingly present as the anions and their ^{31}P NMR signals move progressively to higher field so precise δ_P values cannot be given. Reaction was generally allowed to continue to completion (T raised where very slow) and after evaporation of the solvent the identity of the ester product (as the Bu^{t}NH$_2$ salt) was confirmed by ^{1}H NMR spectroscopy and ES mass spectrometry. In cases where ^{31}P NMR spectroscopy pointed to significant pyrophosphonate byproduct supporting evidence was provided by the mass spectrum.

§ Beyond *ca*. 40% completion first order plots showed some clear curvature. This is not unexpected given that the substrate is increasingly present as the relatively unreactive *tert*-butylammonium salt rather than the free acid. Values of the pseudo-first-order rate constant (k) are inevitably rather approximate.

¶ Although P=O substrates are generally (much) more reactive than their P=S counterparts in S_N2(P), the substrate **7** is not a normal P=S compound because of tautomerism (HO–P=S ⇌ O=P–SH) or, in the zwitterionic form, the additional negative charge on the sulfur and/or oxygen atoms.

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