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Phosphoramidic acid monoesters as phosphorylating agents: steric effects and reluctance to form monomeric metaphosphate intermediates

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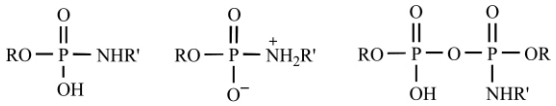
The formation of phosphate diesters $(RO)_2P(X)OH$ (R = Et, Pr^i or Pr^i_2CH) by phosphorylation of ROH with $ROP(X)(NPr^i_2)OH$ is insensitive to steric effects when X = S but not when X = O; this is consistent with a unimolecular mechanism and a thiometaphosphate (ROPOS) intermediate when X = S but a bimolecular $S_N2(P)$ mechanism when X = O.

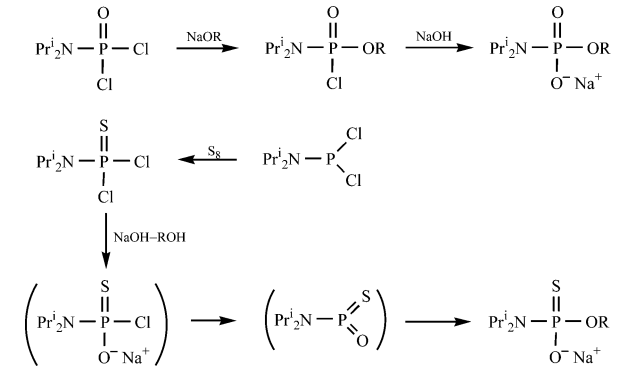
Early work on the synthesis of biologically significant pyrophosphates made use of phosphoramidic acid monoesters **1** as phosphoryl donors.[1] A particular attraction was their selectivity for phosphate anions as acceptors, allowing unprotected alcohol hydroxyl groups (as in nucleotides) to be present without detriment to pyrophosphate formation.[1] This selectivity, together with some kinetic results, was thought indicative of a bimolecular $S_N2(P)$ mechanism, in which there is direct attack of the phosphate acceptor on the donor (as the zwitterion **2**), as opposed to a unimolecular elimination–addition mechanism involving a reactive (unselective) monomeric metaphosphate ($ROPO_2$) intermediate.[1,2]



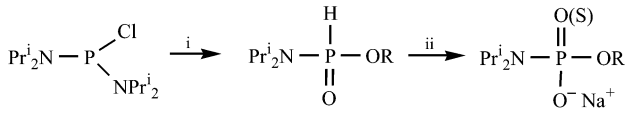
1 **2** **3**

Later work showed that alcohol hydroxyl groups can be phosphorylated efficiently, provided the alcohol is in excess and the N atom of the donor carries a bulky substituent (mesityl, adamantyl) to restrict formation of the pyrophosphate **3** by self-phosphorylation.[3] The P=S analogues of **1** were found to react with alcohols in the same way and at similar rates.[4,5] Detailed kinetic studies led to the conclusion that these reactions do proceed by elimination–addition with a monomeric metaphosphate ($ROPO_2$) or thiometaphosphate (ROPOS) as the product-forming species.[3,4] Analysis of the kinetic results is not straightforward, however, and recent observations on the behaviour of phosphonamidic acids [$RP(O)(OH)NHBu^t$][6] suggest that more clear-cut evidence should be sought. We have therefore looked at steric effects in the reactions of phosphoramidic acid monoesters and their P=S counterparts with alcohols.

Our approach first required the synthesis of amidic acid esters having alkoxy groups of differing steric impact (EtO, Pr^iO and Pr^i_2CHO) and crucially a very bulky amino group (NPr^i_2) to inhibit self-phosphorylation as much as possible. The EtO and Pr^iO compounds were prepared (as salts) quite easily (Scheme 1; R = Et or Pr^i) but the highly congested Pr^i_2CHO compounds proved troublesome. The H-phosphonamidate **4** (Scheme 2; R = $CHPr^i_2$) was formed readily enough but the oxidation (I_2 + H_2O) and sulfuration (elemental S) reactions were impossibly slow under normal conditions.[7] With a stronger base (DBU), a more concentrated solution (in pyridine), an elevated temperature (40 or 55 °C) and a prolonged reaction time (32 or 69 h) both could be accomplished, albeit not very cleanly. All six substrates **5** and **7** were eventually obtained pure (≥98% by ^{31}P NMR), but as oils except for **7** (R = Pr^i_2CH).† They were sufficiently stable in solution ($CDCl_3$) at room temperature to allow characterisation by ^1H, ^{13}C and ^{31}P NMR spectroscopy [δ_P *ca.* 59 for **5**, 11 for **7**; with ^1H coupling, tt (R = Et) or dt (R = Pr^i or Pr^i_2CH), J_{POCH} 8–13, J_{PNCH} 19] and electrospray MS [$(M–H)^-$, 100%].



Scheme 1



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Scheme 2 Reagents: (i) ROH + Et_3N then H_2O; (ii) I_2 – H_2O (or S_8) + Et_3N + DBU in pyridine then NaOH.

The reactions of both the P=O compounds **7** and their P=S counterparts **5** were examined at 70 °C using dilute solutions (~0.03 mol dm^{-3}) in $CDCl_3$ containing a large excess of the alcohol ROH (EtOH, Pr^iOH or Pr^i_2CHOH) (1.2 mol dm^{-3}) corresponding to the alkoxy group (RO) in the substrate.

For the P=S compounds (δ_P ~ 67 in $CDCl_3$ when ROH present)‡ reaction was practically complete within 2 h and gave the expected symmetrical thiophosphate diester **6** (R = Et, Pr^i or Pr^i_2CH) as the diisopropylamine salt (δ_P ~ 53; with ^1H coupling, quintet J_{PH} 8 or t, J_{PH} 11 or t, J_{PH} 12) [*m*/*z* (–ES) 169, 197 or 309; *m*/*z* (+ES) 102]. This was essentially the only product (> 95%) (identity confirmed by ^1H and ^{13}C NMR spectroscopy), pyrophosphate formation being of no importance.

Monitoring the progress of the reactions by ^{31}P NMR spectroscopy afforded approximate values of the pseudo-first order rate constants (k_s) (Table 1); these correspond to half lives of 22 (R = Et), 19 (R = Pr^i) and 4.5 min (R = Pr^i_2CH).§ Clearly there is no decrease in reactivity on going from the EtO to the Pr^iO system while the most hindered Pr^i_2CHO system is actually more reactive than the others, possibly because the substrate is less effectively stabilised (solvated) by the alcohol.

Both observations—clean reaction with the alcohol (present in large excess) in preference to pyrophosphate formation and a rate that is insensitive to steric hindrance—are consistent with a dissociative mechanism (Scheme 3, top) in which the substrate **5** (as the zwitterion) eliminates Pr^i_2NH in the rate-limiting step and forms a reactive (unselective) and sterically-accessible three-coordinate thiometaphosphate intermediate as the product-forming species.

For the P=O substrates (δ_P ~ 9 in $CDCl_3$ + ROH) the reaction of **7** (R = Et) with EtOH gave the expected phosphate diester **8**, δ_P

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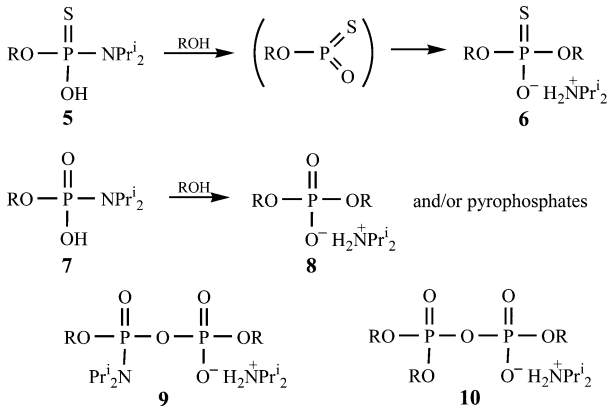
Table 1 Approximate pseudo-first order rate constants (k) for reactions of ROP(X)(OH)NPr$^i_2$ (X = O or S) (~0.03 mol dm^{-3}) in $CDCl_3$ containing ROH (1.2 mol dm^{-3}) at 70 °C

	10^5 k/s^{-1}		
	X = O (k_o)	X = S (k_s)	k_o/k_s
R = Et	4.4	52	8.5×10^{-2}
R = Pr^i	0.39	60	6.5×10^{-3}
R = Pr$^i_2$CH	0.013	250	5.2×10^{-5}



Scheme 3

−0.8 (with ^{1}H coupling, quintet, J_{PH} 6.5) [m/z (−ES) 153] but now some 15% of the total ^{31}P NMR spectrum (^{1}H decoupled) was accounted for by two pairs of phosphorus-coupled doublets, δ_P −3.6 and −12.6 (J_{PP} 24) and δ_P −12.4 and −12.7 (J_{PP} 19); these we attribute to the pyrophosphates **9** and **10** (R = Et) [m/z (−ES) 316 and 261] resulting from self-phosphorylation and phosphorylation of the phosphate diester product. The picture was similar for the reaction of **7** (R = Pr^i) with Pr^{i}OH except that the phosphate diester **8**, δ_P −2.5 (with ^{1}H coupling, t, J_{PH} 8) [m/z (−ES) 181] was less dominant, some 40% of the total phosphorus being accounted for by the pyrophosphates **9** [δ_P −4.8 and −13.7 (both d, J_{PP} 22); m/z (−ES) 344] and **10** [δ_P −13.4 and −14.8 (both d, J_{PP} 19); m/z (−ES) 303]. These reactions were slower than the equivalent P=S reactions (Table 1), by a factor of 12 when R = Et ($t_{\frac{1}{2}}$ 4.4 h) but 155 when R = Pr^i ($t_{\frac{1}{2}}$ 49 h).

For the most hindered substrate **7** (R = Pr$^i_2$CH) with Pr$^i_2$CHOH the reaction was very slow—over 10^4 times slower than the corresponding P=S reaction—and after 2 months was still only about 50% complete. In that time the only substantial product was the pyrophosphate **9** resulting from self-phosphorylation [δ_P −4.3 and −11.1 (both d, J_{PP} 15); with ^{1}H coupling, ddt (J_{PP} 15, J_{PH} 10, 20) and dd (J_{PP} 15, J_{PH} 10) respectively] [m/z (−ES) 456]. There were some other small signals in the ^{31}P NMR spectrum but most of these also showed P–P coupling and were probably due to triphosphate [m/z (−ES) 634] or polyphosphates. There was no evidence (NMR or MS) of more than a trace (≤1%) of the phosphate diester **8** or of the pyrophosphate **10** into which it might have been converted. In this case it seems there is little if any phosphorylation of the alcohol.

It is hard to imagine that these P=O reactions proceed by a dissociative elimination–addition mechanism: if they did the system having R = Pr$^i_2$CH would surely not be 300 times less reactive than that with R = Et, and the reactive and sterically accessible metaphosphate intermediate ($ROPO_2$) would surely not discriminate in favour of phosphate and against the alcohol (present in large excess) to the extent that is seen, with R = Pr$^i_2$CH especially. Rather would we expect behaviour similar to that seen in the P=S reactions. On the other hand, reaction by an associative S_N2(P) mechanism with a five coordinate transition state certainly would be susceptible to steric hindrance and might well be highly selective for phosphate when the phosphoryl reaction centre is very congested and the alternative alcohol nucleophile is very bulky (Pr$^i_2$CHOH).

We do not question the earlier experimental results (obtained with less hindered systems)[3,4] but we think the interpretation must be in doubt, at least for the *N*-alkyl compounds.¶ If metaphosphate formation cannot compete with S_N2(P) in our P=O reactions, even when steric factors make S_N2(P) especially unfavourable, it is difficult to see how it could have been important in the earlier P=O reactions with alcohols. The large kinetic isotope effect seen with ^{15}N-labelled substrate does accord well with unimolecular metaphosphate formation but, as noted by Jankowski,[8] it is not necessarily incompatible with S_N2(P) if P–N bond breaking is far advanced in the bimolecular transition state. We conclude that phosphoramidic acid monoesters are not generally effective as sources of monomeric metaphosphates in the way that the corresponding P=S compounds are. As with other types of three coordinate P^V intermediate[9] monomeric metaphosphates seem to be formed (much) less readily than their P=S counterparts in phosphoryl transfer reactions.

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Notes and references

† In every case the final stage of preparation involved extraction (light petroleum) of impurities from an aqueous solution of the sodium salt, acidification, and extraction of the free acid (but not the remaining impurities) into light petroleum.

‡ In the reactions Pr$^i_2$NH is liberated. As reaction proceeds the substrate is increasingly present as the anion and the ^{31}P NMR signal moves progressively to higher field; it also tends to broaden making integration less precise.

§ Rate constants for the P=S reactions (k_s) are based on 3 or 4 spectra (in addition to t = 0) recorded at regular intervals to ≥80% completion and for the P=O compounds (k_o) at least 6 spectra to ≥75% completion. In the case of **7** (R = Pr^i) + Pr^{i}OH the first order plot showed some curvature so that k_o would be *ca.* 20% greater than the value shown (Table 1) if based only on the earlier spectra.

¶ Factors complicating interpretation include increasing conversion of the substrate into the (less reactive) salt by the amine released during the reaction and consumption of substrate not only by phosphorylation of the alcohol but also by further phosphorylation of the initial product and by self-phosphorylation.

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