Phosphonamidothioic acids as thiophosphonylating agents: stereochemistry of reactions of *N*-*tert*-butyl-*P*-phenylphosphonamidothioic acid with alcohols

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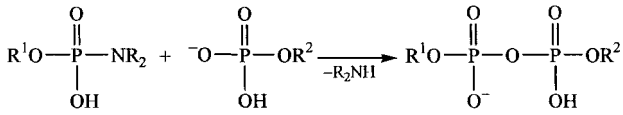
Enantiopure PhP(S)(OH)NHBu^t reacts with alcohols in CH_2Cl_2 to give PhP(S)(OH)OR (R = Me, Pr^i, Bu^t); reaction is completely non-stereospecific with Bu^{t}OH and largely so with Pr^{i}OH and very low concentrations of MeOH, pointing to the involvement of a thiometaphosphonate (PhPOS) intermediate.

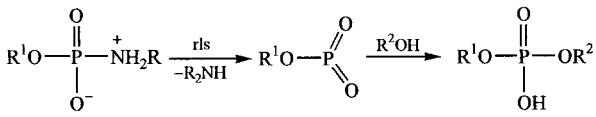
Early work on the synthesis of biologically important pyrophosphates and triphosphates made use of phosphoramidic acid monoesters **1** as phosphorylating agents (Scheme 1).[1] In



1 **2** **3**

Scheme 1

principle the phosphoryl transfer could involve a monomeric metaphosphate intermediate (R^1OPO_2) but the kinetics indicated rather a bimolecular reaction,[1,2] *i.e.* direct nucleophilic attack of the acceptor **2** to give the product **3**. More recently Jankowski and Quin[3] have found that phosphoramidic acid monoesters will also phosphorylate alcohols efficiently, even (or especially) when bimolecular reaction is impeded by steric factors in the donor and acceptor. For these reactions the kinetics,[3] including kinetic isotope effects,[4] appear to indicate the dominance of a unimolecular mechanism (Scheme 2; R^1 = Et, R = 1-adamantyl or mesityl), *i.e.* decomposition of the



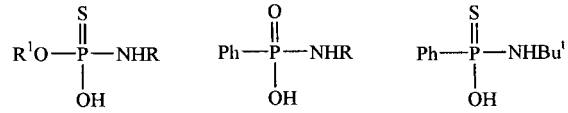
4 **5** **6**

Scheme 2

zwitterionic form **4** of the donor to release the monomeric metaphosphate **5** which is then trapped by the alcohol to give the product **6**. Moreover, the thiophosphorylation[5] of alcohols by phosphoramidothioic monoesters **7** and phosphonylation[6] by phosphonamidic acids **8** seem to be mechanistically similar.

It should be possible to distinguish between bimolecular and unimolecular mechanisms by examining the stereochemistry of reaction. A P=O donor compound (*e.g.* **1** or **8**) will not be chiral at phosphorus unless one of the oxygen (^{16}O) atoms is replaced by an isotope (^{18}O), but a P=S donor compound (*e.g.* **7** or **9**) is inherently chiral. We have therefore sought to obtain the phosphonamidothioic acid **9** as a single enantiomer and ascertain the stereochemistry of its reactions with alcohols.

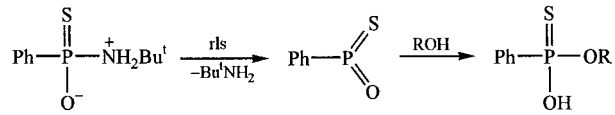
Racemic phosphonamidothioic acid **9** was prepared from $PhPCl_2$ by a published procedure[7] and was resolved using α-methylbenzylamine. From the less soluble (Et_2O) of the diastereoisomeric salts formed with (*R*)-(+)-$PhMeCHNH_2$ the acid **9** was obtained as a single enantiomer (≥99%) after



7 **8** **9**

recrystallisation (Et_2O–light petroleum), mp 82–83 °C (lit.,[7] 81.5–82.5 °C for the racemate); $[\alpha]_D$ + 21.7 (*c* 1.2 in CH_2Cl_2); salt with (*S*)-(−)-$PhMeCHNH_2$, $\delta_P(C_6D_6)$ 54.3; $\delta_H(C_6D_6)$ 1.22 (NBu^t) [addition of racemic **9** introduced new peaks at higher field, $\Delta\delta_P$ 2.1 ppm, $\Delta\delta_H$ 0.11 ppm].†

The reactions of the amidic acid (+)-**9** were examined at 30 °C as dilute solutions (0.02 mol dm^{-3}) in CH_2Cl_2 containing an excess (10 equiv.) of the appropriate alcohol (0.20 mol dm^{-3}). Reaction was halted at 50–60% completion (0.4–0.8 h) and the product **12** (Scheme 3) and unreacted substrate were isolated as a mixture of the free acids. This mixture was treated with (*S*)-(−)-$PhMeCHNH_2$ to form diastereoisomeric salts of the acids. Analysis by $^{31}P\{^1H\}$ NMR spectroscopy (C_6D_6 solution) revealed the diastereoisomer ratios for the salts and by implication the enantiomer ratios of the acids. In every case the unreacted substrate was found to be still a single enantiomer, showing that it is configurationally stable under the conditions of reaction. Any departures from enantiopurity in the products must therefore be a reflection of how they are formed from (+)-**9**.‡



10 **11** **12**

Scheme 3

With MeOH the product **12** (R = Me) was obtained with one enantiomer in large excess (ee 76%) [salt: $\delta_P(C_6D_6)$ 72.8 and 72.5, ratio 88 : 12; $\delta_H(C_6D_6)$ 3.36 (major) and 3.35 (both d, J_{PH} 13.5, OMe)] but with Pr^{i}OH the excess of one of the enantiomers of **12** (R = Pr^i) was modest (ee 15%) [salt: δ_P 68.7 and 68.35, ratio 57.5 : 42.5; δ_H 1.34, 0.88 (major) and 1.32, 0.87 (all d, J_{HH} 6, OCH*Me*$_2$)] and with Bu^{t}OH the product **12** (R = Bu^t) was practically racemic [salt: δ_P 60.3 and 60.2; δ_H 1.47 and 1.46 (both s, OBu^t)].§ A reasonable explanation is that there are competing stereospecific and non-stereospecific pathways and that the relative importance of each is dependent on the identity of the alcohol nucleophile. Also, given the earlier mechanistic evidence, it seems likely that these pathways are bimolecular and unimolecular respectively.¶

The bimolecular pathway would presumably involve in-line attack [$S_N2(P)$] of the alcohol on the zwitterionic form **10** of the substrate, giving the product **12** with inversion of configuration at phosphorus.[8] Steric interactions in the five-coordinate transition state will be more severe with bulky alcohols and reaction by this pathway will be correspondingly less favourable. The unimolecular pathway would involve unassisted decomposition of the zwitterion **10** and liberation of the

thiometaphosphonate **11** (Scheme 3); this, being planar (trigonal) and open to attack at either face by the alcohol, will give the product **12** as the racemate. In this case, the alcohol does not bond to phosphorus in the rate-limiting step; the unimolecular pathway will therefore acquire increasing relative importance as the bimolecular pathway becomes less favourable, *i.e.* as the bulk of the alcohol nucleophile increases.

As a test of mechanistic duality the dependence of the stereochemistry of reaction on the concentration of the nucleophile was examined. With lower concentrations of alcohol the non-stereospecific unimolecular pathway should assume greater importance while higher concentrations should favour the stereospecific bimolecular pathway. In the event, reducing the concentration of MeOH or Pr^iOH to 0.05 mol dm^{-3} gave the product **12** with an enantiomer ratio of 70 : 30 (R = Me) or 51 : 49 (R = Pr^i) and increasing it to 0.80 mol dm^{-3} gave an enantiomer ratio of 98 : 2 (R = Me) or 58.5 : 14.5 (R = Pr^i). With Bu^tOH the product was practically racemic at all alcohol concentrations, implying a negligible contribution from stereospecific bimolecular reaction.§

In one case—the 0.20 mol dm^{-3} MeOH reaction—the dependence of the stereochemistry on the temperature was also examined. Relative to the reaction at 30 °C (enantiomer ratio of product **12**, 88 : 12), reducing the temperature increased the overall stereospecificity of reaction (enantiomer ratio 96 : 4 at 0 °C) and increasing the temperature reduced it (72 : 28 at 60 °C). This implies a more ordered transition state for the stereospecific pathway, consistent with it being of higher molecularity.

That the monomeric thiometaphosphonate **11** plays an important part in the reactions of **9** with alcohols seems certain, but the nature of the competing stereospecific process is less clear. It shows the characteristics expected of an associative $S_N2(P)$ reaction but so might a dissociative reaction if it involves preassociation of the substrate and nucleophile.[9] Then the nucleophile will already be in place when the zwitterion **10** decomposes and the thiometaphosphonate is formed. This may now be trapped stereoselectively, by attack of the alcohol on one face before the leaving group (H_2NBu^t) has diffused away from the other. The reactions of **9** with alcohols may therefore proceed *entirely via* the thiometaphosphonate, in a free (liberated) state or associated with the nucleophile. The stereochemistry observed with **9** does, we think, support the view of Jankowski and Quin that metaphosphate intermediates are involved in the reactions of related amidic acids with alcohols.

Notes and references

† The free amidic acid **9** begins to decompose as soon as it is dissolved in an aprotic solvent. All operations involving solutions of **9** were conducted with cooling and executed as rapidly as possile. The value of $[\alpha]_D$ must be considered approximate.

‡ The products **12** were isolated from reactions allowed to proceed to ⩾90% completion and were purified and characterised as their dicyclohexylammonium salts [^1H and ^{31}P NMR and IR spectroscopy; mass spectrometry (ES and −FAB) including accurate mass measurement].

§ The ^{31}P NMR signals for the diastereoisomeric salts of **12** (R = Bu^t) were not quite fully resolved and in this case the enantiomer ratio is not as precise (±2% in each component) as for **12** (R = Me) or **12** (R = Pr^i).

¶ With Pr^iOH and Bu^tOH the substrate **9** and product **12** (salts with $PhMeCHNH_2$) accounted for only ~90% of the $^{31}P\{^1H\}$ NMR spectrum. The most prominent of the minor peaks were doublets (J_{PP} 39 Hz) at *ca.* $\delta_P(C_6D_6)$ 67 and 62.5, most likely due to the pyrophosphonate $PhP(S)(O^-)OP(S)(NHBu^t)Ph$ [*m/z* (−ES) 384] resulting from reaction of **9** with itself instead of with the alcohol (*cf.* ref. 3, 5 and 6).

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