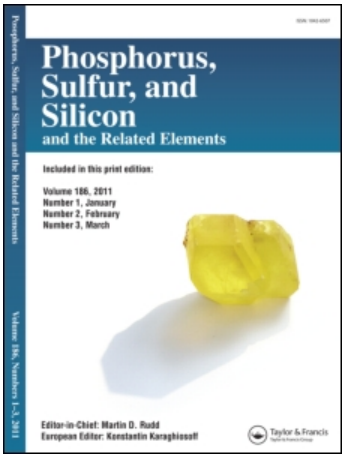

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EXPLORING CAGE CHIRALITY OF PHOSPHORUS SULFIDE AMIDES AND IMIDES

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Chirality of bicyclic P_4S_3 skeletons has been explored by reaction of α- or β-$P_4S_3I_2$ with enantiomerically pure or racemic $H_2NCHMePh$, to give diastereomers of products with one or two exocyclic amide substituents, or of cage structures containing a bridging imide group. ^{31}P NMR spectra show diastereomeric differences in chemical shifts of all four phosphorus atoms in the product molecules. Comparison of observed with predicted numbers of diastereomers is a useful extra tool for identification of unseparated new compounds by NMR.

Keywords: chiral; phosphorus; cage; NMR; amide; imide

INTRODUCTION

A simple one-stage synthesis from the elements gives α-$P_4S_3I_2$, which has only C_2 symmetry, so is chiral, purely by the nature of its skeleton (Figure 1).[1] Each of the phosphorus atoms is a

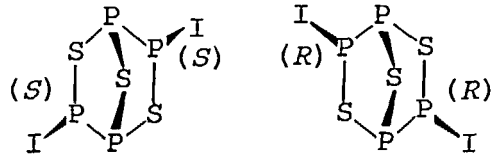


FIGURE 1 Enantiomers of α-$P_4S_3I_2$

chiral centre, but writing in parentheses the chirality of the phosphorus atoms which carry the substituents is a convenient shorthand for the chiral properties of the skeleton. Synthesis of α-$P_4S_3I_2$ from the elements gives a racemic mixture, and, so far, the two known crystal structures each contain both enantiomers in the unit cell, related by crystallographic symmetry.[1,2]

Iodide in α-$P_4S_3I_2$ can be replaced readily by a wide variety of somewhat anionic substituents. Thus, reaction with primary amines yields amides and imides, but none of these substituents have been chiral.[3] Introduction of chiral substituents will give diastereomers: substitution for one iodide gives two diastereomers, in which the chirality of the substituent either 'matches' [e.g. *S*(*SS*)] or does not 'match' [*R*(*SS*)] the chirality of the phosphorus to which it is attached. Substitution for both iodides gives three diastereomers [*S*(*SS*)*S*, *S*(*SS*)*R*, *R*(*SS*)*R*].

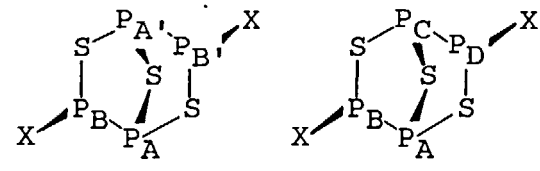


FIGURE 2 Diastereomers of α-$P_4S_3X_2$

The α-P_4S_3 skeleton has four phosphorus NMR chemical shifts and six P–P coupling constants, all of which can be different between diastereomers. For diastereomers *S*(*SS*)*S* or *R*(*SS*)*R*, substituent chirality matches, or does not match, on both sides of the molecule equally, so the C_2 symmetry is retained, and the phosphorus NMR spectrum is of an AA'BB' spin system. If a racemic substitution reagent is used, so that the two substituents can have opposite chirality, then diastereomer *S*(*SS*)*R* can also be formed. The C_2 symmetry is then broken, leaving an ABCD spin system in which all four phosphorus nuclei are chemically non-equivalent (Figure 2).

Comparable substitutions can be made on the usually less stable β-P_4S_3 skeleton (Figure 3), starting with β-$P_4S_3I_2$ which can

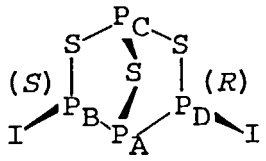


FIGURE 3 The β-P_4S_3 skeleton

be prepared by reaction of P_4S_3 with iodine.[4] Instead of a C_2 axis, the skeleton has a plane of symmetry, and P_B and P_D have opposite chirality instead of the same chirality. Disubstitution using enantiomerically pure *S* substitution reagent will give only the asymmetric diastereomer *S*(*SR*)*S*, in which P_B and P_D are chemically non-equivalent, while racemic reagent gives also the symmetric diastereomers *S*(*SR*)*R* and *R*(*SR*)*S* which retain C_s symmetry and hence AB_2C phosphorus spin systems.

In the present work, the chiral properties of P_4S_3 skeletons have been investigated using α–methylbenzylamine as a substitution reagent, either as the fully-resolved *S* enantiomer, or as the racemic mixture, reacting with racemic α- or β-$P_4S_3I_2$ as substrates.

Most substituents go *exo* to the *nido*-α-P_4S_3 cage, that is, substitution for iodide goes with retention of configuration at phosphorus. Primary amines are almost unique in giving minor disubstitution products in which one group is *endo* and the other *exo*.[3] These are observed sometimes, so they are kinetic products in a non-equilibrium situation. An amide substituent with one N—H bond remaining can undergo a condensation reaction with a P–I group. For the known compounds α-P_4S_3(*exo*-NHQ)(*exo*-I) this is likely to be an intermolecular condensation leading to polymer, but in the unknown α-P_4S_3(*endo*-NHQ)(*exo*-I) the amide group NHQ should be well placed for an intramolecular ring closure condensation to give a nitrogen-bridged cage α-P_4S_3(μ-NQ), which is always found.

For a chiral imide substituent NQ, two diastereomers (*RR*)μ-*S* and (*RR*)μ-*R* of α-P_4S_3(μ-NQ) are possible. Since the enantiomers of these, indistinguishable from them by NMR, are (*SS*)μ-*R* and (*SS*)μ-*S* respectively (Figure 4), the NMR spectra of both diastereomers will be observed if racemic α-$P_4S_3I_2$ is taken, irrespectively of whether enantiomerically pure or racemic amine is

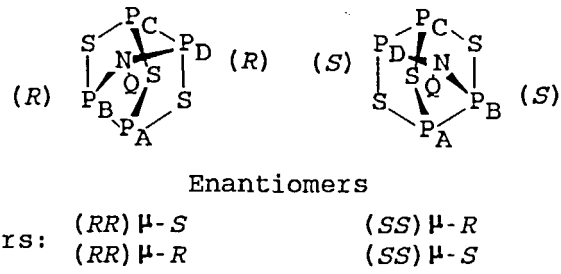


FIGURE 4 α-$P_4S_3(\mu$-NQ)

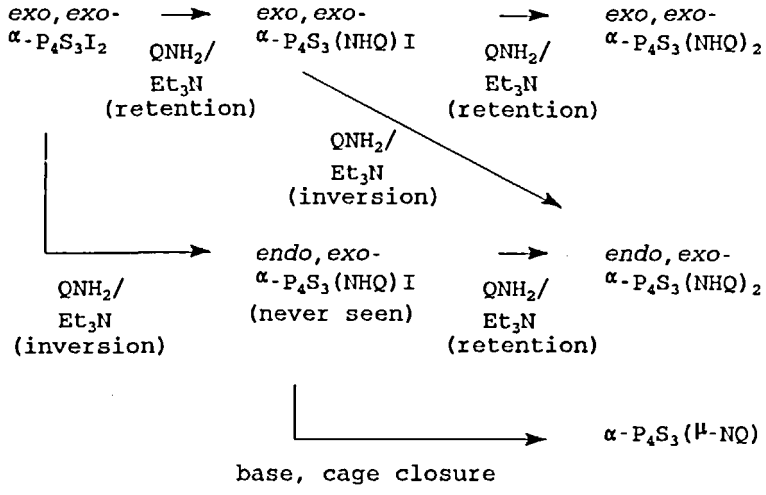
used. Conversely, if pure (*S*)-amine is taken, the reaction to give α-$P_4S_3(\mu$-NQ) could be used to diagnose any enantiomeric enrichment of α-$P_4S_3I_2$ which might be achieved by another method.

According to *ab initio* calculations of geometry on α-$P_4S_3(NH_2)_2$ or α-$P_4S_3(\mu$-NH),[5,3] amido or imido derivatives containing the α-P_4S_3 skeleton are practically or completely planar at nitrogen, probably because of π-bonding to phosphorus, even though the phosphorus is in a low oxidation state. In α-$P_4S_3(\mu$-NQ) the planarity at nitrogen and the C_2 symmetry of the α-P_4S_3 skeleton mean that, on rapid rotation about the C—N bond on the NMR timescale, P_A will appear chemically equivalent to P_C, and similarly P_B to P_D. For each diastereomer a AA'BB' spin system is observed. Because it is planar, there can be no chirality at nitrogen, so the chiral centre in amide or imide substituents must be at least two bonds away from a phosphorus nucleus. It is thus not immediately predictable which of the four phosphorus atoms of the skeleton will show the biggest diastereomeric NMR shifts.

RESULTS AND DISCUSSION

Reactions and Observed Products

Addition of a solution containing *S*- or *racemic*-$H_2NCHMePh$, along with Et_3N, to a suspension of α-$P_4S_3I_2$ in toluene gave a solution containing products as anticipated in the Introduction and as



SCHEME 1 α-P_4S_3 amides and imide from a primary amine

summarised in Scheme 1. Except for *endo,exo*-α-$P_4S_3(NHQ)_2$ (Q = CHMePh), which unexpectedly failed to appear when racemic amine was used, the ^{31}P NMR spectra of all of the predicted diastereomers were observed and fully analysed, including computer fitting using the program NUMARIT.[6] Et_3N was found to be required as a base to remove eliminated HI. If a corresponding extra quantity of $H_2NCHMePh$ was used instead for this purpose, reaction proceeded to give α-P_4S_4 as the only compound seen in significant concentration in the ^{31}P NMR spectrum of the solution, and it is very probable that the main reaction was to produce insoluble polymer.

A reactant ratio α-$P_4S_3I_2$: H_2NQ : Et_3N of 1 : 2 : 2 led to a solution containing *exo,exo*-α-$P_4S_3(NHQ)_2$ (87 mol% of ^{31}P), *endo,exo*-α-$P_4S_3(NHQ)_2$ (3 mol%) and α-$P_4S_3(\mu$-NQ) (10 mol%). The ratio of symmetric diastereomers of *exo,exo*-α-$P_4S_3(NHQ)_2$ was 54 : 46, while for α-$P_4S_3(\mu$-NQ) it was 53 : 47.

Use of a deficiency of primary amine did not lead to increase in the diastereomer ratio for either product by kinetic resolution: thus a reactant ratio 2 : 1 : 2 gave a solution containing 36 mol%

exo,exo-α-$P_4S_3(NHQ)_2$ with diastereomer ratio 49.5 : 50.5, and 55 mol% α-P_4S_3(μ-NQ) with diastereomer ratio 51 : 49. Two equivalents of Et_3N to one of H_2NQ were used in this experiment to favour the formation of α-P_4S_3(μ-NQ), but this also favoured intermolecular condensation to give polymer.

When the reactants were taken in ratio 1 : 0.75 : 0.75, *exo,exo*-α-P_4S_3(NHQ)I was produced as a major initial product (35 mol%; diastereomer ratio 56 : 44), along with *exo,exo*-α-$P_4S_3(NHQ)_2$ (8 mol%), α-P_4S_3(μ-NQ) (41 mol%; diastereomer ratio 60 : 40) and α-$P_4S_3I_2$ (15 mol%). Of these compounds, *exo,exo*-α-P_4S_3(NHQ)I was unstable, decomposing in a closed NMR tube in the dark at ambient temperature. When the NMR spectrum of a similar product was accumulated over 14.7 hours instead of over 80 minutes as above, the measured relative concentrations of *exo,exo*-α-P_4S_3(NHQ)I and α-P_4S_3(μ-NQ) were 18 and 60 mol% respectively, reflecting the condensation of the amide iodide to the imide. An interesting series of reactions then followed. After one day, *exo,exo*-α-P_4S_3(NHQ)I and *exo,exo*-α-$P_4S_3(NHQ)_2$ had disappeared, while the relative concentration of α-P_4S_3(μ-NQ) had fallen to 10 mol%, as it isomerised to β-P_4S_3(μ-NQ) (57 mol%). After one week, only 23 mol% of β-P_4S_3(μ-NQ) remained: its imide bridge was opened to give β-P_4S_3(*endo*-NHQ)(*exo*-I) (23 mol%). Simultaneously, skeletal decomposition gave P_4S_2(μ-NQ) (18 mol%), and P_4S_3 (20 mol%) was formed. A similar decomposition for Q = Bu^t had been observed previously,[3] but observation at intervals in the present case has allowed the sequence of intermediates to be elucidated.

In the Bu^t case, we assigned the *endo,exo*-β product, on the basis of NMR chemical shift and coupling comparisons, as β-P_4S_3(*endo*-NHQ)(*exo*-NHQ), rather than as the amide iodide. If Q is chiral, it should be possible to distinguish between the two possibilities by counting diastereomers. If racemic amine is used, chirality of substituent and skeleton can 'match' or 'mismatch' for the *endo* and the *exo* substituent independently in the diamide, giving four diastereomers, whereas there will be only two

diastereomers of the amide iodide. In the present work, taking either pure *S* amine or the racemic mixture led to the same two diastereomers, supporting the assignment to β-P_4S_3(*endo*-NHQ)(*exo*-I). In an attempt to demonstrate this further, a slight excess of a 1 : 1 mixture of H_2NQ and Et_3N was added to the product solution. The remaining α-$P_4S_3I_2$ reacted to give *exo,exo*-α-$P_4S_3(NHQ)_2$, but the *endo,exo*-β product remained unaffected. It seems that the iodide in β-P_4S_3(*endo*-NHQ)(*exo*-I) is peculiarly resistant to replacement by amide, which is why a series of such compounds (Q = Me, Bu^t, Ph) probably were formed in the previous work, in substitution reactions of β-$P_4S_3I_2$,[3] and thought to be diamides.

For *exo,exo*-P_4S_3 compounds generally the β- skeleton is unstable with respect to the α-. *Ab initio* (RHF/3-21G*) calculations for the imide-bridged skeletons now show that, in contrast, β-$P_4S_3(\mu$-NH) is more stable than α-$P_4S_3(\mu$-NH) by an insignificant amount (1.49 kJ mol^{-1}) instead of being less stable. While this supports the current observation of isomerisation, the mechanism cannot be simply an intramolecular migration of a sulfur atom to an adjacent edge of the approximate tetrahedron of phosphorus atoms in the skeleton, since, in the other experiments described above, using different reagent ratios, α-$P_4S_3(\mu$-NQ) was stable for weeks in the product solutions. The key difference appears to be the deficiency of Et_3N, allowing HI to be eliminated when *exo,exo*-α-P_4S_3(NHQ)I decomposed. HI in solution is the most likely temporary sink for iodide, in between the decomposition of *exo,exo*-α-P_4S_3(NHQ)I and the formation of β-P_4S_3(*endo*-NHQ)(*exo*-I). It is interesting that (presumably) α-P_4S_3(*endo*-NHQ)(*exo*-I) should spontaneously lose HI to give α-$P_4S_3(\mu$-NQ), whereas β-$P_4S_3(\mu$-NQ) should be opened by HI, even though the β-compound is the more stable of the imides.

Reaction of β-$P_4S_3I_2$, H_2NQ and Et_3N at 0 °C in ratio 1 : 2 : 2 gave a solution containing *exo,exo*-β-$P_4S_3(NHQ)_2$ (56 mol%). In contrast to the α-P_4S_3 case, only a trace of the imido-bridged product β-$P_4S_3(\mu$-NQ) was formed, and no *endo,exo*-β products were seen. Use of racemic amine gave three diastereomers of

exo,exo-β-$P_4S_3(NHQ)_2$ as expected, in ratio asym. : sym. : sym. = 51 : 29 : 20. The statistical ratio is 50 : 25 : 25. Even after 16 hours, P_4S_3 was a major decomposition product (30 mol%), as was $HP(S)(NHQ)_2$ (10 mol%), assigned by comparison of ^{31}P chemical shift (40.10 ppm) and $^1J(^{31}P-^1H)$ (541.3 Hz) with similar compounds,[7] and by counting its diastereomers.

NMR Spectra

Full details of the NMR results, including coupling constants, will be published separately: only an overview of points of interest concerning diastereomeric shifts is presented here. Where there are two symmetric diastereomers, e.g. *S*(*SS*)*S* and *R*(*SS*)*R* for *exo,exo*-α-$P_4S_3(NHQ)_2$, we are unable at present to distinguish which set of NMR parameters belongs to which. Similarly, while the spectrum of diastereomer *S*(*SS*)*R* was readily distinguishable because of this molecule's lack of symmetry, we do not know which chemical shifts corresponded to the 'matching' and which to the 'mismatching' side of the molecule. For this reason, all of the differences in chemical shifts presented here could have either sign. Q represents the group CHMePh.

exo,exo-α-$P_4S_3(NHQ)_2$

Here the phosphorus atoms attached to the amide groups showed the larger chemical shift difference between diastereomers *S*(*SS*)*S* and *R*(*SS*)*R*: $\Delta\delta(P_B)$ was 0.71 ppm, compared with $\Delta\delta(P_A)$ 0.06 ppm for the more distant bridgehead atoms (Figure 2). It is clear, however, that the effect of matching or mismatching chirality is not purely local. When the matching and mismatching combinations were within the same molecule, they produced a much bigger difference in chemical shift: $\delta(P_B)-\delta(P_D)$ in diastereomer *S*(*SS*)*R* was 4.22 ppm. Similarly, comparing the two diastereomers of α-P_4S_3(*exo*-NHQ)(*exo*-I), $\Delta\delta(P_B)$ for phosphorus carrying the amide group was -2.01 ppm, whereas $\Delta\delta(P_D)$ for phosphorus carrying the iodide was 2.98 ppm, i.e. the net effect on chemical shift of the chirality of the amide group was greatest for the most distant phosphorus atom. Enantiomeric substituents provide a unique tool

for investigation of substituent effects such as these on NMR parameters, since electronic influences may be held almost constant.

exo,exo-β-$P_4S_3(NHQ)_2$

In asymmetric diastereomer *S(SR)S* (Figure 3) the internal shift $\delta(P_B)-\delta(P_D)$ was 1.64 ppm. $^2J(P_BP_D)$ was 225.17 Hz. As in the α-P_4S_3 case, $\Delta\delta(P_B)$ between the symmetric diastereomers was smaller, at 0.28 ppm. Here, however, the bridgehead chemical shifts were more influenced by amide chirality: $\Delta\delta(P_A)$ was 3.42 ppm and $\Delta\delta(P_C)$ 1.78 ppm. C_s symmetry means that both substituents will have the same influence on the geometry at P_A, so their effects augment each other, whereas, for the α-P_4S_3 case, C_2 symmetry means that the two substituents can have opposing influences on a particular bridgehead atom, e.g. P_A.

α-$P_4S_3(\mu$-NQ)

The C(Me)(Ph)—H bond of the bridging imide substituent NQ is likely to eclipse a N—P bridge bond in the most stable N—C bond rotamers. In one diastereomer the phenyl group will then be nearer to a sulfur bridgehead phosphorus atom, while in the other it will be nearer to a sulfur atom. This explains why the sulfur bridgehead diastereomeric shift $\Delta\delta(P_A)$ (Figure 4) was bigger (1.08 ppm) than the nitrogen bridgehead shift $\Delta\delta(P_B)$ (−0.11 ppm).

β-P_4S_3(*endo*-NHQ)(*exo*-I)

The following are the measured NMR parameters for one diastereomer, compared with those previously assigned to β-P_4S_3(*endo*-NHBu^t)(*exo*-NHBu^t),[3] given in parentheses. $\delta(P_A)$ 36.39 (25.21), $\delta(P_B)$ 167.01 (170.91), $\delta(P_C)$ 202.27 (202.85), $\delta(P_D)$ 141.19 (133.50) ppm; $^1J(P_AP_B)$ −199.4 (−198.9), $^1J(P_AP_D)$ −258.3 (−254.2), $^2J(P_AP_C)$ 42.4 (45.3), $^2J(P_BP_C)$ 8.6 (6.0), $^2J(P_CP_D)$ 15.2 (15.5), $^2J(P_BP_D)$ 33.0 (33.9) Hz. This shows clearly that the two compounds are of similar type. The largest of the diastereomeric shifts was $\Delta\delta(P_A)$ (2.86 ppm), possibly because the *endo*-amide group was positioned above P_A.

$P_4S_2(NQ)$

This has a cage structure like P_4S_3, but with a sulfur atom replaced by an imido bridge (Figure 5). Because the nitrogen geometry is planar, the skeleton has a plane of symmetry relating P_A and P_B, so that they have opposite chirality. The chiral centre in NQ is three bonds distant from P_A or P_B, and rendered them chemically non-equivalent by only 0.35 ppm. $^1J(P_AP_B)$ was −125.85 Hz, so J/δ was 2.93 at 121.5 MHz. About 1500 times more scans were needed to reveal the weak lines than the strong lines in the P_A, P_B multiplet.

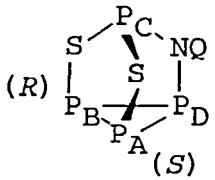


FIGURE 5 $P_4S_2(NQ)$

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