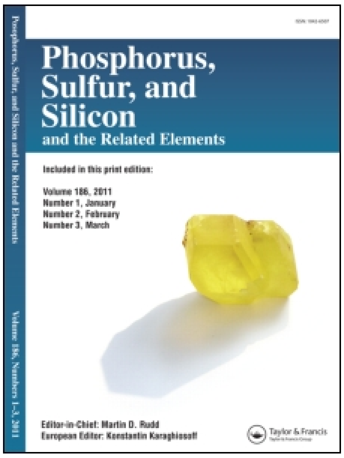

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Investigations into the Oxidative Stability of Hydroxymethyl- and Bis(Hydroxymethyl)-Phosphines

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Investigations into the Oxidative Stability of Hydroxymethyl- and Bis(Hydroxymethyl)-Phosphines

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Polydentate ligands containing the bis(hydroxymethyl)phosphine unit have been reported to exhibit enhanced oxidative stability, which would make them attractive for use in ^{99m}Tc-radiopharmaceutical imaging agents. Benzylethyl(hydroxymethyl)-phosphine, benzylbis(hydroxymethyl)phosphine and benzyldiethylphosphine were prepared in order to investigate the origin of this oxidative stability. Little evidence was found to indicate that the hydroxymethylphosphines show an enhanced level of stability, but it was demonstrated that the reaction conditions employed in their preparation generated a number of closely related by-products, which are likely to limit the usefulness of the hydroxymethylphosphines in commercial radiopharmaceutical applications.

Keywords Hydroxymethylphosphine; Oxidation; Stability; Tc-99m Radiopharmaceuticals

INTRODUCTION

As part of an ongoing programme to develop new ligands for technetium-99m based radiopharmaceutical imaging agents, we have investigated the potential for utilising the bis(hydroxymethyl)phosphine group as a means of producing more hydrophilic, air stable phosphine-containing ligands.

In particular, we have investigated the preparation of benzyldiethylphosphine **1**, benzylethyl(hydroxymethyl)phosphine **2** and benzylbis (hydroxymethyl)phosphine **3** as model systems for evaluating claims that chelate systems containing the bis(hydroxymethyl)-phosphine unit display enhanced oxidative stability[1] (Scheme 1).

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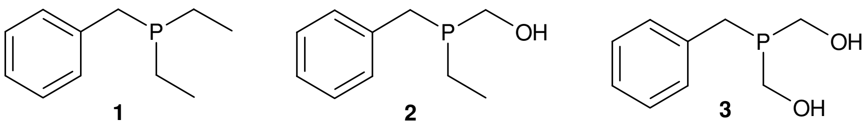
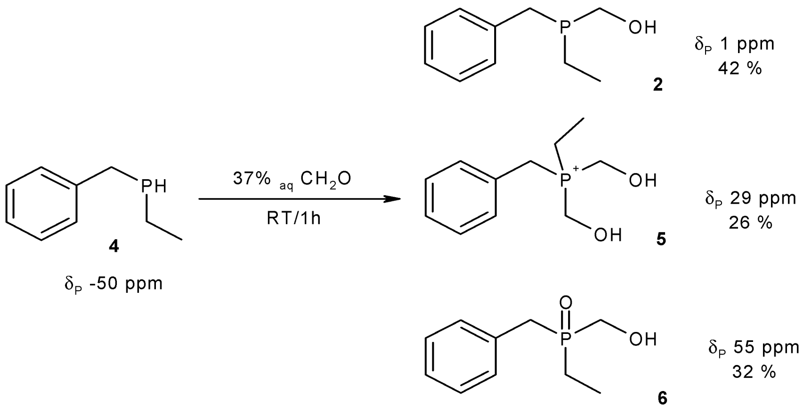


SCHEME 1

RESULTS AND DISCUSSION

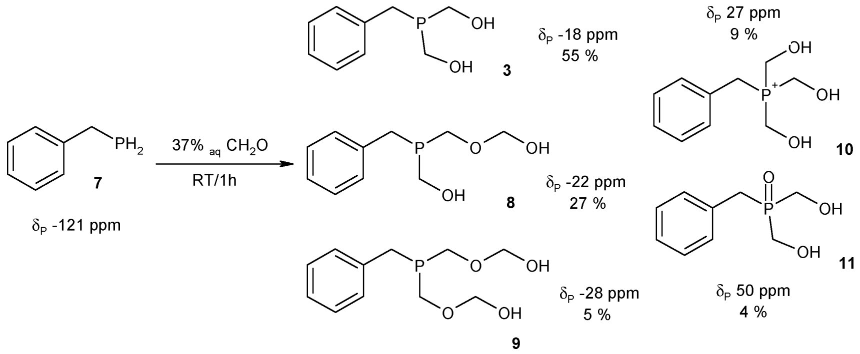
Benzylethyl(hydroxymethyl)phosphine **2** was synthesised using the approach established by Katti.[2] However, the reaction of benzylethylphosphine **4** with formaldehyde (Scheme 2) generated not only the desired product **2**, but also the corresponding phosphonium salt **5** and the phosphine oxide **6**. Moreover, the hydroxymethylphosphine **2** was found to convert to the corresponding phosphine oxide **6** even when operating under an inert atmosphere, thereby demonstrating that the mono(hydroxymethyl)phosphine **2** does not exhibit high oxidative stability.



SCHEME 2[3]

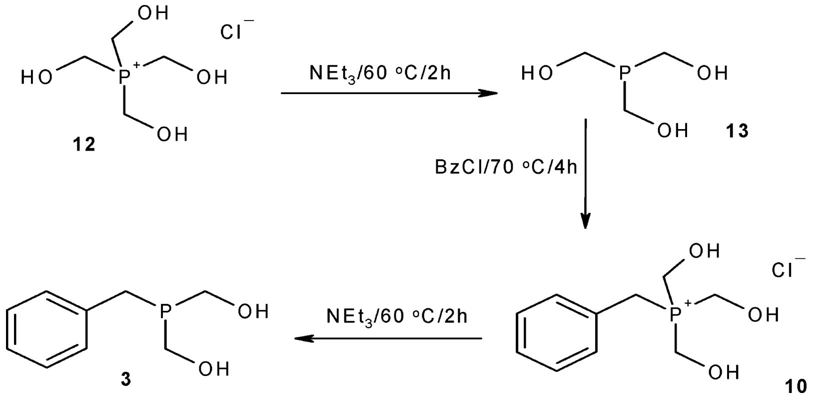
We subsequently investigated the oxidative stability of benzylbis(hydroxymethyl)phosphine **3**. While treatment of benzylphosphine **7** with aqueous formaldehyde gave the bis(hydroxymethyl)phosphine **3** as the main product, four other products were also observed and identified as the hemiacetals **8** and **9**, the phosphonium salt **10** and the phosphine oxide **11** (Scheme 3).

Due to difficulties experienced in isolating the products from the reaction mixture, it was thought prudent to investigate an alternative approach for the preparation of benzylbis(hydroxymethyl)phosphine **3**. Based on Vullo's observation[4] that tris(hydroxymethyl)phosphine **13**



SCHEME 3

could be prepared by exact neutralisation of tetrakis(hydroxymethyl) phosphonium chloride **12**, Petrov developed a method to prepare a series of alkyl- and aryl-(hydroxymethyl)phosphines by reaction of their corresponding phosphonium salt with triethylamine.[5] We therefore investigated this approach (Scheme 4). Interestingly the same by-products **(8–11)** were again observed in this reaction.



SCHEME 4

In order to facilitate purification, the hydroxymethylphosphines **3**, **8** and **9** were converted to their phosphine sulfide derivatives. Benzylbis(hydroxymethyl)phosphine sulfide **14** was successfully isolated as colourless crystals suitable for analysis by single crystal X-ray crystallography, (the structure is shown in Figure 1).[6] Reduction of the phosphine sulfide **14** afforded benzylbis(hydroxymethyl)phosphine **3** in a pure state.

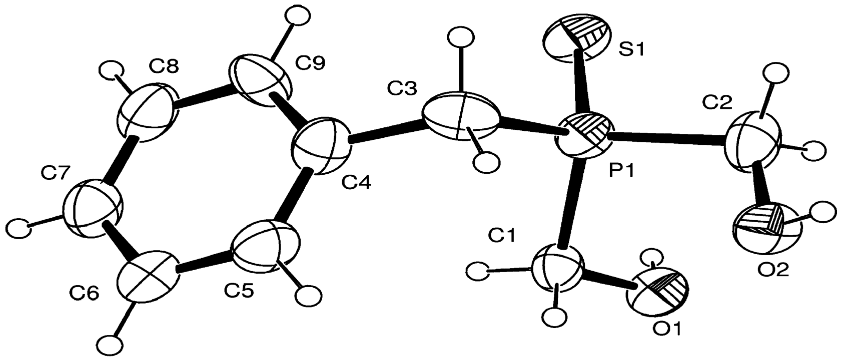


FIGURE 1 ORTEP view of benzylbis(hydroxymethyl)phosphine sulfide **(14)**.

Further investigation of the bis(hydroxymethyl)phosphine **3** confirmed that it not only readily oxidised on exposure to air, but would react with formaldehyde to give the hemiacetal derivatives **8** and **9**. Work is still ongoing to isolate pure samples of the hemiacetal derivatives.

CONCLUSION

It is clear that the simple hydroxymethylphosphines that we have prepared do not exhibit unusually high oxidative stability. We must therefore conclude that the previously reported[1] oxidative stability of the hydroxymethylphosphine-containing polydentate ligands results from a stabilising influence of the overall structure of these systems rather than the intrinsic stability of the hydroxymethylphosphine unit. In addition, the synthesis of hydroxymethylphosphines via the routes described are complicated by the formation of hemiacetal derivatives with the consequence that hydroxymethylphosphine chelates are unlikely to be attractive for use in radiopharmaceutical imaging agents where the ligands are required in high levels of purity.

EXPERIMENTAL

Preparation of Hydroxymethylphosphines

via Katti's Method[1]

The parent phosphine (**4** or **7**) was carefully added to a freshly prepared, degassed solution of 37% aqueous formaldehyde. The reaction mixture was stirred under an atmosphere of anhydrous argon for 1 h at room temperature and formation of the required product confirmed by NMR spectroscopy.[7]

via Petrov's Method[5]

The parent phosphonium salt (**5** or **10**) was added to an excess of anhydrous triethylamine. The resulting solution was heated at 60°C, under an atmosphere of anhydrous argon, with vigorous stirring for 3 h. After this time, the solution was cooled to room temperature and the unwanted triethylamine hydrochloride salt was removed by filtration. The remaining triethylamine solvent was removed from the filtrate by distillation at atmospheric pressure and formation of the required product was confirmed by NMR spectroscopy.

Benzylbis(hydroxymethyl)phosphine 3

Sulfur was added to a solution of the crude benzylbis(hydroxymethyl)phosphine in anhydrous benzene and the reaction mixture was heated under reflux in an atmosphere of anhydrous argon, for 24 h. After this time, the solution was cooled, filtered and the solvent was removed under reduced pressure. The resulting dark red oil was purified by flash chromatography on silica eluting with a solvent gradient of 100% hexane to 100% ethyl acetate. A sample of benzylbis(hydroxymethyl)phosphine sulfide **14**, suitable for single crystal X-ray crystallography was obtained by recrystalisation from ethyl acetate.[8] A pure sample of benzylbis(hydroxymethyl)phosphine **3** was obtained by reduction of the corresponding phosphine sulfide with lithium aluminium hydride in anhydrous 1,4-dioxane.

REFERENCES

[1] K. V. Katti, K. Raghuraman, N. Pillarsetty, W. A. Volkert, S. S. Jurisson, and T. J. Hoffman, *Technetium, Rhenium and Other Metals in Chemistry and Nuclear Medicine 6*; M. Nicolini, G. Bandoli, and U. Mazzi, Eds. (SGE Editorali, Padova, Italy, 2002), pp. 69–72.

[2] K. V. Katti, H. Gali, C. J. Smith, and D. E. Berning, *Acc. Chem. Res.*, **32,** 9 (1999).

[3] ^{31}P NMR chemical shifts are quoted relative to an 85% solution of phosphoric acid in D_2O, as an external reference. The % yields are ^{31}P NMR integration %.

[4] W. J. Vullo, *J. Org. Chem.*, **33,** 3665 (1968).

[5] K. A. Petrov, V. A. Parshina, and M. B. Luzanova, *J. Gen. Chem. USSR*, **32,** 542 (1962).

[6] X-ray crystallography data was collected at 120 K using a Nonius Kappa CCD area detector diffractometer mounted at the window of a molybdenum rotating anode (50 KV, 90 mA, $\lambda = 0.71069$ Å). The crystal-to-detector distance was 30 mm and ϕ and Ω scans (1.0° increments, 20 s exposure time) were carried out to fill the Ewald sphere. Data collection and processing were carried out using COLLECT, DENZO and maXus and empirical absorption correction was applied using SORTAV. The structure was solved by the heavy-atom method using DIRDIF-99 and refined anisotropically

(non-hydrogen atoms) by full-matrix least-squares on F^2 using the SHELXL-97 program. The H atoms were calculated geometrically and refined with the riding model. The programs ORTEP-3 and PLATON were used for drawing the molecule. WINGX was used to prepare material for publication.

[7] ^{31}P NMR spectra were recorded on a JEOL EX 270 with the sample in an evacuated WILMAD® NMR tube with a J. Young valve.

[8] The data have been deposited with the Cambridge Crystallographic Data Center as CCDC 676677; available online at: http://www.ccdc.cam.ac.uk/data_request/cif