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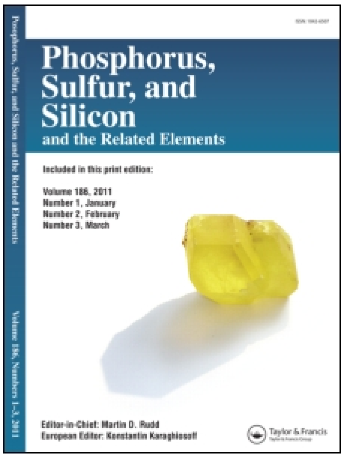

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Phosphine-Containing Ligands and the Search for a Tc-99m Based Myocardial Imaging Agent

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A strategy used to develop several potential ^{99m}Tc-based myocardial imaging agents is described. Ether-substituted 1,2- and 1,3-diphosphine ligands were prepared and used to produce a range of cationic Tc-99m complexes for subsequent screening. Ligand/core combinations were optimised in several cases to produce agents showing good heart uptake and retention in both animals and humans. A range of phosphine-containing polydentate ligands has also been prepared and their potential for use in myocardial imaging agents assessed. A tridentate phosphine/amine/thiolate chelate system has been developed which gives a $[^{99m}Tc(PNS)_2]^+$ complex showing good heart uptake in the rat. Synthetic routes to ether-substituted derivatives of this PNS ligand system have also been developed.

Keywords: diphosphines; technetium-99m; heart imaging; ligands; cationic complex

INTRODUCTION

Technetium-99m is an ideal isotope for use in medical imaging.[1] It has a short half life (*ca.* 6 h) and the γ rays it emits are of an ideal energy (140 keV) for detection by a γ camera. Moreover, it is cheap and readily available due to the widespread availability of small portable generators. To produce a biological imaging agent based on Tc-99m it is necessary to develop a functionalised chelating system which can coordinate to the radioactive metal ion and also provide the biological targeting capability needed to direct the agent to its chosen target.

It has been known for some time that cationic species are taken up by heart tissue and this has been used as a strategy to develop a Tc-99m based heart imaging agent. Two

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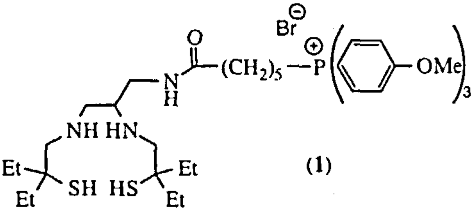
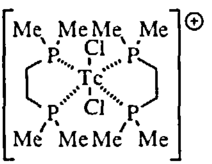
approaches were investigated for the preparation of complexes of Tc-99m possessing a positive charge. The first involved the addition of a cationic centre, such as a phosphonium, ammonium or sulfonium salt to a chelate system known to produce a neutral complex with technetium. The functionalised ligand (**1**) is an example of one of the systems prepared and comprises a phosphonium centre linked to a bis(amine thiol) chelate system. In general this approach proved disappointing.[2] The alternative approach, which proved more successful, involved the preparation of chelate systems which would give cationic technetium complexes with intrinsic positive charge. This approach had been pioneered by Deutsch and co-workers[3] who had shown that cationic complexes of technetium(III) such as (**2**) could be prepared from 1,2-diphosphine ligands and that these showed good uptake in the heart tissues in dogs. The performance of these agents in humans, however, was disappointing. Agents were either not retained in human heart tissue, as with (**2**), or were slow to clear from non-target tissue.



(**1**)

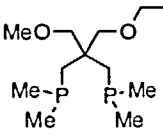


(**2**)

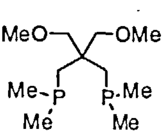
It has been proposed that reduction *in vivo*, producing a neutral complex, may account for the lack of retention of (**2**) in heart tissue[4] while the binding of some agents to plasma proteins is thought to account for their observed retention in the bloodstream and high uptake in the liver.

The strategy investigated to overcome these problems was twofold. Firstly, diphosphine ligands were combined with a range of technetium cores to prepare complexes exhibiting a range of technetium oxidation states and redox behaviour. Secondly, substituents were attached to the diphosphine ligands to reduce plasma protein binding. Different pendant functional groups were attached to the 1,2-bis(dimethylphosphino)ethane and 1,3-bis(dimethylphosphino)propane chelate systems and their impact on the degree of plasma protein binding in the resulting cationic technetium complexes assessed.[5] Derivatives of 1,1 bis(dimethylphosphino)methane were not found to label easily and were quickly dropped from the synthetic programme. Of the substituents investigated pendant ether groups showed the greatest promise. They were relatively inert and therefore robust to the conditions needed for labelling, they did not interfere with complex formation, and they offered the potential for relatively subtle changes in the characteristics of the final technetium complex.

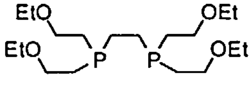
Where possible, the ether substituents were introduced so as to avoid the formation of chiral centres. For this reason, 1,3-diphosphines with substitution at the centre of the hydrocarbon bridge, as in (**3**) and (**4**), or 1,2-diphosphines with substitution on the alkyl groups on phosphorus, as in (5), proved attractive and a wide range of these was prepared.



(3)

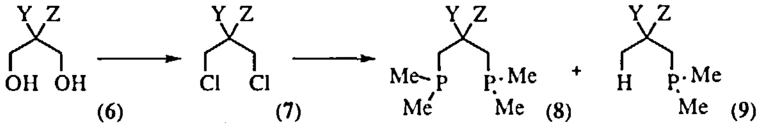


(4)



(5)

Key precursors for the backbone-substituted 1,3-diphosphines (8) were the diols (6; Y and/or Z are ether-containing substituents) which are accessible by a variety of routes. These were converted first to the corresponding dichlorides (7) by reaction with triphenyl phosphine in carbon tetrachloride and then to the final diphosphines (8) by reaction with the lithium salt of dimethylphosphine in either ether, tetrahydrofuran or liquid ammonia.[6] Choice of the halide was important since in cases where the use of corresponding dibromides was investigated a substantial quantity of the monophosphine (9) was produced together with some $Me_2P—PMe_2$. This free radical reaction can be substantially reduced by use of the dichloride although even here evidence for free radical involvement during the formation of the diphosphines was still often observed in the form of CIDNP enhanced signals for the ^{31}P NMR resonances of the products. Where the monophosphines were produced it was necessary to purify the diphosphines (8) by distillation or *via* their sulphide or oxide derivatives.



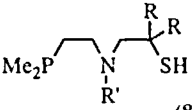
Diphosphines can stabilise technetium in a number of oxidation states and so for each ligand prepared it was possible to prepare a number of cationic technetium complexes for evaluation. Although a wide range of ligand cores were initially investigated it became clear that the 'dioxo' (10), 'nitrosyl' (11) and 'tris' (12) complexes were exhibiting the most encouraging results. The optimum ligand/core combinations for these particular cores were found to be [10; L = (5)], [11; L = (4)] and [12; L = (3)]. Studies in man have shown that while [12; L = (3)] exhibited reasonable uptake in the heart there was unsatisfactory clearance from the liver. However, both [10; L = (5)] and [11; L = (4)] exhibited both good myocardial uptake and non-target clearance. The former of these is now commercially available under the name Myoview.

$\left[{}^{99m}TcO_2L_2\right]^+$ (10)

$\left[{}^{99m}Tc(NO)L_2Cl\right]^+$ (11)

$\left[{}^{99m}TcL_3\right]^+$ (12)

A range of linear and tripodal phosphine-containing polydentate ligands with nitrogen and sulfur donor atoms have also been synthesised with the aim of preparing novel cationic complexes of technetium.[6] This has involved the use of dimethylvinylphosphine sulphide as a convenient precursor for the introduction of the 2-dimethylphosphinoethyl unit.[7] Encouraging results have been obtained from the tridentate monoanionic P—N—S type system (**12**; R = R' = Me) which forms a $[^{99m}Tc(PNS)_2]^+$ complex showing good heart uptake and retention in the rat. Derivatives of this system possessing ether substituents such as (**12**; R = CH_2OMe, R' = Me) and (**12**; R = Me, R' = CH_2CH_2OMe) have been synthesised for further evaluation.


(8)

ACKNOWLEDGEMENTS

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