Recent advances in the chemistry of water-soluble phosphines—Catalytic and biomedical aspects

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Hydroformylation of functionalized phosphorus(III) hydrides has resulted in the development of new classes of bis-, tris-, tetrakis- and hexaphosphines that are soluble and oxidatively stable in aqueous media. The coordination chemistry of the representative bisphosphines with Pd(II), Pt(II) and Re(V) precursors demonstrates the chelating modes of bonding of the P(III) centres. These metal complexes exhibit selective partitioning in the aqueous phase in preference to the organic phase suggesting their usefulness in biphasic catalysis. The biodistribution studies (in rats) of a Tc-99m complex of one of the water-soluble phosphines demonstrate the efficient renal clearance of the complex. The neutral and the lipophilic characteristics of this phosphine and the glomerular filtration pathway of its Tc-99m complex present a new concept in drug clearance.

THE chemistry of water-soluble transition metal/organometallic compounds has attracted considerable attention in recent years because of their usefulness in biphasic catalysis[1–4] and biomedicine[5–8]. Most transition metal complexes tend to show instability in aqueous media because of complex redox processes mediated by water. In order to maintain aqueous solubility and high-kinetic inertness in water, it is important to use appropriate functional groups as ligands for bonding to specific transition metals. In this context, water-soluble phosphines have become essential building blocks for the development of transition metal complexes that are soluble in water. The term 'water-solubility' when referred to phosphines may sound rather unusual because tertiary phosphines, in general, are oxidatively unstable and produce their corresponding phosphine oxides upon interaction with the oxygen in water. However, the pioneering investigations of various workers[9–17] have demonstrated that the solubility of phosphines in water can be achieved via side group modifications of tertiary arylphosphines. Representative examples of water-soluble phosphines derived from various parent arylphosphines are summarized in Figure 1.

The rhodium complex of the water-soluble trisulphonated triphenylphosphine (TPPTS) is currently used as a catalyst in the Ruhrchemie Rhone Poulenc's (RCH/RP) oxo process for the hydroformylation of propylene into *n*-butanal at the industrial scales[1]. In this process of biphasic (aqueous-organic) catalysis, the reactants and products stay in the organic phase while the catalyst remains in the aqueous phase. The RCH/RP process for the hydroformylation of propylene has not only demonstrated minimum catalyst losses, to account for a 10% reduction in costs compared with other traditional processes, but also has shown better selectivity of products[1]. Recently Herrmann *et al.*[18,19] have developed a new water-soluble phosphine tailored with bulky substituents on its backbone: bisdisulphonatodiphenylphosphinomethyl tetrasulphonato binaphthene (BINAS). This BINAS system forms water-soluble Rh complexes and when used under biphasic conditions for the hydroformylation of propylene, has demonstrated superior properties than the TPPTS-Rh system in terms of catalytic activity, highest *normal/iso ratios* of aldehyde products and lowest Rh concentrations[18,19].

The development of water-soluble transition metal complexes of specific metals and metallic radioisotopes is also important because of their potential utility in pharmaceutical and radiopharmaceutical applications respectively[5–8]. For example, the design and synthesis of ligands that can lead to water-soluble and *in vitro/in vivo*-stable Technetium-99m (Tc-99m) or Rhenium-188 (Re-188) complexes may aid the development of new radiopharmaceuticals for the diagnosis and therapy of human cancer[20–25]. In fact, recently two Tc-99m complexes derived from functionalized phosphines have been

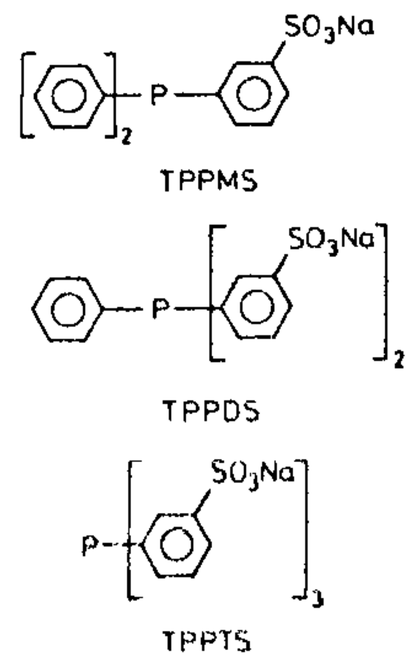


Figure 1. Representative examples of water-soluble phosphines.

approved by the food and drug administration (FDA) of USA, for human use as heart imaging agents[26,27]. These two diagnostic drugs are currently available for human use throughout the world. Rhenium-188 is a beta emitter and the conjugation of its water-soluble complexes to specific biomolecules has been implicated as an important basis in the development of 'tumour-specific' radiopharmaceuticals for therapy of certain human cancers[5–8]. Technetium-99m (a gamma emitter for diagnosis of tumours) and Rhenium-188 (a beta emitter for tumour therapy) are considered as matched pairs because of their congener relationship within the periodic table. The π-acid electronic characteristics of functionalized phosphines are considered to be most appropriate to generate well-defined and kinetically inert complexes of Technetium and Rhenium for radiopharmaceutical applications[5–8]. Therefore, the success in the development of water-soluble catalysts or the discovery of new 'site-specific' radiopharmaceuticals for the diagnosis and therapy of cancer are expected to depend on the fundamental developments in the design and synthesis of new water-soluble phosphines.

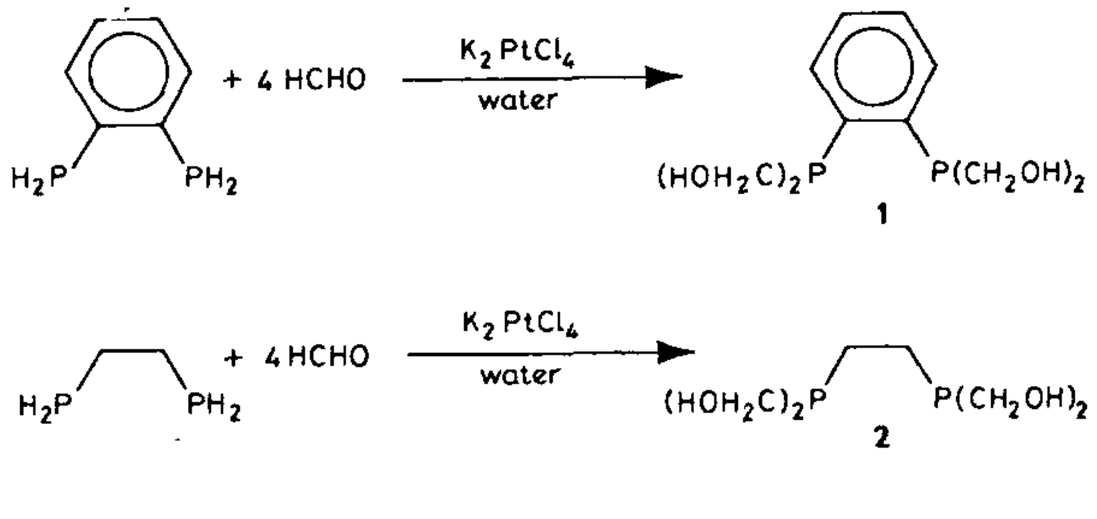
The utility of mono-, di- or tri-sulphonated arylphosphines has become a common modality in the development of water-soluble transition metal complexes (Figure 1). While the sulphonated phosphines offer convenient access to water-soluble ligands in bulk quantities, the lack of their purity and the often encountered, sulphonate-assisted oxidation of phosphines have become major barriers in the utility of these ligands in specific catalytic applications.

Functional groups with high water-solubility and low lipophillic characteristics are the essential criteria for their use as ligands in the design of pharmaceuticals or radiopharmaceuticals. In this context, the sulphonated arylphosphines, although highly soluble in water, are unsuited because they display high lipophilicity. Therefore, drugs derived from such ligands may show uncharacteristic biodistribution properties and in turn adverse toxic side effects.

From the aforementioned applications of water-soluble phosphines in the areas of biphasic catalysis and biomedicine, it is clear that new developments in the design of water-soluble phosphines will result in greater strides in the areas of catalysis and medical science. As part of our ongoing research on the fundamental main group chemistry aimed at the design and development of new multifunctional ligand frameworks[28–35], we have recently discovered new classes of phosphines that have shown remarkable oxidative-stability and solubility in aqueous media[36–40]. This account will describe recent results obtained in our laboratory on (a) new synthetic approaches to water-soluble phosphines; (b) biphasic reactions of these chelating bisphosphines with transition metal precursors to produce water-soluble transition metal and radiometal complexes, and (c) relevance of this fundamental chemistry in the development of biphasic catalysts and also in the design of new radiopharamaceuticals with efficient bioclearance characteristics.

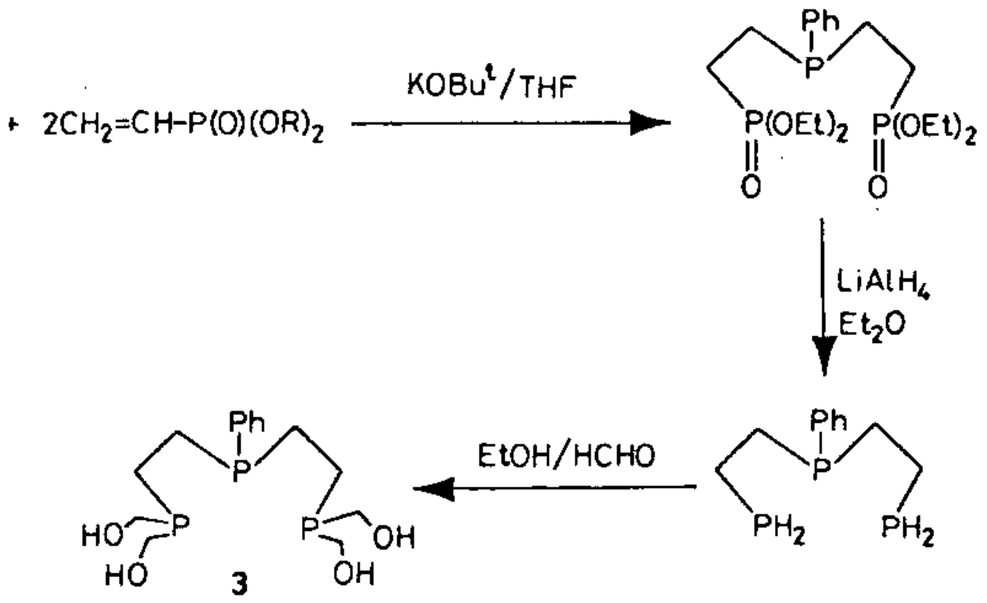
Synthesis

The approach, developed in our laboratory, for the synthesis of water-soluble bisphosphines involved the hydroformylation of P–H bonds, of appropriate phosphines, as outlined in Scheme 1 (refs 36–39). It is important to recognize that hydroformylation reactions are usually referred in the context of metal-mediated hydroformylation of olefins. However, hydroformylation reactions involving main group centers (e.g. P–H or S–H) have remained largely unexplored[41].

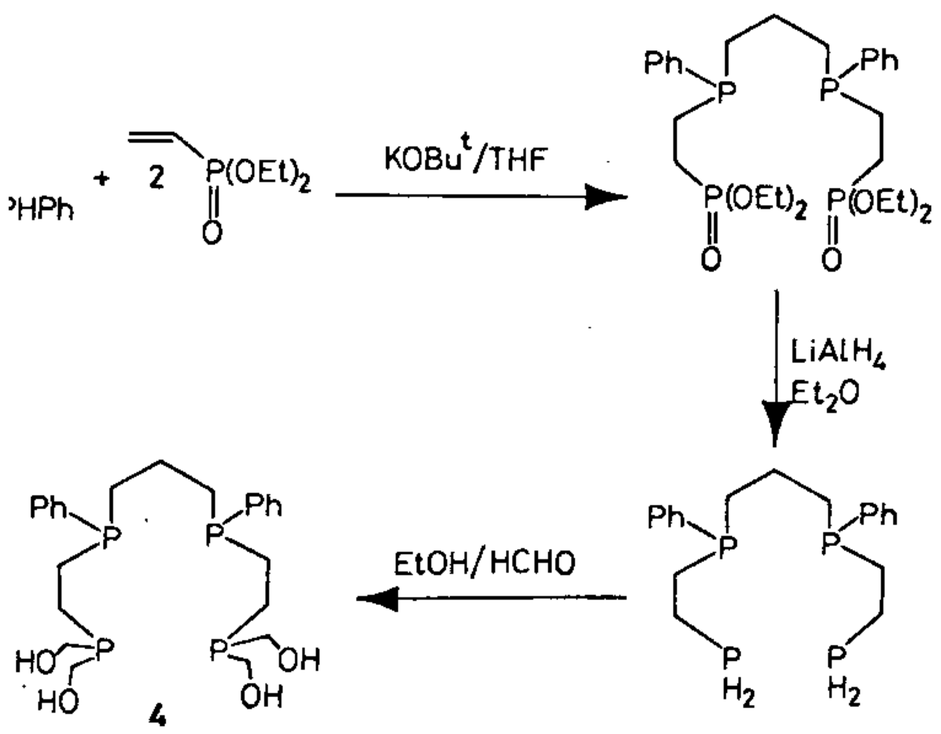


Scheme 1.

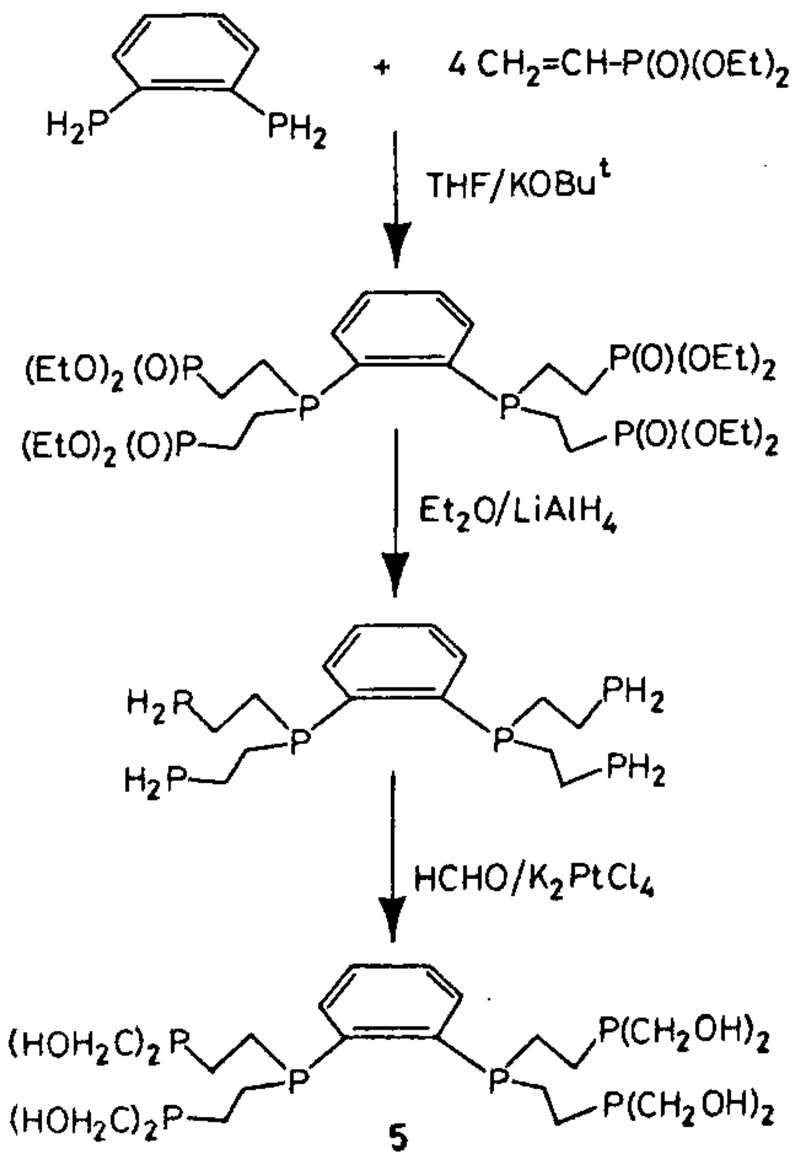
The reactions outlined in Scheme 1 not only produce the products in high yields (> 90%) but also the resulting new water-soluble phosphines have remarkable oxidative-stability in aqueous media (vide infra)[36–38]. Therefore, it may be conceived that the hydroformylation reactions of P–H bonds are fundamental to the discovery of functionalized water-soluble phosphines. In this context, our laboratory has explored the utility of the reactions outlined in Scheme 1 to produce the tri, tetra and even the hexaphosphines as described in Schemes 2, 3 and 4 respectively[42]. All the new phosphines, described in Schemes 1–4, are oils and are highly soluble in water. They were characterized by ^{1}H and ^{31}P NMR spectroscopy and high resolution fast atom bombardment (FAB) mass spectrometry. In some instances, the structural proof has come from the X-ray crystallographic investigations of the metal complexes derived from this new generation of ligands (vide infra). The ^{31}P NMR spectroscopic data for all the phosphines are summarized in Table 1. The P–H bonded-precursors used in the synthesis of compounds **1–5** resonate around –125 ppm in their ^{31}P NMR spectra. In sharp contrast, the water-soluble phosphines **1–5** resonate at considerably down fields (–25 to –30 ppm). These distinct chemical shift differen-



Scheme 2.



Scheme 3.



Scheme 4.

ces have allowed us to monitor the progress of these reactions (Schemes 1–4) through ^{31}P NMR spectroscopy[38].

Oxidative stability in aqueous media

The aqueous solubility of the new phosphines **1–5** alone will not guarantee their applications in biphasic catalysis or specific biomedical use. Their oxidative stability in aqueous media and also under specific *in vitro*/*in vivo* conditions are essential criteria for the development of water-soluble transition metal or radiometal complexes for use as biphasic catalysts or radiopharmaceuticals respectively. Detailed studies carried out in our laboratory have demonstrated the remarkable oxidative-stability of phosphines **1–5** in aqueous media. In fact, representative ^{31}P NMR spectra, depicted in Figure 2, indicate that

Table 1. ^{31}P NMR spectroscopic data for the water-soluble phosphines and their metal complexes[a]

Compound	$P(CH_2OH)$	P(Ph)
1	–31.2(s)	
2	–20.0(s)	
3	–21.3(d)[b]	–17.6(t)[b]
4	–22.0(d)[c]	–20.5(d)[c]
5[d]	–20.2(m)	–29.0(m)
6	57.5(s)[e]	
7	66.8(s)	
8	49.7(s)[f]	
9	57.4(s)	
10	29.8(s)	

[a]Spectra were recorded using aqueous solutions of compounds **1–10**; data from refs 36–39; [b] $^3J_{P-P} = 34.0$ Hz; [c] $^3J_{P-P} = 39.0$ Hz; [d]two diastereoisomers and racemic mixtures are possible for this compound; [e] $^1J_{PtP} = 2165$ Hz; [f] $^1J_{PtP} = 2203$ Hz.

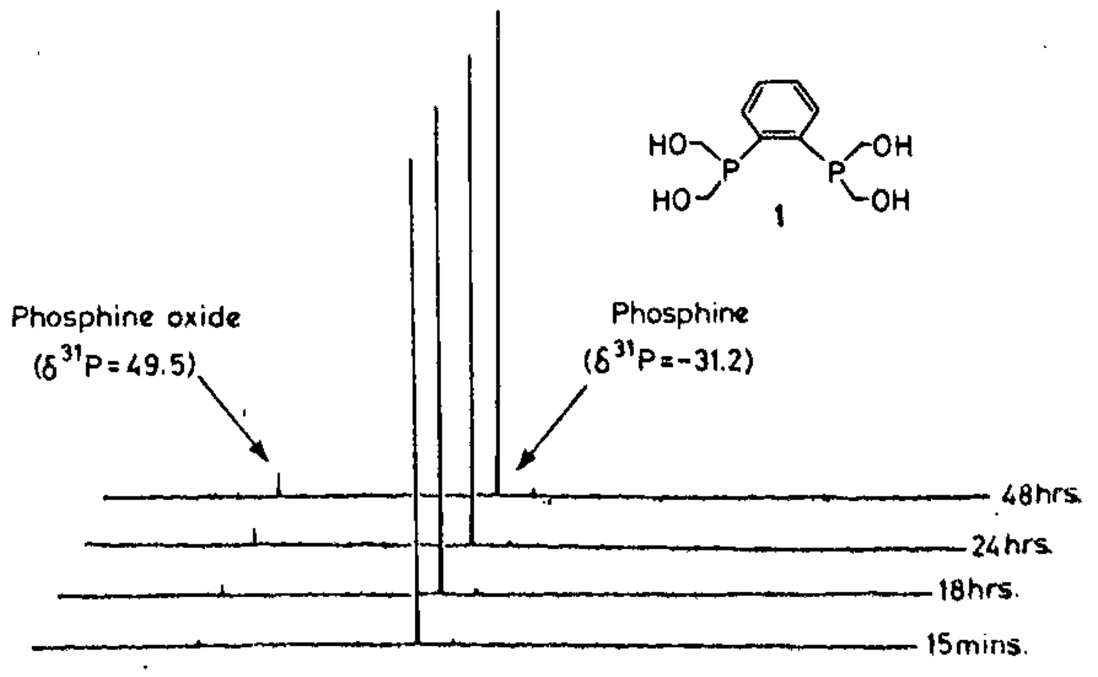


Figure 2. ^{31}P NMR spectra (121.5 MHz) of an aqueous solution of **1** at various time intervals.

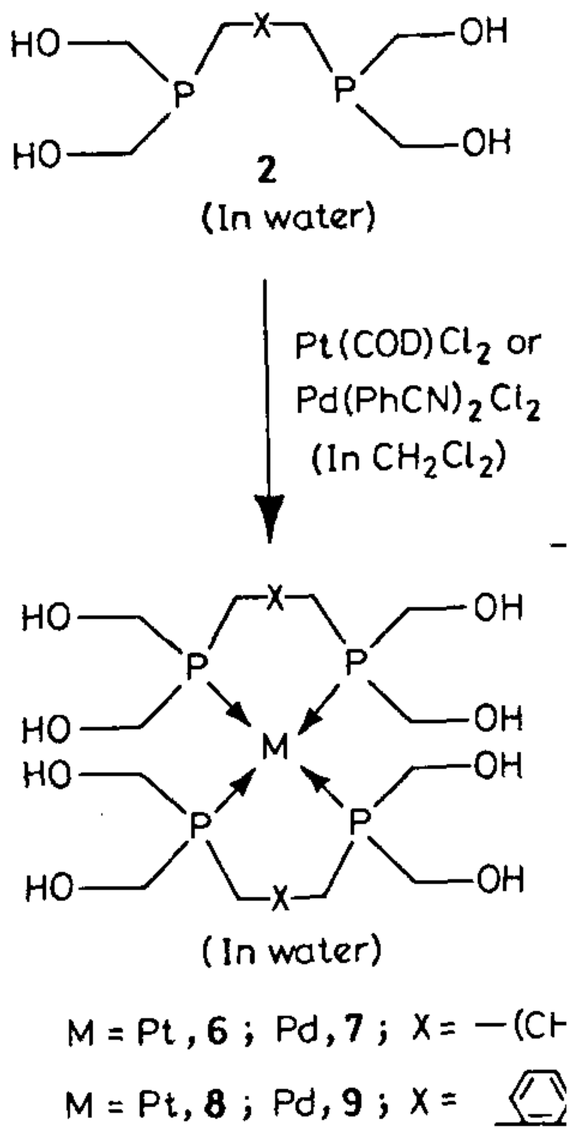
only less than 10% of the water-soluble phosphine **1** is oxidized to the corresponding phosphine oxide even after seven days in aqueous media. These studies were carried out by stirring the solutions of phosphines in degassed-water in open-air. The aliquots, at various time intervals, were monitored by ^{31}P NMR spectroscopy. In general, alkanebisphosphines (e.g. $R_2P(CH_2)_nPR_2$; R = Me; $n = 1$–3) tend to be oxidatively unstable. In fact, $(CH_3)_2P–CH_2–CH_2–P(CH_3)_2$, which has a similar chain length as $(CH_2OH)_2P–CH_2–CH_2–P(CH_2OH)_2$, **1**, ignites instantaneously upon contact with the atmospheric moisture. The ability of alkyl hydroxy groups to impart oxidative-stability to the P^{III} centres (in **1–5**), particularly for extended durations in aqueous media, is considered to be significant in the development of transition metal chemistry in environmentally benign media (i.e. water).

Coordination chemistry: Implications in biphasic catalysis

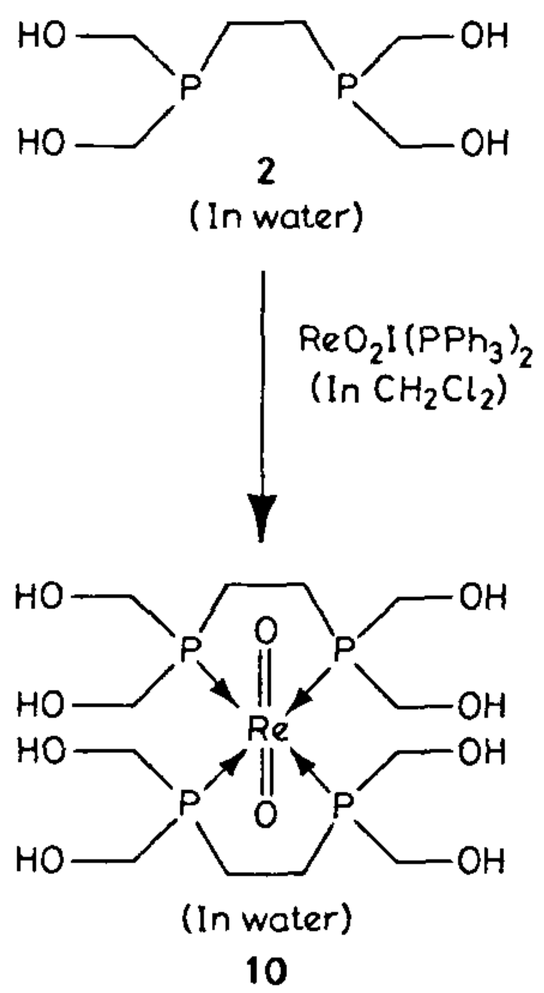
The chelating nature of **1** and **2** and the presence of three to six P^{III} centers in **3–5** provide useful avenues for the development of new classes of transition metal chelates. In addition, the water-soluble properties of **1–5** present unique prospects in their reactions with transition metal precursors under biphasic (i.e. aqueous-organic) reaction conditions. For example, the chelating phosphines **1** or **2**, dissolved in water, react with $PdCl_2(PhCN)_2$ and $PtCl_2(COD)$ (COD = cyclooctadiene); dissolved in CH_2Cl_2, under biphasic conditions to produce the corresponding water-soluble Pd(II) or Pt(II) complexes in near quantitative yields (Scheme 5). The reactions outlined in Scheme 5 are 'strictly' biphasic because upon simple shaking of solutions of ligands (in aqueous media) and metal precursors (in organic media), more than 98% of the metal precursors are transferred into the aqueous media. The metal complexes are isolated from the aqueous phase upon simple separation from the organic phase. The water-soluble bisphosphines **1** and **2** also react with early-transition metal precursors to afford a water-soluble Re(V) complex **10** as described in Scheme 6.

The Pd(II) and Pt(II) complexes **6–9** (Scheme 5) are stable in aqueous media for several weeks[36,37]. This remarkable kinetic inertness of these transition metal compounds may be attributed to the high nucleophilicity of the P^{III} centers in the parent ligands (e.g. **1–2**). Phosphine ligands with high nucleophilicity are expected to involve efficient π-back bonding with the metal centers enabling the formation of strong and kinetically inert M–P bonds.

The new water-soluble transition metal compounds **6–10** were fully characterized by ^1H and ^{31}P NMR spectroscopy (Table 1)[36–39]. The X-ray crystallographic investigations of representative exam plexes have confirmed their mole Single crystals of **6**, **9** and **10**, crystallographic analysis, were ob evaporations of their aqueous soluti of **6** and **9** comprise of centrosymme



Scheme 5.



Scheme 6.

two ligands bonded to Pt(II) or Pd(II) centres in a *cis* fashion and the metals display square planar geometries[36,37]. The Pt–P (2.309 Å) and Pd–P (2.317 Å) distances are within the normal range as seen in other alkyl-substituted phosphine complexes of these metals[43,44]. The X-ray structure of **10** confirmed the dioxo core around the octahedral Re(V) metal centre[38]. The Re–P distances (2.477 Å) are within the normal range as noted in a number of other phosphine complexes of Re(V) (ref. 45). Interestingly, in all the complexes **6**, **9** and **10** no inter or intramolecular interactions were noticed despite the fact that $-CH_2OH$ groups, in general, are prone to hydrogen bonding interactions.

What is the relevance of the reactions depicted in Schemes 5 and 6 to biphasic catalysis? In biphasic catalysis, the catalyst is expected to remain in the aqueous phase to enable the efficient separation of products from the organic phase. The preferential solubility of transition metal catalysts in aqueous media enable high-recovery of catalysts after catalytic reactions and present enormous scope for achieving cost efficiency in specific chemical transformations. Modern chemical industries are, therefore, switching from the traditional monophasic catalysis to biphasic catalyst technologies. The *oxo* process, for the production of *n*-butanal, carried out by Rhone Poulenc is the premier example of the success of a biphasic catalyst system at the industrial scales. The Pd(II) and Pt(II) complexes of water-soluble biphosphines **1** and **2**, as described in Scheme 5, possess near-ideal properties for their use in biphasic catalysis because they show stability in aqueous media and selective partition from the organic into aqueous media. Besides the nature of the backbone of the water-soluble bisphosphine, **1** or **2**, has little or no effect on the overall kinetic inertness of the resulting Pd(II) or Pt(II) complexes.

The chemical modifications of the traditional sulphonated-arylphosphines (Figure 1) are difficult, making it impracticable to tune the lipophilicities of these ligands. Systematic variations in the lipophilicities of ligands and their metal complexes are important in the development of 'counterphase transfer catalysts' wherein catalysts from the aqueous phase will interact with the lipophilic substrate molecules from the organic phase[46]. As the number of carbon centres in the chemical frameworks of the water-soluble phosphines (**1–5**) increases (Schemes 1–4), the liphophilic property of the individual ligands also increase accordingly. Therefore, our new approach to ligand design (Schemes 1–4) affords phosphines of appropriate aqueous solubility and lipophilicity for use in the development of counterphase transition metal catalysts.

Biomedical applications

Targeting of radiopharmaceuticals for specific tumours and organs is, generally, carried out by incorporating a targeting moiety on the radiometal complex as illustrated in Figure 3. Latest developments in biotechnology have provided useful targeting vectors (e.g. proteins, peptides). The radiolabeling of these biomolecules with a diagnostic (e.g. Tc-99m) or therapeutic (e.g. ^{188}Re) radioisotope is expected to produce radiopharmaceuticals for use in cancer diagnosis and therapy respectively[5,6]. The success of the approach depicted in Figure 3 depends on the biodistribution of the radiolabeled ligand itself. The characteristics of ligand systems that are most suited in the design and development of site-specific radiopharmaceuticals include: (a) solubility and stability in aqueous media, (b) stability under *in vivo* environment, and (c) minimal or no association with blood plasma and also efficient clearance from the human body through urine.

As part of our ongoing effort in the development of ligand systems for use in nuclear medicine[28–40], new water-soluble phosphines (**11–12**), as outlined in Scheme 7, have been synthesized. In fact, the Tc-99m complexes of **11–12** have shown near-ideal *in vitro* and *in vivo* properties for their use in the design of site-specific radiopharmaceuticals. For example, the ligand **12**, upon simple mixing with an aqueous solution of Tc-99m

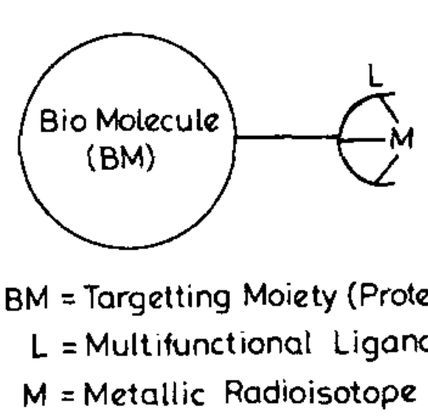
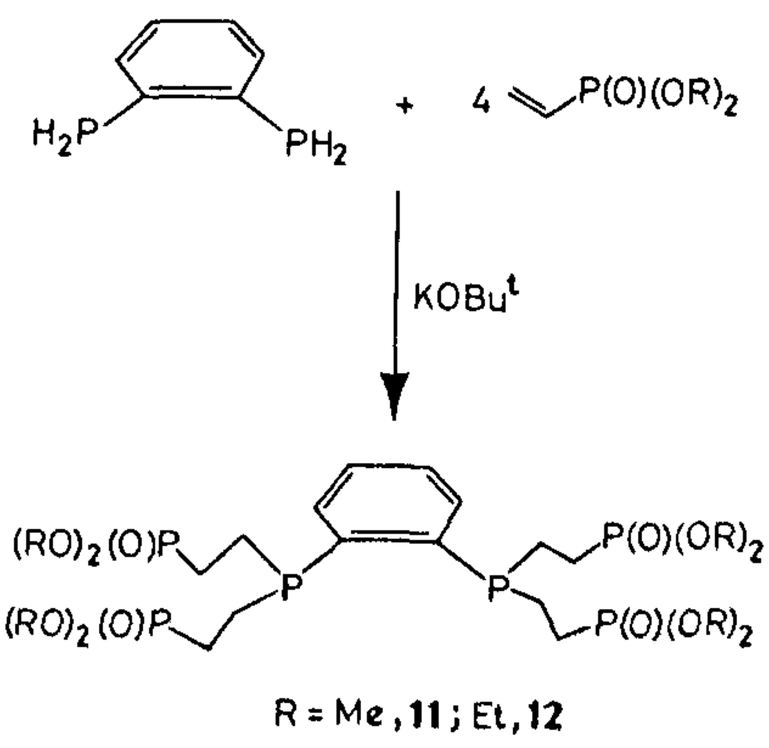
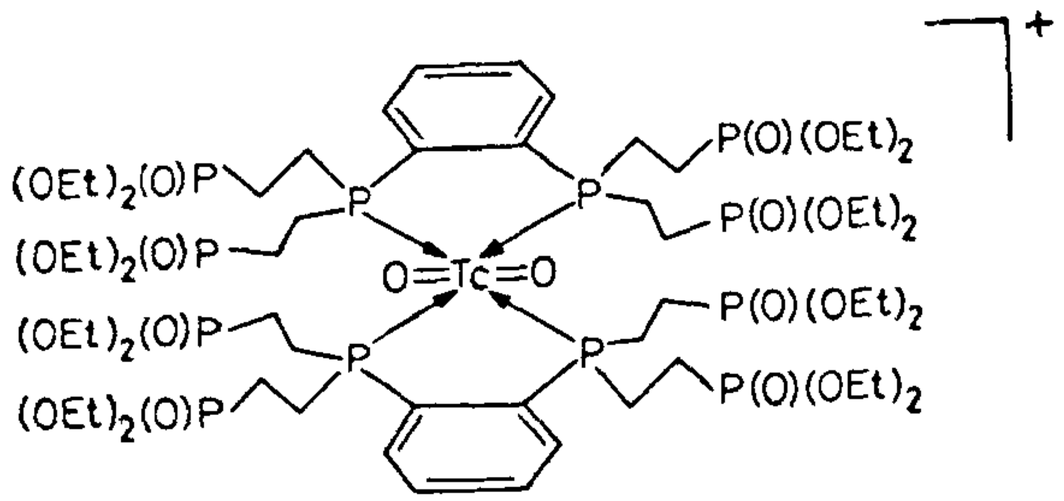


Figure 3. Representation of a labelled biomolecule for 'site-specific' cancer diagnosis or therapy.



Scheme 7.



13

Figure 4. Representation of structure of the Tc-99m complex **13**.

O_4^-, produces the technetium complex **13** in > 99% yield. Based on the parallel studies of the reactions of this phosphine **12** with non-radioactive ReO_4^- and comparisons of HPLC and electrophoresis data for the Re and Tc complexes, the structure of complex **13** is depicted in Figure 4 (refs 47,48).

Detailed biodistribution studies, on rats and mice, of the Tc-99m complex **13** demonstrate that it has minimal or no interaction with blood plasma and, more importantly, is cleared through the urine efficiently. A typical biodistribution analysis of this compound is shown in Table 2. The biodistribution studies of **13** in rats demonstrate that the uptake of this Tc-99m complex in blood at 5, 30, 60 and 240 min are 15.97, 4.81, 1.53 and 0.67% respectively (complete biodistribution data for 60 and 120 min are summarized in Table 2)[47,48]. The gradual drop of percentage injected dose (% ID) of **13** in blood is accompanied by a concomitant increase in the bladder (Table 2). In fact, at 120 min % ID in bladder is as high as 91.3%. This biodistribution pattern suggests that **13** is cleared from the body by a glomerular filtration pathway. At 60 or 120 min, the % ID in other organs is minimum or zero, suggesting that **13** is not only cleared efficiently but also does not localize in non-target organs. The fast glomerular filtration rate (GFR) and the efficient clearance from non-target organs make **13** ideal for use as a new drug for renal imaging[47,48]. In fact, the biodistribution analysis of **13** in rats and other animals matches the GFR clearance characteristics of commercially used renal imaging agents. It is also important to recognize that **13** was not decomposed in the animal body as evidenced by the identical HPLC profiles of pre-injected and urine samples[47].

Renal clearance of radiopharmaceuticals is, usually, effected by the use of highly anionic ligands (e.g. diethylenetetraminepentaacetic acid (DTPA)). Such radiopharmaceuticals are derived from the interaction of appropriate Tc-99m precursors with DTPA in the presence of an external reducing agent (e.g. Sn (II)). The use of neutral ligands **11** or **12** to formulate radiopharmaceuticals (e.g. **13**) with efficient renal clearance properties, as demonstrated in our discovery,

Table 2. Biodistribution of Tc-99m complex **13** in anesthetized rats as a function of time after injection[a]

Organ	Percentage injected dose (ID) per organ[b]	
	1 h	2 h
Brain	0.00 ± 0.00	0.00 ± 0.00
Blood	1.53 ± 0.38	0.67 ± 0.10
Heart	0.02 ± 0.00	0.01 ± 0.02
Lung	0.11 ± 0.00	0.06 ± 0.03
Liver	0.74 ± 0.07	0.63 ± 0.17
Spleen	0.01 ± 0.01	0.01 ± 0.01
Stomach	0.55 ± 0.26	0.65 ± 0.20
Large intestine	0.18 ± 0.02	0.15 ± 0.04
Small intestine	1.21 ± 0.18	1.19 ± 0.30
Kidneys	1.92 ± 0.41	2.47 ± 1.58
Bladder	88.96 ± 2.00	91.30 ± 2.11
Muscle	0.02 ± 0.01	0.03 ± 0.00
Carcass	6.09 ± 1.73	3.37 ± 0.17

[a]Sprague–Dawley rats (180–240 g) anesthetized with Napentobarbitol (50 mg/kg-IP) were injected intravenously; data from refs 47, 48.
[b]Percentage ID/organ values are mean ± SD; $n = 5$ for each group; percentage ID in whole blood estimated assuming whole blood volume as 6.5% of body weight.

has opened-up a new concept in clearance of drugs glomerular filtration pathway. The biodistribution stu of **13** have also demonstrated that this compound p sesses optimum *in vivo* stability and bioclearance c acteristics for its use in the development of 'site-speci radiopharmaceuticals. Currently, our laboratory is dir ing its efforts to incorporate specific biomolecules water-soluble phosphines (e.g. **11** or **12**) to deve biomolecule functionalized-ligand frameworks. ultimate objective envisages radiolabeling of ligands are pre-functionalized with biomolecules to proc 'tumour-specific' radiopharmaceuticals (Figure 3).

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Correction

In "S. Chandrasekhar and C. V. Raman—Some letters" (*Curr. Sci.*, 1996, **70**, 104–107) by S. Ramaseshan, read "... (I appreciate Chandrasekhar's fine work in astrophysics and *latterly* ..." instead of "... *particularly* ..." on page 105, 3rd column, 5th line; and "Reading these letters ... during this period (1930–*1961*, ..." instead of "... *1967* ..." on page 107, 3rd column, 13th line.

Erratum

Advt: Indian Institute of Tropical Meteorology, Pune (*Curr. Sci.*, 1995, **69**, 884–885)

On page 885, read "Upper age limit is relaxable by five years for candidates belonging to SC/ST and as per rules for Ex-servicemen and physically handicapped persons" and not as printed.