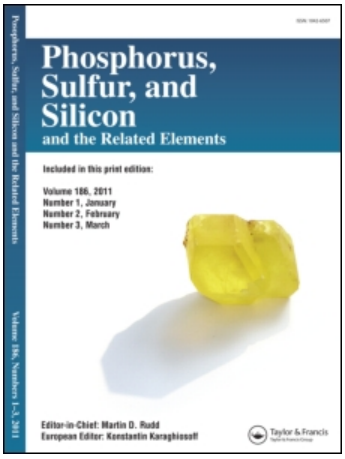

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THE POTENTIAL OF PHOSPHINIMINES AS BUILDING BLOCKS FOR A NEW GENERATION OF RADIOPHARMACEUTICALS.

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Abstract Reaction of $Ph_3P{=}NSiMe_3$ with NH_4ReO_4 produced the ion pair $Ph_3P{=}NH_2^+ReO_4^-$ which was characterized by spectroscopic data and X-ray crystallography. The thermolysis of this ion pair gave the neutral Re(VII) complex: $Ph_3P{=}N\text{-}ReO_3$ in good yields. The reactions of $^{99m}TcO_4^-$ or $^{188}ReO_4^-$ with $Ph_3P{=}N\text{-}SiMe_3$ also produced the metallic radioisotope analogues of the ion pair: $Ph_3P{=}NH_2^+MO_4^-$ (M = ^{99m}Tc or ^{188}Re) which on heating produce the neutral species $Ph_3P{=}N\text{-}MO_3$ (M = ^{99m}Tc or ^{188}Re). The implications of such small molecule ^{99m}Tc or ^{188}Re complexes for the development of a new genre of radiopharmaceuticals will be discussed.

INTRODUCTION

The development of fundamental coordination chemistries of rhenium and technetium continue to make significant impact in the discovery of new radiopharmaceuticals of radiorhenium and technetium 99m for applications in nuclear medicine. New ligand systems are being extensively used to produce complexes of ^{99m}Tc or radiorhenium with the hope of producing radiopharmaceuticals of optimum *in vivo* and *in vitro* stabilities. Despite the use of a variety of ligand systems which include macrocyclic amines, aminethiols, isocyanides, boronic acid derivatives, tertiary phosphines, and many more systems to develop new ^{99m}Tc and ^{188}Re complexes, synthetic methods which produce stable ^{99m}Tc or ^{188}Re complexes in high yields, high radiochemical purities, at neutral pH, at RT and without the use of an external reducing agent (e.g. Sn[II]) by simple mixing of $^{99m}TcO_4^-$ or $^{188}ReO_4^-$ with the ligand solutions is rare. The development of new chemistry which would aid in such simple methodology to produce radiopharmaceuticals may lead to significant advantages in nuclear medicine, radiochemistry and biochemistry.

RESULTS AND DISCUSSION

As part of our ongoing research on the labelling of small molecule ligand systems with ^{99m}Tc and ^{188}Re radionuclides for diagnostic and therapeutic application [1-3], we have recently discovered that the treatment of triphenylphosphinimine; Ph_3P-$NSiMe_3$ **1**, with $^{99m}TcO_4^-$ or $^{188}ReO_4^-$ and ReO_4^-, produces stable ion pairs of the type: $Ph_3P{=}NH_2{}^+{}^{99m}TcO_4$, **2**, or $Ph_3P{=}NH_2{}^+{}^{188}ReO_4^-$, **3**, and $Ph_3P{=}NH_2{}^+ReO_4^-$, **4**, respectively. The radiolabeling approach shown in Scheme 1 is unprecedented and unique because it demonstrates that by simple mixing of **1** in toluene with saline solutions of $^{99m}TcO_4^-$ or $^{188}ReO_4^-$ results in the formation of **2** and **3** in >95% yields at 25°C in 10-20 min. The characterization of **2** and **3** was carried out by radiochemical and chromatographic techniques. The thin layer radiographic scanning of **2** and **3** shown in Figure 1 reveals that the two complexes migrate from the point of spotting in saline (Rf=0.94 for **2**; 0.91 for **3**), ethyl acetate (Rf=0.90 for **2**; 0.88 for **3**) and acetone (Rf=0.85 for **2**; 0.82 for **3**) and indicate the ion pair characteristics of **2** and **3**.

As a chemical model to the reactions of **1** with $^{99m}TcO_4^-$ or $^{188}ReO_4^-$, we have investigated the reactivity of $Ph_3P{=}NSiMe_3$ **1** with NH_4ReO_4 under conditions similar to those used at the tracer levels. Saline solutions of NH_4ReO_4 reacted with Ph_3P-$NSiMe_3$ **1** in THF or toluene to produce $Ph_3P{=}NH_2{}^+ReO_4^-$ **4** in near quantitative yields. Analytical, spectroscopic (^{31}P NMR and IR) data and single crystal X-ray crystallographic analysis confirmed its chemical constitution. The P-N bond length (1.636 (7) A) found in the Re(VII) ion pair **4** is within the range reported for a number of phosphinimine complexes of early transition metals [4]. The TLC Rf values of **4** in different solvents as measured by UV/Vis were similar to those observed for its radiochemcial analogue **3** and confirms the ion pair formulation for **2** and **3**. Toluene or acetonitrile solutions of **4** when boiled for 4-6 hrs produced the neutral Re(VII) complex $Ph_3P{=}N$-ReO_3 **5** in near quantitative yields (Scheme 1).

Similarly when toluene solutions of the ^{99m}Tc and ^{188}Re ion pair compounds **2** and **3**, respectively, when boiled for 15-30 min, resulted in near quantitative transformation to the neutral lipophilic complexes $Ph_3P{=}N$-$^{99m}TcO_3$ **6** and $Ph_3P{=}N$-$^{188}ReO_3$ **7** respectively (Scheme 1). The TLC Rf values of **6** and **7** were identical to those for the non radioactive analogue **5**. The TLC radiographic scanning of **6** and **7** (Figure 1) showed the complexes to migrate in acetone Rf=0.91 for **6**; 0.90 for **7**) and ethyl acetate (Rf=0.80 for **6**; 0.76 for **7**) and to stay at the origin in saline (Rf of 0.0 for both **6** and **7**): typical characteristics of neutral lipophilic molecules.

Scheme 1

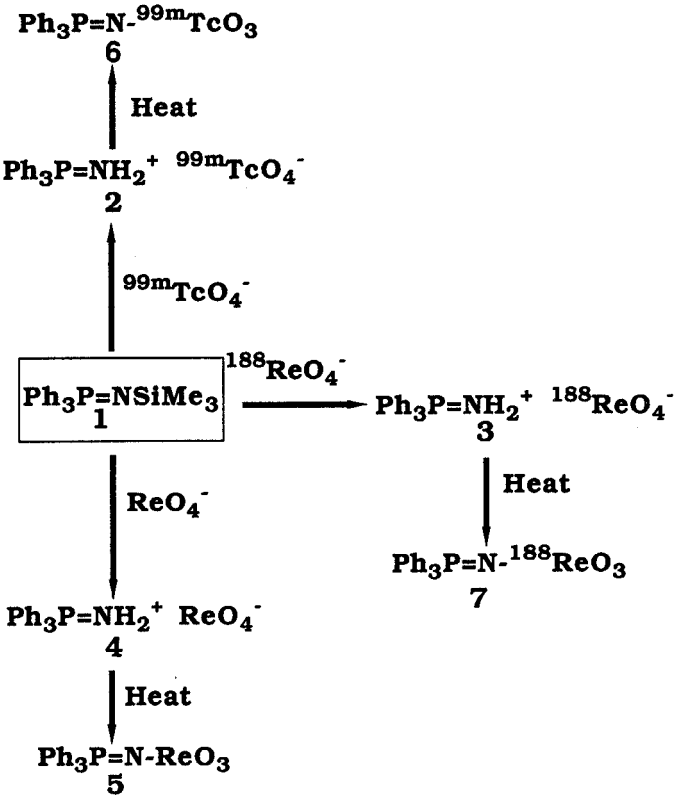
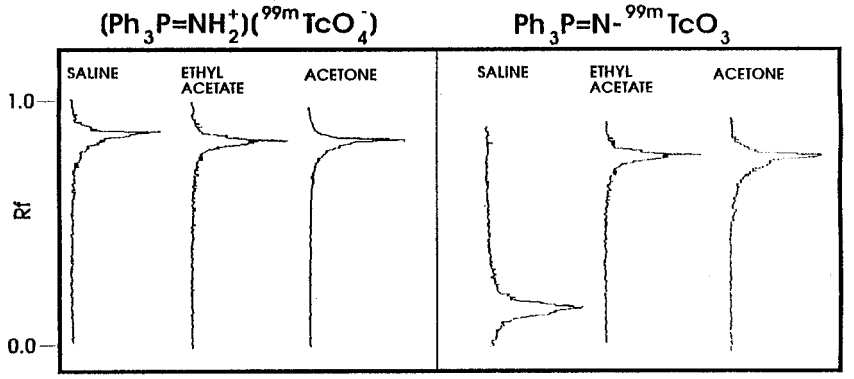


Figure 1. PAPER CHROMATOGRAPHY



CONCLUSIONS

The diagnostically (^{99m}Tc) and therapeutically (^{188}Re) important radioisotopes are easily accessible (in generator form) as $^{99m}TcO_4^-$ and $^{188}ReO_4^-$ in nuclear medicine clinics throughout the world. The simplicity and efficacy of labelling of the phosphinimine ligand **1**, by $^{99m}TcO_4^-$ and $^{188}ReO_4^-$, respectively, as shown in the present investigation has opened up a new dimension in the production of the "shake and shoot" type of radiopharmaceuticals. The substitutional chemistry of the tetrahedral P(V) center in **1** is extensive and such tuning of substitutents on the phosphorus may become the most practical approach to develop a new generation of radiopharmaceuticals with optimum biolocalization and biodistribution characteristics for diagnostic and therapeutic applications in nuclear medicine.

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