Organometallic Phosphinimines as Building Blocks for Potential New Radiopharmaceuticals.

Synthesis, Structure and Reactivity of Ph₃P=NH₂⁺ReO₄⁻

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Introduction

There is a resurgence of interest in the use of organometallic phosphinimines (e.g.; Ph₃P=N−SiMe₃ (1)) as novel ligand systems for transition metals and actinide metals [1]. Phosphinimines of the type 1 have shown versatility in their ability to donate 1, 2, or 4 electrons to transition metals to produce kinetically stable compounds with most early transition metals. The N-Silylphosphinimines of the type 1 are prolific in their reactions with metal precursors because reactions with the metal halides proceeds through the facile elimination of Me₃SiX, whereas, metal oxides also react smoothly through the migration of Me₃Si from the iminato nitrogen onto the oxygen of the metal center. Despite the diversity in structure and reactivity of phosphinimines as noted above, there are no reports of the reactions of this class of ligand systems with metallic radioisotopes. The development of fundamental coordination chemistry 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. A number of different ligand systems which include macrocyclic amines [2], aminothiols [3], amidethiols [4], isocyanides [5], boronic acid derivatives [6], phosphines [7], phosphonates [8] and many other ligand frameworks [9] have been used in the past to produce stable complexes of radiorehenium and technetium. In this communication, we report the use of an organometallic phosphinimine, Ph₃P=N−SiMe₃ (1), to produce complexes of rhenium Ph₃P=NH₂·ReO₄ (2) and Ph₃P=N−ReO₃ (3) and also the corresponding ¹⁸⁸Re analogues Ph₃P=NH₂·¹⁸⁸ReO₄ (4) and Ph₃P=N·¹⁸⁸ReO₃ (5).

Results and Discussion

We have investigated the reaction of Ph₃P=N−SiMe₃ (1) with NH₄⁺·ReO₄⁻ with the intent of extending the chemistry to the corresponding tetraxo anion of ¹⁸⁸Re and ¹⁹⁸mTc [10]. Aqueous solutions of NH₄ReO₄ on treatment with a solution of Ph₃P=N−SiMe₃ (1) in CH₃CN resulted in a near quantitative yield of the ion pair Ph₃P=NH₂·ReO₄ (2) (Scheme 1) which was isolated as a colorless crystalline solid upon recrystallization from CH₃CN. Analytical, spectroscopic (³¹P NMR and IR) data and single crystal X-ray crystallographic analysis (Fig. 1) confirmed its chemical constitution.

The structure reveals the presence of hydrogen bonding between the iminato hydrogens and the oxygen atoms of the ReO₄⁻ anion. The P–N bond length (1.636(7) Å) (Table I) found in the Re(VII) ion pair 2 is within the range observed for a recently reported non-metallated free phosphinimine ion pair of the type: R₂R’P=NH₂·Cl⁻ [11]. The absence of any significant elongation of the P–N bond in 2...
Scheme 1.

Fig. 1. ORTEP drawing of Ph₃P=NH₂ + ReO₄⁻ (4) showing 50% thermal ellipsoids. The interaction between O(1) or O(3) and the imine N is through hydrogen bonding.

as compared to the free phosphinimine may suggest some delocalization of electronic charge from the Re(VII) center onto the P-N bond. This is further indicated by the fact that the P-N bond length in 2 is very similar to the P-N bond lengths reported for a number of phosphinimine complexes of early transition metals [1]. The ion pair is soluble in ethyl alcohol and other common organic solvents (e.g., CHCl₃, toluene and THF). The addition of water to the CH₃CN solutions of 2 (1:1) did not result in the dissociation of the ion pair and such solutions also did not show a temperature dependency of the ³¹P NMR chemical shifts. The ion pair 2 has a sharp melting point of 160 °C and remelts without decomposition at the same temperature. It is non-hygroscopic and can be stored in an open atmosphere for months. The dual neutral and ionic type of solubility properties, the melting behavior and the unusual stability of this salt in alcohol is noteworthy. The toluene or acetonitrile solution of 2 upon boiling for 4-6 h produced the neutral Re(VII) phosphinimine complex Ph₃P=N-ReO₃ (Scheme 1) in near quantitative yields. The neutral complex 3 was also obtained in 60% yield by heating the solid ion pair 2 in vacuo at 185 °C for 1.5 h. The electron impact mass spectrum of 3 showed the parent ion (510; 80%) and the solution molecular weight measurements of 3 revealed that it is monomeric in solution.

Roesky et al. have reported an approach to the formation of 3 in 38% yield from the reaction of Ph₃P=N-SiMe₃ with Re₂O₇ [12]. Our methodology to produce 3 serves as a model to extend the reactions of Ph₃P=N-SiMe₃ with the tetraoxo anions of ⁹⁹mTc or ¹⁸⁸Re. The extension of this chemistry to produce the ⁹⁹mTc or ¹⁸⁸Re analogues of 2 and 3 would also be worthwhile in the context of developing organic soluble ⁹⁹mTc or ¹⁸⁸Re.

Simple mixing of an aqueous solution of ¹⁸⁸ReO₄⁻ with a CH₃CN solution of Ph₃P=N-SiMe₃ (1) at
25 °C produced the 188Re analogue of the ion pair 2 in 98% yields (Scheme 1). Upon heating the toluene extract of Ph3P=NH·188ReO4− (4), at 80 °C for 30 min the tracer level analogue of 3, Ph3P=N188ReO3− (5), was obtained in > 95% yields. The ion pair and the neutral complex 5 were found to be quite stable in dry toluene with minimal or no decomposition occurring for up to 18 h. The TLC Rf values of 5 matched closely with those of its non-tracer analogue 3. The TLC Rf values (Table I) for 2 and its 188Re analogue 4 are in perfect agreement to indicate that the species formed at the tracer level is indeed the one identified to be Ph3P=NH·ReO4− at the non-tracer level. The thin layer chromatographic scanning of 4 and 5 eluted in acetone and ethyl acetate showed sharp single peaks which indicate that both the ion pair and the neutral complexes of 188Re were singular chemical species. The complexes are generally insoluble in aqueous media because they contain three phenyl groups bound to phosphorus.

Conclusions

99mTc and 188Re are commonly used radioisotopes for diagnosis and therapy of cancer in nuclear medicine. In most parts of the world these two radioisotopes are readily available in their tetraoxo anion (i.e., MO₄⁻) form. The direct interaction of MO₄⁻ (M = Re and 188Re) with an organometallic phosphinimine to produce a complex of rhenium as demonstrated in this communication, may set a new trend in the application of unconventional ligand systems in the development of a new generation of radiopharmaceuticals. The substitutional chemistry of the tetrahedral P(V) center in 1 is extensive and such tuning of substituents on the phosphorus may become the most practical approach to develop new classes of radiopharmaceuticals with improved biolocalization and biodistribution characteristics.

Experimental

The trimethylsilylphosphinimine Ph3P=N–SiMe3 (1) was prepared according to reported procedures [13]. NH4ReO4 was used as supplied by Aldrich U.S.A. NH₄⁺188ReO₄⁻ was obtained from a 188W/188Re generator as supplied by the University of Missouri Research Reactor.

Preparation of Ph3P=NH₂·ReO₄⁻ (2)

To a CH₃CN (100 ml) solution of Ph3P=N–SiMe3 (1) (4.11 g, 11.77 mmol) was added an aqueous solution (10 ml) of NH₄ReO₄ (3.15 g, 11.77 mmol) dropwise at 25 °C. The mixture was stirred for 1 h before the volatiles and the aqueous solvents were removed in vacuo to produce a white crystalline solid of Ph3P=NH·ReO4⁻ (2). The final purification of 2 was achieved by recrystallization from CH₃CN; cooling the solutions to 0 °C produced cubic shaped X-ray quality crystals of 2 (86%), m.p. 160 °C. 31P NMR (CDCl₃; 85% H₃PO₄) δ 35.10; IR (Nujol) νNH₂ 3176 cm⁻¹.

Analysis

Calcd C 40.89 H 3.20 N 2.65%,
Found C 40.85 H 3.15 N 2.62%.

Preparation of Ph3P=N–ReO3 (3)

A solution of 2 (2.55 g, 5.0 mmol) in acetonitrile (100 ml) was heated under reflux for 6 h before the solvent was removed in vacuo to obtain a colorless solid of Ph3P=N–ReO3 (3). Recrystallization of 3 from CH₃CN produced analytically pure 3. Yield 78%; m.p. 192 °C (decomp.), Lit. m.p. [27] 193 °C (decomp.). 31P NMR (CDCl₃; 85% H₃PO₄) δ 38.2.

Analysis for C₁₈H₁₅N₃PReO₃

Calcd C 42.35 H 2.96 N 2.74%,
Found C 42.29 H 2.93 N 2.72%.

Roesky et al. [12] have independently reported the formation of 3 (δ 31P = 37.9) in 38% yield from the reaction of Re₂O₇ with Ph₃P=N–SiMe₃.

Preparation of Ph₃P=NH₂·188ReO₄⁻ (4)

Typically the 188Re complex was prepared by mixing 100 μCi (370 kBq) of 188ReO₄⁻ in a 0.1 ml saline solution with Ph₃P=N–SiMe₃ (1) (10–15 mg) in a 1 ml toluene solution. The mixture was vortexed for 1 min at r.t. 5 min following vortexing, an aliquot of the organic layer was removed and the radiochemical purity (RCP) of the 188Re complex 2 was measured. Caution: Rhenium-188 is a β emitter (E = 1.12 MeV; t₁/₂ = 17 h). All work has been done in laboratories approved for the use of radioactive materials.

Preparation of Ph₃P=N–188ReO₃ (5)

A toluene extract of Ph₃P=NH₂·188ReO₄⁻ (2 ml; 100–150 μCi) was heated at 80 °C for 30 min. An aliquot of the solution was used to determine the radiochemical purity (RCP) (95%) of Ph₃P=N–188ReO₃ by radiographic scanning methods as described below.
Table II. TLC $R_f$ values for Re$^a$- and $^{188}$Re$^b$-phosphiniminato complexes.

<table>
<thead>
<tr>
<th>Complex</th>
<th>Acetone $R_f$</th>
<th>Saline $R_f$</th>
<th>Ethyl acetate $R_f$</th>
</tr>
</thead>
<tbody>
<tr>
<td>NH$_4^+$ReO$_4^-$</td>
<td>0.97</td>
<td>0.90</td>
<td>0.00</td>
</tr>
<tr>
<td>Ph$_3$P=NH$_2^+$ReO$_4^-$</td>
<td>0.85</td>
<td>0.88</td>
<td>0.80</td>
</tr>
<tr>
<td>Ph$_3$P=NH$_2^{188}$ReO$_4^-$</td>
<td>0.86</td>
<td>0.88</td>
<td>0.80</td>
</tr>
<tr>
<td>Ph$_3$P=N-ReO$_4^-$</td>
<td>0.82</td>
<td>0.00</td>
<td>0.75</td>
</tr>
<tr>
<td>Ph$<em>3$P=N-$</em>{188}$ReO$_4^-$</td>
<td>0.82</td>
<td>0.00</td>
<td>0.73</td>
</tr>
</tbody>
</table>

$^a$ $R_f$ values determined by conventional TLC chromatography; $^b$ $R_f$ values determined by radiographic scanning of the chromatographic strips (see Experimental for details).

Chromatographic and radiographic scanning studies

The radiochemical purity (RCP) of the $^{188}$Re complexes were determined by paper chromatography (PC) and on instant thin layer chromatography-silica gel (ITLC-SG). PC and ITLC-SG analysis involved spotting 10 $\mu$l of the complex near the bottom (origin) of the strips. The strips were then developed in 0.9% aqueous saline, ethyl acetate and acetone. Determination of the $R_f$'s and quantitation of the migration of activity on the paper strips were made using AMBIS radiochromatographic scanning system and/or by cutting 1 cm sections of the strips and counting each section in a NaI well counter. The RCP's of the samples at r.t. were measured for 24 h to study their stability as a function of time. The complexes were formed in typically >95% yields and showed no significant decomposition over a period of 24 h. Blanks of $^{188}$ReO$_4^-$ were done on PC and ITLC-SG. Typically, NH$_4^+$-$^{188}$ReO$_4^-$ showed an $R_f$ of 0.97 in acetone, an $R_f$ of 0.00 in ethyl acetate and an $R_f$ of 0.9 in saline on both paper and thin-layer-silica gel strips.

Single crystal X-ray structural analysis of Ph$_3$P=NH$_2^+$ReO$_4^-$ (2)

Crystal data for C$_{18}$H$_{15}$NPReO$_4$ (4): orthorhombic P 2$_2_1_2$, $a = 11.1809(9)$; $b = 11.4598(11)$; $c = 14.5957(9)$ Å; $V = 1870.2(3)$ Å$^3$; $Z = 4$; $D_{calc} = 1.870$ g cm$^{-3}$; $\lambda$ (MoK$\alpha$) = 0.70930 Å, $\mu = 6.69$ mm$^{-1}$. An Enraf-Nonius CAD-4 diffractometer was used to collect 3622 independent reflections on a colorless cubic shaped crystal. Of these 3215 were observed ($I \geq 2.5\sigma(I)$). The structure was solved by direct methods. All non-hydrogen atoms were refined anisotropically. The hydrogen atoms were included in idealized positions. R = 0.029, $R_w$ = 0.042.

Table III. Atomic parameters $x$, $y$, $z$ and $B_{iso}$. E.S.Ds. refer to the last digit printed.

<table>
<thead>
<tr>
<th></th>
<th>$x$</th>
<th>$y$</th>
<th>$z$</th>
<th>$B_{iso}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Re</td>
<td>0.34177(3)</td>
<td>0.28070(3)</td>
<td>0.138223(19)</td>
<td>2.762(14)</td>
</tr>
<tr>
<td>O1</td>
<td>0.1892(7)</td>
<td>0.2718(7)</td>
<td>0.1340(6)</td>
<td>5.9(4)</td>
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<tr>
<td>O2</td>
<td>0.3844(9)</td>
<td>0.2918(9)</td>
<td>0.2489(5)</td>
<td>6.5(4)</td>
</tr>
<tr>
<td>O3</td>
<td>0.3952(9)</td>
<td>0.3975(8)</td>
<td>0.0794(6)</td>
<td>6.7(4)</td>
</tr>
<tr>
<td>O4</td>
<td>0.4003(7)</td>
<td>0.1539(7)</td>
<td>0.0972(5)</td>
<td>5.0(3)</td>
</tr>
<tr>
<td>P</td>
<td>0.99840(16)</td>
<td>0.97329(15)</td>
<td>0.14356(13)</td>
<td>2.57(7)</td>
</tr>
<tr>
<td>N</td>
<td>1.0577(6)</td>
<td>1.0640(7)</td>
<td>0.0699(5)</td>
<td>3.6(3)</td>
</tr>
<tr>
<td>C1</td>
<td>1.1111(7)</td>
<td>0.9397(7)</td>
<td>0.2270(5)</td>
<td>2.6(3)</td>
</tr>
<tr>
<td>C2</td>
<td>1.2295(7)</td>
<td>0.9675(7)</td>
<td>0.2097(6)</td>
<td>3.4(3)</td>
</tr>
<tr>
<td>C3</td>
<td>1.3169(9)</td>
<td>0.9346(9)</td>
<td>0.2751(8)</td>
<td>4.7(4)</td>
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<tr>
<td>C4</td>
<td>1.2841(9)</td>
<td>0.8739(8)</td>
<td>0.3496(7)</td>
<td>4.0(4)</td>
</tr>
<tr>
<td>C5</td>
<td>1.1647(10)</td>
<td>0.8439(10)</td>
<td>0.3660(6)</td>
<td>4.8(5)</td>
</tr>
<tr>
<td>C6</td>
<td>1.0798(8)</td>
<td>0.8752(8)</td>
<td>0.3055(6)</td>
<td>3.5(3)</td>
</tr>
<tr>
<td>C7</td>
<td>0.8667(7)</td>
<td>1.0253(7)</td>
<td>0.1969(6)</td>
<td>3.1(3)</td>
</tr>
<tr>
<td>C8</td>
<td>0.7591(9)</td>
<td>1.0257(8)</td>
<td>0.1449(7)</td>
<td>4.3(4)</td>
</tr>
<tr>
<td>C9</td>
<td>0.6579(9)</td>
<td>1.0754(9)</td>
<td>0.1816(10)</td>
<td>5.2(5)</td>
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<td>C10</td>
<td>0.6602(10)</td>
<td>1.1189(8)</td>
<td>0.2679(11)</td>
<td>5.8(6)</td>
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<tr>
<td>C11</td>
<td>0.7585(10)</td>
<td>1.1026(9)</td>
<td>0.3205(9)</td>
<td>5.0(5)</td>
</tr>
<tr>
<td>C12</td>
<td>0.8633(9)</td>
<td>1.0741(8)</td>
<td>0.2839(6)</td>
<td>3.7(5)</td>
</tr>
<tr>
<td>C13</td>
<td>0.9627(7)</td>
<td>0.8414(7)</td>
<td>0.0816(5)</td>
<td>2.8(3)</td>
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<tr>
<td>C14</td>
<td>0.8765(8)</td>
<td>0.7665(7)</td>
<td>0.1160(6)</td>
<td>3.2(3)</td>
</tr>
<tr>
<td>C15</td>
<td>0.8571(9)</td>
<td>0.6593(8)</td>
<td>0.0739(7)</td>
<td>4.3(4)</td>
</tr>
<tr>
<td>C16</td>
<td>0.9229(12)</td>
<td>0.6310(8)</td>
<td>-0.0031(6)</td>
<td>5.0(5)</td>
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<tr>
<td>C17</td>
<td>1.0058(14)</td>
<td>0.7029(11)</td>
<td>-0.0369(7)</td>
<td>5.7(5)</td>
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<tr>
<td>C18</td>
<td>1.0277(10)</td>
<td>0.8119(9)</td>
<td>0.0047(7)</td>
<td>4.5(4)</td>
</tr>
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</table>

$B_{iso}$ is the mean of the principal axes of the displacement ellipsoid.

The final difference map had maximum and minimum densities of +0.870 and -1.130 eÅ$^{-3}$, respectively. The positional parameters and their estimated standard deviations are summarized in Table III. Atomic scattering factors and anomalous dispersion corrections were taken from the International Table for X-Ray Crystallography [14]. All calculations were performed with NRCVAX [15].

Further details may be obtained from: Fachinformationszentrum Karlsruhe, Gesellschaft für wissenschaftlich-technische Information mbH, D-76344 Eggenstein-Leopoldshafen, by quoting the Registry-No. CSD 57422, the names of the authors and the journal citation.

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