Syntheses and Characterization of Chemically Flexible, Water-Soluble Dithio−Bis(phosphine) Compounds: $(HOH_2C)_2P(CH_2)_2S(CH_2)_3S(CH_2)_2P(CH_2OH)_2$, $(HOH_2C)_2PCH_2CH_2S(CH_2)_4SCH_2CH_2P(CH_2OH)_2$, and $(HOH_2C)_2PCH_2CH_2CH_2S(CH_2)_3SCH_2CH_2CH_2P(CH_2OH)_2$. Systematic Investigation of the Effect of Chain Length on the Coordination Chemistry of Rhenium(V). X-ray Crystal Structures of $[ReO_2(HOH_2C)_2P(CH_2)_2S(CH_2)_3S(CH_2)_2P(CH_2OH)_2]_2(Cl)_2$, $[ReO_2(HOH_2C)_2P(CH_2)_2S(CH_2)_4S(CH_2)_2P(CH_2OH)_2]_2(ReO_4^-)_2$, and $[ReO_2(HOH_2C)_2P(CH_2)_3S(CH_2)_3S(CH_2)_3P(CH_2OH)_2](Cl)$

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The water-soluble dithio−bis(phosphine)s $(HOH_2C)_2P(CH_2)_2S(CH_2)_3S(CH_2)_2P(CH_2OH)_2$ (**1**), $(HOH_2C)_2PCH_2CH_2S(CH_2)_4SCH_2CH_2P(CH_2OH)_2$ (**4**), and $(HOH_2C)_2PCH_2CH_2CH_2S(CH_2)_3SCH_2CH_2CH_2P(CH_2OH)_2$ (**7**) were synthesized in near-quantitative yield by the formylation of their appropriate phosphine hydride precursors in the presence of formaldehyde and oxygen-free ethanol. The reactions of **1**, **4**, and **7** with $[ReO_2(C_5H_5N)_4](Cl)$ in refluxing water produced the water-soluble Re(V) complexes $[ReO_2(HOH_2C)_2P(CH_2)_2S(CH_2)_3S(CH_2)_2P(CH_2OH)_2]_2(Cl)_2$ (**8**), $[ReO_2(HOH_2C)_2P(CH_2)_2S(CH_2)_4S(CH_2)_2P(CH_2OH)_2]_2(ReO_4^-)_2$ (**9**), and $[ReO_2(HOH_2C)_2P(CH_2)_3S(CH_2)_3S(CH_2)_3P(CH_2OH)_2](Cl)$ (**10**). The X-ray crystallographic analysis of **8**−**10**, reported in this paper, confirmed the dioxorhenium(V) structures. All of the compounds were characterized by ^1H, ^{13}C, and ^{31}P NMR spectroscopy. HPLC chromatographic analysis of **8**−**10** demonstrated purities of >98% for each of the new complexes formed. X-ray data for $[ReO_2(HOH_2C)_2P(CH_2)_2S(CH_2)_3S(CH_2)_2P(CH_2OH)_2]_2(Cl)_2$ (**8**): monoclinic, $P2_1/n$, $a = 10.7982(5)$ Å, $b = 23.486(1)$ Å, $c = 15.4408(8)$ Å, $\beta = 94.539(1)°$, $Z = 4$, $R = 0.0246$ (wR2 = 0.0574). For $[ReO_2(HOH_2C)_2P(CH_2)_2S(CH_2)_4S(CH_2)_2P(CH_2OH)_2]_2(ReO_4^-)_2$ (**9**): triclinic, $P\bar{1}$, $a = 10.3762(5)$ Å, $b = 12.1099(6)$ Å, $c = 18.7555(9)$ Å, $\alpha = 90.259(1)°$, $\beta = 91.900(1)°$, $\gamma = 104.965(1)°$, $Z = 2$, $R = 0.0546$ (wR2 = 0.1412). For $[ReO_2(HOH_2C)_2P(CH_2)_3S(CH_2)_3S(CH_2)_3P(CH_2OH)_2](Cl)$ (**10**): monoclinic, $P2_1/n$, $a = 10.6224(6)$ Å, $b = 12.5532(8)$ Å, $c = 18.5767(11)$ Å, $\beta = 103.663(10)°$, $Z = 4$, $R = 0.0261$ (wR2 = 0.0656).

Introduction

Rhenium-188, a β-emitting radionuclide (E_β(max) = 2.12 MeV), has a half-life of 17 h and is available from a $^{188}W/^{188}Re$ radionuclide generator at no carrier added levels.[1−5] Because of its excellent physical properties, relatively low cost, and ready availability in high specific activities, Re-188 has become a logical choice for the development of biomolecular labeled radiopharmaceuticals for use in the treatment of cancer *via* site-specific or tumor-directed therapy.[6,7] There is also considerable interest in labeling monoclonal antibodies and small peptides with ^{99m}Tc for the development of new diagnostic imaging agents for use in the early detection of cancer.[8] Technetium-99m is a γ-emitting radionuclide (E_γ = 140 keV), has a half-life of 6.02 h, and is available from a $^{99}Mo/^{99m}Tc$ generator system.[9] Its ideal physical properties, low cost, and ready availability make it the most widely used radioisotope for diagnostic applications in nuclear medicine.[10,11] When effective site-specific therapeutic or diagnostic radiopharmaceuticals are developed, many important factors must be considered. It is essential that the metallic radionuclide (e.g. Re-188 or Tc-99m), upon interaction with a bifunctional chelating agent, should form an *in vivo* stable complex in high specific activities with 1:1 metal to ligand stoichiometry. These

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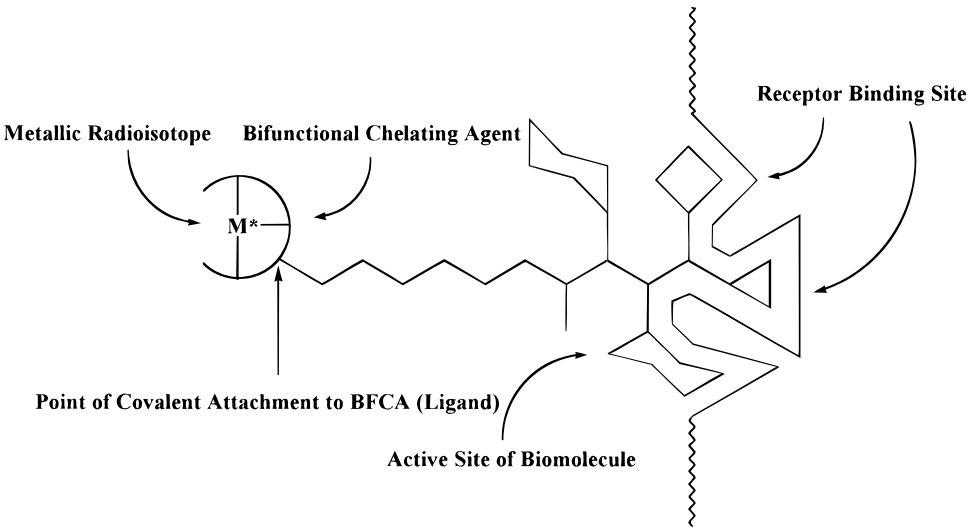

Figure 1. Representative model of radiolabeling bioactive molecules.

stringent requirements restrict the choice to only a few ligand backbones and, therefore, necessitate the design and development of new bifunctional chelating agents. Most importantly, a detailed understanding of the coordination chemistry of new ligand systems with nonradioactive rhenium is important for the subsequent extension of these reactions at the tracer levels to label bifunctional chelating agents using Re-188.

Functionalized phosphines constitute an important family of ligands for use in nuclear medicine. For example, the Tc-99m-based radiopharmaceuticals Tetrafosmin and Technecard, which are currently being used as *in vivo* heart imaging agents, are derived from bischelating and monochelating phosphines of the type $(EtO(CH_2)_2)_2P(CH_2)_2P((CH_2)_2OEt)_2$ and $P(CH_2CH_2OCH_3)_3$, respectively.[12−14] Studies by Deutsch et al. have demonstrated that technetium (or rhenium) forms *in vivo* stable and kinetically inert bonds with phosphines.[14−19] Therefore, new developments in the design of phosphine ligands may aid in the discovery of new, performance-effective, radiopharmaceuticals. In particular, the synthesis of functionalized phosphine frameworks that would result in the formation of Tc-99m or Re-188 complexes with 1:1 metal to ligand stoichiometries becomes important in the context of design and development of radiopharmaceuticals produced *via* the labeling of specific biomolecules (e.g. peptides or proteins), for use in tumor-specific diagnosis or therapy of human metastases. In this approach of designing diagnostic or therapeutic radiopharmaceuticals, it is important that the bifunctional chelating agent (ligand) be bound to a point of the biomolecule away from the active site (e.g. amino acid sequence necessary for receptor binding). Radiolabeling of the biomolecule/ligand complex with Tc-99m or Re-188 can then be carried out *via* strong covalent interactions of the metal center with specific donor atoms of the ligand, with no destruction of receptor specificity (Figure 1). Simple aryl- or alkyl-functionalized phosphines (e.g. PPh_3 or $(H_3C)_2PCH_2CH_2P(CH_3)_2$) produce strong and *in vivo* stable metal−phosphorus bonds. However, they are unsuited for use in the design of biomolecular labeled radiopharmaceuticals because, most often, the coordination chemistry of these ligands produces complexes with more than one ligand per metal center. The chemical modifications of $(H_3C)_2PCH_2CH_2P(CH_3)_2$ (dmpe) and other related alkylphosphines present difficulties in forming complexes with one ligand per metal center. Furthermore, their oxidative instability and pyrophoric nature limit their use in the development of bifunctional chelating agents *via* ligand modification reactions. Several groups have investigated the coordination chemistry of technetium and rhenium with sulfur/nitrogen- and phosphine-containing ligands.[20−22] However, the presence of bulky aryl substituents on the phosphines often limits their degree of solubility in aqueous solutions, making them unsuitable for bifunctional chelating agents.

Our recent studies have demonstrated that a new class of chelating bis(phosphine)s of the type $((HOH_2C)_2PCH_2CH_2P(CH_2OH)_2$ (bis((hydroxymethyl)phosphino)ethane, HMPE) and $(HOH_2C)_2PC_6H_4P(CH_2OH)_2$ (bis((hydroxymethyl)phosphino)-benzene, HMPB) are oxidatively stable in air and also in aqueous solutions.[23,24] These properties coupled with the high *in vitro*/*in vivo* stability of Tc-99m complexes derived from HMPE and HMPB presented prospects for further modification of (hydroxymethyl)phosphine-based ligands.[24] As part of our ongoing studies in the design and development of functionalized phosphines[23−32] for use in nuclear medicine, we report herein

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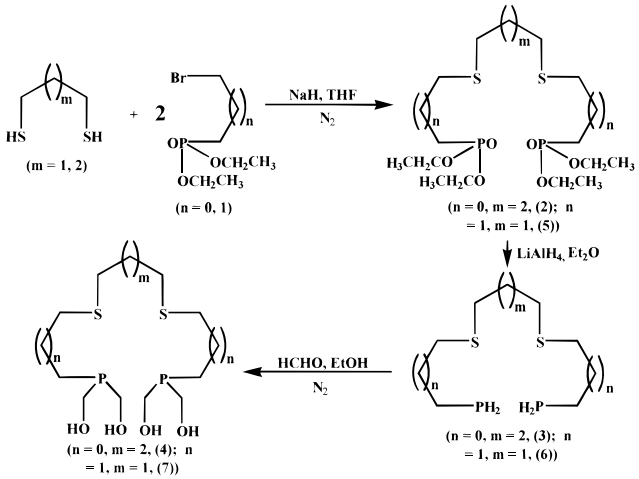
Scheme 1



(a) the synthesis of a new series of water-soluble ligands based on dithio−bis(phosphine) backbones, 1,3-bis((bis((hydroxymethyl)phosphino)ethyl)thio)propane, $(HOH_2C)_2P(CH_2)_2S(CH_2)_3S(CH_2)_2P(CH_2OH)_2$ (**1**), 1,4-bis((bis((hydroxymethyl)phosphino)ethyl)thio)butane, $(HOH_2C)_2PCH_2CH_2S(CH_2)_4SCH_2CH_2P(CH_2OH)_2$ (**4**), and 1,3-bis((bis((hydroxymethyl)phosphino)propyl)thio)propane, $(HOH_2C)_2PCH_2CH_2CH_2S(CH_2)_3SCH_2CH_2CH_2P(CH_2OH)_2]$ (**7**), (b) their coordination chemistry with Re(V), demonstrating the importance of ligand chain size in producing complexes with 1:1 metal to ligand ratios, and (c) X-ray crystal structures of $[ReO_2(HOH_2C)_2P(CH_2)_2S(CH_2)_3S(CH_2)_2P(CH_2OH)_2]_2(Cl)_2$ (**8**), $[ReO_2(HOH_2C)_2P(CH_2)_2S(CH_2)_4S(CH_2)_2P(CH_2OH)_2]_2(ReO_4^-)_2$ (**9**), and $[ReO_2(HOH_2C)_2P(CH_2)_3S(CH_2)_3S(CH_2)_3P(CH_2OH)_2](Cl)$ (**10**). *In vitro* studies demonstrating the kinetic inertness of new water-soluble Re(V) complexes derived from dithio−bis(phosphine) ligands are also described.

Results and Discussion

The syntheses of the thioether-functionalized bis(phosphine)s **1**, **4**, and **7** were accomplished in a two-step procedure (Scheme 1). The dithio−bis(phosphine) **1** was synthesized as previously reported and used without further purification.[32] The thioether-functionalized bisphosphonates $(EtO)_2(O)PCH_2CH_2S(CH_2)_4SCH_2CH_2P(O)(OEt)_2$ (**2**) and $(EtO)_2(O)PCH_2CH_2CH_2S(CH_2)_3SCH_2CH_2CH_2P(O)(OEt)_2$ (**5**) were prepared *via* the reactions of the dithiols $HS(CH_2)_4SH$ and $HS(CH_2)_3SH$ with the appropriate phosphonate precursors $BrCH_2CH_2P(O)(OEt)_2$ and $BrCH_2CH_2CH_2P(O)(OEt)_2$ in the presence of NaH in freshly distilled THF. The phosphine hydrides $H_2PCH_2CH_2S(CH_2)_4SCH_2CH_2PH_2$ (**3**) and $H_2PCH_2CH_2CH_2S(CH_2)_3SCH_2CH_2CH_2PH_2$ (**6**) were prepared by reduction of the bisphosphonates **2** and **5** in diethyl ether using lithium aluminum hydride. The (hydroxymethyl)phosphine ligands **4** and **7** were prepared by formylation of the P−H bonds of **2** and **5** in oxygen-free ethanol in the presence of aqueous formaldehyde.

The new compounds **2**−**7** were characterized by ^1H, ^{13}C, and ^{31}P NMR spectroscopy. For characterization purposes, **4** and **7** were converted to their corresponding phosphonium salts in the presence of excess formaldehyde and 3 N HCl (eq 1). Fast

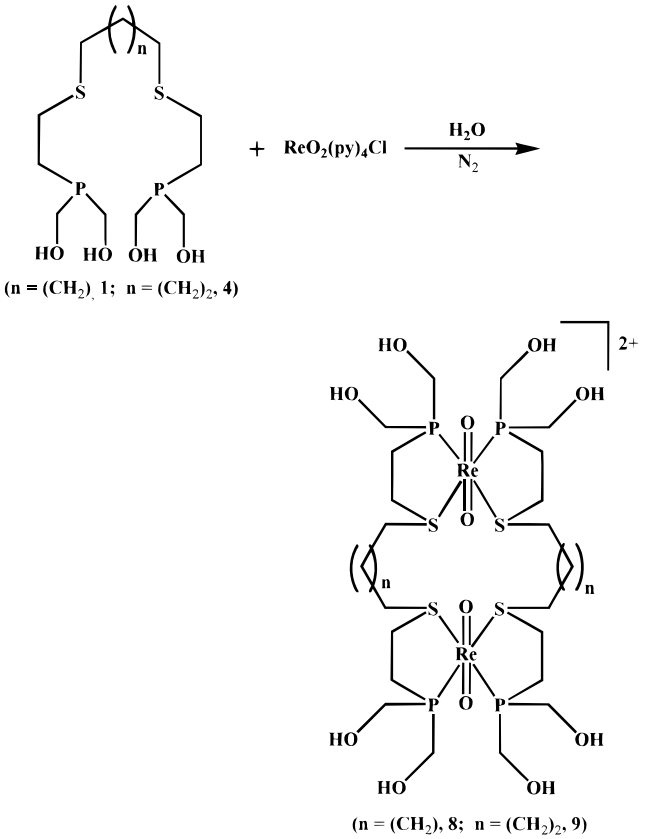
$$(HOH_2C)_2P(CH_2)_XS(CH_2)_YS(CH_2)_XP(CH_2OH)_2 + 2HCHO + 2HCl \rightarrow [(HOH_2C)_3P(CH_2)_XS(CH_2)_YS(CH_2)_XP(CH_2OH)_3]Cl_2 \quad (1)$$

$$X = 2, 3; Y = 3, 4$$

atom bombardment mass spectrometry was used to identify the molecular ions for all of the compounds, excluding the bis(phosphine) hydrides **3** and **6**. Parent ions at $[M + H^+]$ (*m/z* 451.2) and $[M + H^+]$ (*m/z* 465.2) were observed for the bisphosphonate compounds **2** and **5**. The new (hydroxymethyl)phosphine ligands **4** and **7** show parent ions at $[M + H^+]$ (*m/z* 395.1) and $[M + H^+]$ (*m/z* 409.1) corresponding to the phosphine oxides, respectively. Compounds **2** and **5** resonate as singlet signals at 29.4 and 31.8 ppm in the ^{31}P NMR spectrum. The formation of the thioether-functionalized bis(phosphine) hydrides **3** and **6** from their corresponding bisphosphonates **2** and **5** were monitored by ^{31}P NMR spectroscopy. The phosphine hydrides **3** and **6** resonate as singlet signals in the ^{31}P NMR spectrum at −136.8 and −137.5 ppm, respectively. The dithio−bis(phosphine) ligands **4** and **7** resonate as singlet signals in the ^{31}P NMR spectrum at −25.5 and −25.6 ppm, respectively.

The water solubility of ligands **1**, **4**, and **7** necessitated the development of their coordination chemistry in aqueous media. Interaction of compound **1** with $[ReO_2(C_5H_5N)_4](Cl)$, in refluxing water, produced the dicationic complex $[ReO_2(HOH_2C)_2P(CH_2)_2S(CH_2)_3S(CH_2)_2P(CH_2OH)_2]_2(Cl)_2$ (**8**) in 84% yield (Scheme 2). The total reaction time was ∼30 min. The chemical constitution of **8** was verified by ^1H, ^{13}C, and ^{31}P NMR spectroscopic data as well as elemental analyses. Compound **8** resonates as a singlet signal at 38.6 ppm in the ^{31}P NMR spectrum.

Scheme 2



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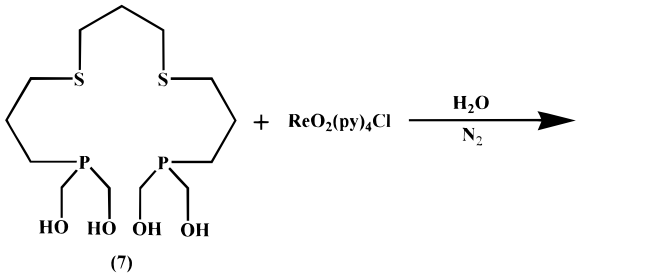
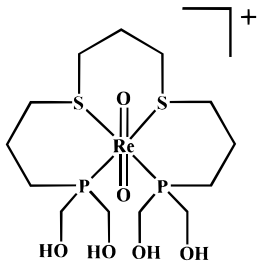
Scheme 3



(7)



(10)

Interaction of compound **4** with $[ReO_2(C_5H_5N)_4](Cl)$, in refluxing water produced the dicationic complex $[ReO_2(HOH_2C)_2P(CH_2)_2S(CH_2)_4S(CH_2)_2P(CH_2OH)_2]_2(ReO_4^-)_2$ (**9**) in 40% yield (Scheme 2). The total reaction time was ∼30 min. The ReO_4^- counterions arise from the presumed oxidation of $[Re^VO_2(C_5H_5N)_4](Cl)$ under such reaction conditions. ^1H, ^{13}C, and ^{31}P NMR spectroscopic data as well as elemental analyses complement its chemical constitution. Compound **9** resonates as a singlet signal at 37.5 ppm in the ^{31}P NMR spectrum.

Compound **7** in water, upon interaction with $[ReO_2(C_5H_5N)_4](Cl)$ in refluxing water, produced the cationic complex $[ReO_2(HOH_2C)_2P(CH_2)_3S(CH_2)_3S(CH_2)_3P(CH_2OH)_2](Cl)$ (**10**) in 80% yield (Scheme 3). The total reaction time was ∼30 min. The chemical constitution of **10** was confirmed by ^1H, ^{13}C, and ^{31}P NMR spectroscopic data and elemental analyses. Compound **10** resonates at −8.6 ppm in the ^{31}P NMR spectrum.

All of the complexes **8**−**10** were analyzed by HPLC in order to further establish the purity of the complexes. Each of the complexes eluted as a singular species, demonstrating ∼98% purity.

X-ray Crystallographic Investigations of 8−**10.** X-ray crystallographic analysis of **8** enabled us to further determine the molecular composition of this compound. Slow evaporation of a methanol/diethyl ether (4:1) solution of **8** produced single crystals suitable for X-ray crystallographic analysis. An ORTEP diagram of **8** is shown in Figure 2. Selected bond distances and bond angles are listed in Table 2. The asymmetric unit consists of one dinuclear complex $[ReO_2(HOH_2C)_2P(CH_2)_2S(CH_2)_3S(CH_2)_2P(CH_2OH)_2]_2$, two chloride anions, and one water molecule. There are no unusual *inter*- or *intra*molecular interactions. The geometry around the rhenium centers is octahedral. The structure reveals a bimetallic complex with the two metal centers sharing two, coordinating, ligands. As revealed by the structure, the phosphorus and sulfur atoms at one end of each ligand are coordinated to a metal center in a chelating fashion, while the phosphorus and sulfur atoms at the other end of the same ligand are coordinated to the second metal center. At each metal center, coordination occurs in a *cis* arrangement of two five-membered $PCH_2CH_2SRe^V$ metallacycles. The two oxygen atoms of the dioxorhenium center are essentially *trans* to one another. The Re(1)−P(1) and Re(1)−P(4) distances are 2.411(9) and 2.405(10) Å. The Re(2)−P(2) and Re(2)−P(3) distances are 2.396(10) and 2.400(9) Å. The Re(1)−S(1) and Re(1)−S(4) distances are 2.534(9) and 2.554(9) Å. The Re(2)−S(2) and Re(2)−S(3) distances are 2.534(9) and 2.580(10) Å, respectively. The average P−Re−P bond angle is 100.01°. The average S−Re−S bond angle is 95.93°. The average of the four P−Re−S bond angles is 82.09°, respectively.

Slow evaporation of a water/methanol (4:1) solution of **9** afforded crystals of suitable quality for X-ray crystallographic analysis. The crystal structure analysis reveals formation of a bimetallic complex similar to that of **8**. The asymmetric unit consists of two unique halves of the complex and two unique perrhenate anions. Each of the complex cations is situated on an inversion center, while the perrhenate anions occupy general positions in the unit cell. The two unique complexes exhibit similar coordination geometries, and an ORTEP diagram of one complete dinuclear dication is shown in Figure 3. Selected bond distances and bond angles are listed in Table 3. The octahedral geometry around the metal centers is defined by coordination of one set of P^{III} and S from two different ligands in a *cis* arrangement to produce the bimetallic Re(V) complex with four $PCH_2CH_2SRe^V$ five-membered metallacycles. The two oxygen atoms of the dioxorhenium center are essentially *trans* to one another. The Re(1a)−P(1a) and Re(1a)−P(2a) distances are 2.414(3) and 2.410(3) Å. The Re(1b)−P(1b) and Re(1b)−P(2b) distances are 2.405(3) and 2.421(3) Å. The Re(1a)−S(1a) and Re(1a)−S(2a) distances are 2.515(3) and 2.536(3) Å. The Re(1b)−S(1b) and Re(1b)−S(2b) distances are 2.538(3) and 2.510(3) Å, respectively. The average P−Re−P bond angle is 101.17°. The average S−Re−S bond angle is 95.11°. The average of the four P−Re−S bond angles is 82.20°, respectively.

The molecular structure of compound **10** was also confirmed by X-ray crystallographic analysis. An ORTEP diagram of **10** is shown in Figure 4, and the selected bond distances and bond angles are listed in Table 4. There are no unusual *inter*- or *intra*molecular interactions. The structure reveals **10** as a monometallic-monoligated complex. The geometry around the rhenium center is octahedral with the metal flapped across P^{III} and S in a *cis* arrangement to produce three six-membered metallacycles. As revealed by the structure, the two oxygen atoms of the dioxorhenium center are essentially *trans* to one another. The Re−P(1) and Re−P(2) distances are 2.425(10) and 2.418 Å. The Re−S(1) and Re−S(2) distances are 2.550(10) and 2.532(10) Å, respectively. The P−Re−P bond angle is 100.84(3)°. The S−Re−S bond angle is 88.10(4)°. The P(1)−Re−S(1) and P(2)−Re−S(2) bond angles are 84.07(3) and 87.02(4)°, respectively.

Conformation of Rings in Rhenium(V) Complexes Derived from 2−3−2, 2−4−2 (Compounds 8 and 9), and 3−3−3 (Compound 10) Dithio−Bis(phosphine) Backbones. Despite the large differences in the Re−S, S−C, C−C, C−P, and P−Re bond distances, the Cremer and Pople treatment[33] is sufficiently general to characterize the puckering of the rings formed in complexes **8**−**10**. The relevant puckering parameters were calculated using the program PARST[34] and are given in Table 5. This plane can be considered to be a rigid reference for each ring by virtue of the near-planar coordination of the sulfur and phosphorus atoms about the metal center, while the constraints on the S−C, C−C, and P−C bonds give rise to ring distortion.

In complex **8**, each of the four unique five-membered rings Re(1)−P(1)−C(3)−C(4)−S(1), Re(1)−P(4)−C(20)−C(19)−S(4), Re(2)−P(3)−C(14)−C(15)−S(3), and Re(2)−P(2)−C(9)−C(8)−S(2) can be described as envelopes with flaps derived from C(3)−C(4), C(19)−C(20), C(8)−C(9), and C(14)−C(15)

(34) Nardelli, M. *Comput. Chem.* **1983**, *7*(3), 95.

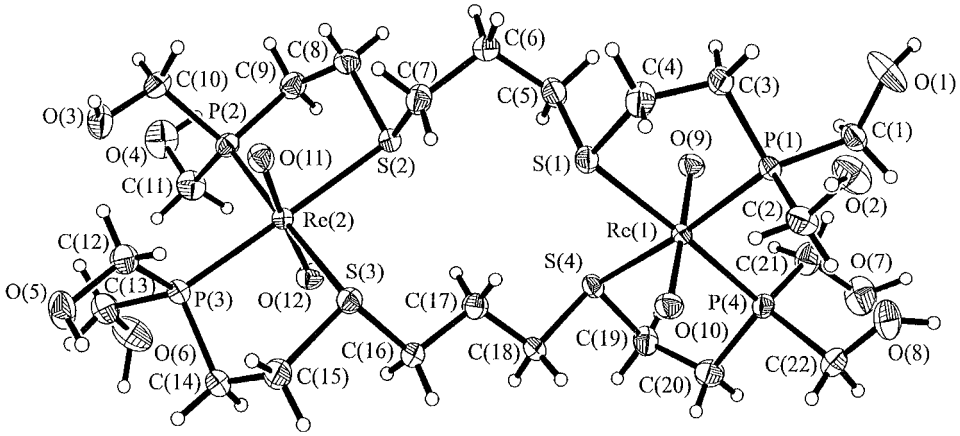


Figure 2. ORTEP drawing of **8**, showing 50% probability ellipsoids.

Table 1. Crystal Data for Complexes **8**−**10**

formula	$C_{22}H_{54}Cl_2O_{13}P_4Re_2S_4$ (**8**)	$C_{24}H_{56}O_{20}P_4Re_4S_4$ (**9**)	$C_{14}H_{34}ClO_7P_2ReS_2$ (**10**)
space group	$P2_1/c$	$P\bar{1}$	$P2_1/n$
fw	1222.07	1661.61	662.15
a, Å	10.7982(5)	10.3762(5)	10.6224(6)
b, Å	23.486(1)	12.1099(6)	12.5532(8)
c, Å	15.4408(8)	18.7555(9)	18.5767(11)
α, deg	90	90.259(1)	90
β, deg	94.539(1)	91.900(1)	103.663(10)
γ, deg	90	104.965(1)	90
T, K	293(2)	293(2)	293(2)
λ, Å	0.7107	0.7107	0.7107
Z	4	2	4
F(000)	2392	1568	1240
V, Å^3	3905.1(3)	2275.3(2)	2407.0(2)
ρ_{calc}, g/cm^3	2.079	2.425	1.739
T_{max}	0.0568	1	1
T_{min}		0.474	0.8147
ρ_{obsd}, g/cm^3	not measd	not measd	not measd
μ, mm^{-1}	6.764	10.999	5.488
R1, wR2[a]	0.0246, 0.0574	0.0546, 0.1412	0.0261, 0.0656

[a] $R1 = \sum||F_o| - |F_c||/\sum|Fo|$. $wR2(SHELXL\text{-}93) = [\sum w(F_o^2 - F_c^2)^2/\sum w(F_o^2)^2]^{1/2}$. Weighting scheme: $w = 1/[\sigma^2(F_o)^2 + (np)^2 + 0.00p]$, $p = (\max(F_o^2) + 2F_c^2)/3$.

Table 2. Selected Bond Distances (Å) and Angles (deg) for **8**

Re(1)−O(10)	1.774(3)	Re(1)−O(9)	1.775(3)
Re(1)−P(4)	2.405(10)	Re(1)−P(1)	2.411(9)
Re(1)−S(4)	2.554(9)	Re(1)−S(1)	2.534(9)
Re(2)−O(12)	1.763(3)	Re(2)−O(11)	1.781(3)
Re(2)−P(3)	2.400(9)	Re(2)−P(2)	2.396(10)
Re(2)−S(3)	2.580(10)	Re(2)−S(2)	2.534(9)
O(10)−Re(1)−O(9)	178.47(12)	O(12)−Re(2)−O(11)	174.25(13)
P(4)−Re(1)−P(1)	100.34(3)	P(2)−Re(2)− P(3)	99.68(3)
S(1)−Re(1)−S(4)	95.90(3)	S(2)−Re(2)−S(3)	95.95(3)
P(1)−Re(1)−S(1)	81.92(3)	P(2)−Re(2)−S(2)	82.79(3)
P(4)−Re(1)−S(4)	82.07(3)	P(3)−Re(2)−S(3)	81.57(3)

respectively. Each of the four rings are in the same molecule of the asymmetric unit.

The structure of the 2−4−2 S_2P_2 Re complex **9** has four unique five-membered rings, two each in the half-molecules, constituting the asymmetric unit. The conformations of rings in complex **9** are essentially similar to those described for **8**, except that ring 4, consisting of Re(1b)−P(2b)−C(8b)−C(7b)−S(2b), may best be described as a twisted envelope (therefore no flap).

The three six-membered rings in complex **10**, Re(1)−P(1)−C(1)−C(2)−C(3), Re(1)−S(1)−C(4)−C(5)−C(6)−S(2), and Re(1)−S(2)−C(7)−C(8)−C(9)−P(2), are in the distorted-chair, half-chair, and distorted-chair conformations, respectively.

***In Vitro* Stability Studies of 8, 9, and 10.** In order to determine the *in vitro* stability of the rhenium S_2P_2 complexes **8**−**10**, the solutions of each were incubated at 25 °C in an aqueous solution of cysteine. Cysteine is a typical model chosen for these particular studies as a number of potential metal-chelating thiol functionalities are present *in vivo* (e.g. serum proteins and glutathione). Typically, compounds **8**−**10** (∼0.01 M) were allowed to interact with a 1 M cysteine solution. ^{31}P NMR spectroscopic data for aliquots of each sample, taken at different time intervals, indicated no observable ligand exchange or complex decomposition. ^{31}P NMR spectra of **8**−**10** over a 24 h time period demonstrated the unusual kinetic inertness of this class of Re(V) water-soluble complexes.

Conclusions

It is important to recognize that the reactions described in Schemes 2 and 3 are regio- and stereoselective, yielding bimetallic complexes with octahedral coordination around Re(V) (e.g. compounds **8** and **9**) and an octahedrally coordinated monometallic complex of Re(V) (e.g. compound **10**), respectively. The fact that no traces of a bimetallic complex (of the type in **8** or **9**) were observed in the reaction of the 3−3−3 S_2P_2 ligand **7** with $[ReO_2(C_5H_5N)_4](Cl)$ (Scheme 3), even in the presence of excess ligand, demonstrates a strong kinetic propensity for forming the monometallic Re(V) complex **10** *via* the six-membered metallacycles. However, in sharp contrast, reactions of the 2−3−2 and 2−4−2 S_2P_2 ligands **1** and **4** with $[ReO_2(C_5H_5N)_4](Cl)$, as described in Scheme 2, produced the bimetallic complexes **8** and **9** as the singular chemical species with no traces of a monometallic complex of the type **10**. These observations signify the importance of ligand chain length, particularly the alkane chain size separating the P^{III} and S centers, on the overall coordination chemistry with Re(V).

Preliminary studies of the reactions of the P_2S_2 ligand **7** with $^{99m}TcO_4^-$ and ^{99m}Tc-citrate indicate the formation of the corresponding ^{99m}Tc complexes in ∼98% yield. Biodistribution studies of this complex in Sprague-Dawley rats indicate its high *in vivo* stability and efficient clearance from the body. Liquid chromatographic studies of urinary samples excised from the bladder further demonstrated the *in vivo* stability as well as lack of decomposition of the complex.[35] Further studies are currently under way to functionalize the S_2P_2 ligands with active sites (e.g. −COOH or −NCS) so that these ligands and their ^{188}Re/^{99m}Tc complexes can be incorporated on specific biomolecules as part of our ultimate objective in the design and development of biomolecular labeled radiopharmaceuticals for use in cancer diagnosis and therapy.

(35) Smith, C. J.; Katti, K. V.; Volkert, W. A. *Nucl. Med. Biol*., in press.

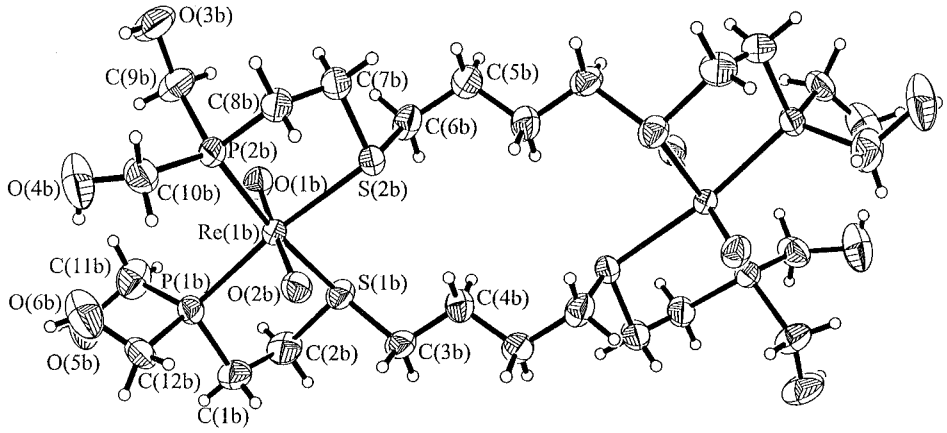


Figure 3. ORTEP drawing of **9**, showing 50% probability ellipsoids.

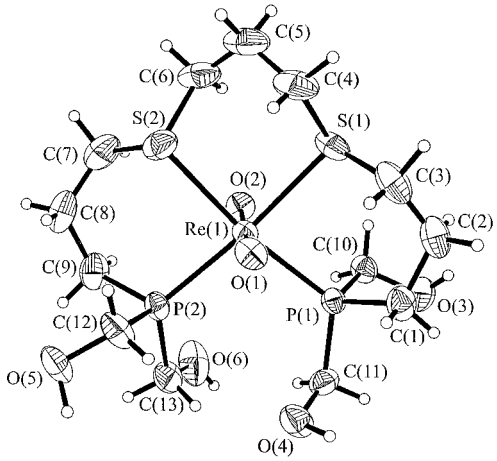


Figure 4. ORTEP drawing of **10**, showing 50% probability ellipsoids.

Table 3. Selected Bond Distances (Å) and Angles (deg) for **9**

Re(1a)−O(1a)	1.754(8)	Re(1a)−O(2a)	1.798(8)
Re(1a)−P(1a)	2.414(3)	Re(1a)−P(2a)	2.410(3)
Re(1a)−S(1a)	2.515(3)	Re(1a)−S(2a)	2.536(3)
Re(1b)−O(1b)	1.749(7)	Re(1b)−O(2b)	1.786(7)
Re(1b)−P(1b)	2.405(3)	Re(1b)−P(2b)	2.421(3)
Re(1b)−S(1b)	2.538(3)	Re(1b)−S(2b)	2.510(3)
O(1a)−Re(1a)−O(2a)	177.2(3)	O(1b)−Re(1b)−O(1b)	176.1(4)
P(1a)−Re(1a)−P(2a)	99.67(10)	P(1b)−Re(1b)−P(2b)	102.66(10)
S(1a)−Re(1a)−S(2a)	95.98(9)	S(1b)−Re(1b)−S(2b)	94.23(9)
P(1a)−Re(1a)−S(1a)	81.76(9)	P(1b)−Re(1b)−S(1b)	82.80(10)
P(2a)−Re(1a)−S(2a)	83.18(9)	P(2b)−Re(1b)−S(2b)	81.07(9)

Table 4. Selected Bond Distances (Å) and Angles (deg) for **10**

Re−O(1)	1.757(3)	Re−O(2)	1.782(3)
Re−P(1)	2.425(10)	Re−P(2)	2.418(10)
Re−S(1)	2.550(10)	Re−S(2)	2.532(11)
O(1)−Re−O(2)	174.70(12)	P(1)−Re−P(2)	100.84(3)
S(1)−Re−S(2)	88.10(4)	P(2)−Re−S(2)	87.02(4)
P(1)−Re−S(1)	84.07(3)	P(1)−Re−S(2)	172.03(4)
P(2)−Re−S(1)	174.98(3)		

Experimental Section

All reactions were carried out under purified nitrogen by standard Schlenk techniques. Solvents were purified by standard methods and distilled under nitrogen prior to use. $(HOH_2C)_2P(CH_2)_2S(CH_2)_3S(CH_2)_2P(CH_2OH)_2$ (**1**) was synthesized as previously described and used without further purification.[32] $[ReO_2(C_5H_5N)_4](Cl)$ was prepared according to the literature procedure and used without further purification.[36] $Br(CH_2)_3PO(OC_2H_5)_2$ was synthesized by refluxing $P(OEt)_3$ in 10 mol excess of $Br(CH_2)_3Br$ for 1 h and then purified by vacuum distillation. Nuclear magnetic resonance spectra were recorded on a Bruker ARX-300 spectrometer using D_2O and $CDCl_3$ as solvents. The ^1H and ^{13}C chemical shifts are reported in ppm, downfield from internal standard $SiMe_4$. The ^{31}P NMR (121.5 MHz) spectra were recorded with 85% H_3PO_4 as an external standard, and positive chemical shifts lie downfield of the standard. Elemental analyses were performed by Oneida Research Services, Inc., Whitesboro, NY. The C and H analyses of ligands **1**, **4**, and **7** are not listed, as purities within the tolerance of 0.3% were unobtainable. This is presumably due to the presence of occluded water in the hydrophilic ligand frameworks. Mass spectral analyses were performed by the Washington University Resource for Biomedical and Bio-Organic Mass Spectrometry, St. Louis, MO.

Synthesis of $(EtO)_2(O)PCH_2CH_2S(CH_2)_4SCH_2CH_2P(O)(OEt)_2$ (2). A sample of 60% NaH in mineral oil (188 mmol) was placed in a two-neck round-bottom flask that was then charged with dry hexane (20 mL). This solution was stirred for 10 min, after which the hexane−mineral oil layer was removed by syringe. The flask was charged with dry tetrahydrofuran (100 mL), followed by dropwise addition of $HS(CH_2)_4SH$ (82 mmol) with constant stirring. The resulting solution was cooled to 0 °C, and $BrCH_2CH_2P(O)(OC_2H_5)_2$ (164 mmol) was added dropwise with constant stirring over a period of 30 min. Excess NaH was quenched by addition of 50 mL of deionized water. The solution was extracted from ethyl acetate (3 × 50 mL) and washed with a saturated sodium chloride solution. The organic layer was dried over anhydrous sodium sulfate. Upon filtration, the solvent was removed *in vacuo* to afford **2** in 90% yield along with a trace amount of diethyl vinylphosphonate. The compounds were separated on a silica gel column (20 cm; 60 mesh) using a 90:10 ethyl acetate to hexane solvent mixture. Removal of the solvent *in vacuo* afforded compound **2** as a viscous, yellow-green oil with an overall yield of 92% (36 g). Low-resolution FAB/MS: calcd for $C_{16}H_{36}O_6P_2S_2$ 450.1428, found [M + H^+], *m/z* 451.2. ^1H NMR ($CDCl_3$): δ 1.34 (t, $^3J_{HH}$ = 7.5 Hz, 12H, OCH_2CH_3), 1.70 (bs, 4H, $SCH_2CH_2CH_2CH_2S$), 2.03 (m, 4H, PCH_2CH_2), 2.56 (bs, 4H, $SCH_2CH_2CH_2CH_2S$), 2.72 (m, 4H, PCH_2CH_2), 4.11 (m, 8H, OCH_2CH_3). ^{13}C NMR ($CDCl_3$): δ 16.1 (d, $^3J_{PC}$ = 5.3 Hz, OCH_2CH_3), 24.5 (d, $^2J_{PC}$ = 3.8 Hz, PCH_2CH_2), 26.4 (d, $^1J_{PC}$ = 136.6 Hz, PCH_2CH_2), 27.9 (s, $SCH_2CH_2CH_2CH_2S$), 31.1 (s, $SCH_2CH_2CH_2CH_2S$), 61.4 (d, $^2J_{PC}$ = 6.8 Hz, OCH_2CH_3). ^{31}P NMR ($CDCl_3$): δ 29.4 (s).

Synthesis of $H_2PCH_2CH_2S(CH_2)_4SCH_2CH_2PH_2$ (3). Compound **2** (31 mmol) was placed in 75 mL of dry diethyl ether and cooled to 0 °C. An ether solution of 1.0 M lithium aluminum hydride (78 mmol, 78 mL) was slowly added dropwise to this solution with constant stirring. After reaction completion was verified (^{31}P NMR), an aqueous solution of 6 N hydrochloric acid (50 mL) was added dropwise to the solution to quench any remaining $LiAlH_4$. The ether layer was separated by cannula, and the solvent was removed *in vacuo* to afford **3** in 92% yield (7.8 g) as a colorless, viscous oil. ^1H NMR ($CDCl_3$): δ 1.68 (m, 4H, PCH_2CH_2), 1.76 (m, 4H, $SCH_2CH_2CH_2CH_2S$), 2.54 (m, 4H, $SCH_2CH_2CH_2CH_2S$), 2.68 (m, 4H, PCH_2CH_2), 2.75 (dt, 4H, $^1J_{PH}$ = 195 Hz, PH_2). ^{13}C NMR ($CDCl_3$): δ 14.5 (d, $^1J_{PC}$ = 10.6 Hz, PCH_2CH_2), 28.1 (s, $SCH_2CH_2CH_2CH_2$), 31.0 (s, $SCH_2CH_2CH_2CH_2S$), 34.7 (d, $^2J_{PC}$ = 1.5 Hz, PCH_2CH_2). ^{31}P NMR ($CDCl_3$): δ −136.8 (s).

Synthesis of $(HOH_2C)_2PCH_2CH_2S(CH_2)_4SCH_2CH_2P(CH_2OH)_2$ (4). Aqueous formaldehyde (124 mmol) was placed in 50 mL of

(36) Beard, J. H.; Casey, J.; Murmann, R. K. *Inorg. Chem*. **1965**, *4*, 797.

Table 5. Out-of-Plane Ring Vibration (Puckering) Parameters[a]

complex	ring	q_2 (Å)	q_3 (Å)	ϕ_2 (deg)	Q (Å)	θ (deg)	conformation
8	Re(1)−P(1)−C(3)*−C(4)−S(1)	0.499(4)		67.1(3)			E
	Re(1)−P(4)−C(20)*−C(19)−S(4)	0.462(4)		68.3(3)			E
	Re(1)−P(2)−C(9)−C(8)*−S(2)	0.499(4)		−71.7(3)			E
	Re(1)−P(3)−C(14)*−C(15)−S(3)	0.543(3)		55.6(30)			E
9	Re(1A)−P(1A)−C(1A)−C(2A)*−S(1A)	0.33(2)		136(3)			E
	Re(1A)−P(2A)−C(8A)*−C(7A)−S(2A)	0.49(1)		−107.4(8)			E
	Re(1B)−P(1B)−C(1B)*−C(2B*−S(1B)	0.48(1)		−103.1(9)			E
	Re(1B)−P(2B)−C(8B)−C(7B)−S(2B)	0.53(1)		85.8(7)			T
10	Re(1)−P(1)−C(1)−C(2)−C(3)−S(1)	0.257(4)	−0.834(4)	150.3(9)	0.873(3)	162.9(3)	C
	Re(1)−S(1)−C(4)−C(5)−C(6)−S(2)	1.083(4)	0.031(4)	−87.8(2)	1.083(4)	88.3(2)	H
	Re(1)−S(2)−C(7)−C(8)−C(9)−P(2)	0.125(4)	0.756(4)	47(2)	0.766(3)	9.4(3)	C

[a] Definitions: q_2, q_3 = puckering amplitudes; ϕ_2 = phase angle; Q = total puckering amplitude; $\theta = 0-2\pi$, such that $q_2 = Q \sin\theta$ and $q_3 = Q \cos\theta$; C = chair; H = half-chair; E = envelope; T = twisted envelope (the asterisk indicates flap).

oxygen-free ethanol and purged with nitrogen gas for 2 h at 25 °C. Compound **3** (29 mmol) was added dropwise to the solution *via* syringe with constant stirring at 25 °C. The reaction was complete in 1 h, as monitored by ^{31}P NMR spectroscopy. Removal of the solvent *in vacuo* afforded compound **4** in 93% yield (10.5 g) as a colorless, viscous oil. Low-resolution FAB/MS: calcd for $C_{12}H_{28}O_4P_2S_2$ 362.1, found [M + H$^+$], *m/z* 395.1. ^{31}P NMR (D_2O): δ −25.5 (s). For characterization purposes, the (hydroxymethyl)phosphine **4** was converted to its corresponding phosphonium chloride salt by addition of 3 N HCl. The reaction mixture was concentrated *in vacuo* and loaded onto a Waters Sep-Pak 35 cm^{-3} (10 g) C18 cartridge. The pure phosphonium salt was isolated as a clear, viscous oil. ^{1}H NMR (D_2O): δ 1.54 (m, 4H, $SCH_2CH_2CH_2CH_2S$), 2.52 (m, 4H, $SCH_2CH_2CH_2CH_2S$), 2.59 (m, 4H, PCH_2CH_2), 2.81 (m, 4H, PCH_2CH_2), 4.53 (m, 12H, PCH_2OH). ^{13}C NMR (D_2O): δ 14.9 (d, $^1J_{PC}$ = 37.7 Hz, PCH_2CH_2), 22.7 (d, $^2J_{PC}$ = 5.3 Hz, PCH_2CH_2), 27.2 (s, $SCH_2CH_2CH_2CH_2S$), 30.2 (s, $SCH_2CH_2CH_2CH_2S$), 50.3 (d, $^1J_{PC}$ = 52.8 Hz, PCH_2OH). ^{31}P NMR (D_2O): δ 28.3 (s).

Synthesis of $(EtO)_2(O)PCH_2CH_2CH_2S(CH_2)_3SCH_2CH_2CH_2P(O)(OEt)_2$ (5). A sample of 60% NaH in mineral oil (184 mmol) was placed in a two-neck round-bottom flask and charged with dry hexane (20 mL). This solution was stirred for 10 min, after which the hexane−mineral oil layer was removed by syringe. The flask was charged with dry tetrahydrofuran (100 mL), followed by dropwise addition of $HS(CH_2)_3SH$ (92 mmol) with constant stirring. The resulting solution was cooled to 0 °C, and $BrCH_2CH_2CH_2P(O)(OC_2H_5)_2$ (184 mmol) was added dropwise with constant stirring over a period of 30 min. Excess NaH was quenched by addition of 50 mL of deionized water. The solution was extracted from ethyl acetate (3 × 50 mL) and washed with a saturated sodium chloride solution. The organic layer was dried over anhydrous sodium sulfate. The final product was purified on a silica gel column (20 cm; 60 mesh) using a 90:10 ethyl acetate to hexane solvent mixture. Removal of the solvent *in vacuo* afforded compound **5** as a viscous, yellow-green oil with an overall yield of 88% (38 g). Low-resolution FAB/MS: calcd for $C_{17}H_{38}O_6P_2S_2$ 464.2, found [M + H$^+$], *m/z* 465.2. ^{1}H NMR ($CDCl_3$): δ 1.25 (t, 12H, $^3J_{HH}$ = 9.0 Hz, OCH_2CH_3), 1.80 (m, 10H, $PCH_2CH_2CH_2$, $PCH_2CH_2CH_2$, $SCH_2CH_2CH_2S$), 2.53 (m, 8H, $PCH_2CH_2CH_2$, $SCH_2CH_2CH_2S$), 4.01 (m, 8H, OCH_2CH_3). ^{13}C NMR ($CDCl_3$): δ 15.9 (d, $^3J_{PC}$ = 5.3 Hz, OCH_2CH_3), 21.9 (d, $^3J_{PC}$ = 4.5 Hz, $PCH_2CH_2CH_2$), 23.9 (d, $^1J_{PC}$ = 141.9 Hz, $PCH_2CH_2CH_2$), 28.6 (s, $SCH_2CH_2CH_2S$), 29.9 (s, $SCH_2CH_2CH_2S$), 31.8 (d, $^2J_{PC}$ = 17.3 Hz, $PCH_2CH_2CH_2$), 60.9 (d, $^2J_{PC}$ = 6.0 Hz, OCH_2CH_3). ^{31}P NMR ($CDCl_3$): δ 31.8 (s).

Synthesis of $H_2PCH_2CH_2CH_2S(CH_2)_3SCH_2CH_2CH_2PH_2$ (6). Compound **5** (32 mmol) was placed in 75 mL of dry diethyl ether and cooled to 0 °C. An ether solution of 1.0 M lithium aluminum hydride (80 mmol, 80 mL) was slowly added dropwise to this solution with constant stirring. Upon reaction completion, an aqueous solution of 6 N hydrochloric acid (50 mL) was added dropwise to the solution to quench any remaining $LiAlH_4$. The ether layer was separated by cannula, and the solvent was removed *in vacuo* to afford **6** in 94% yield (7.8 g) as a colorless, viscous oil. ^{1}H NMR ($CDCl_3$): δ 1.59 (m, 4H, PCH_2CH_2-CH_2), 1.81 (m, 6H, $SCH_2CH_2CH_2$, $SCH_2CH_2CH_2S$), 2.58 (m, 8H, $PCH_2CH_2CH_2$, $PCH_2CH_2CH_2$), 2.69 (dt, 4H, $^1J_{PH}$ = 192.1 Hz, PH_2). ^{13}C NMR ($CDCl_3$): δ 12.9 (d, $^1J_{PC}$ = 9.1 Hz, $PCH_2CH_2CH_2$), 29.2 (s, $SCH_2CH_2CH_2S$), 30.7 (s, $SCH_2CH_2CH_2S$), 32.5 (d, $^2J_{PC}$ = 6.0 Hz, $PCH_2CH_2CH_2$), 32.6 (d, $^3J_{PC}$ = 3.0 Hz, $PCH_2CH_2CH_2$). ^{31}P NMR ($CDCl_3$): δ −137.5.

Synthesis of $(HOH_2C)_2PCH_2CH_2CH_2S(CH_2)_3SCH_2CH_2CH_2P(CH_2OH)_2$ (7). Aqueous formaldehyde (131 mmol) was placed in 50 mL of oxygen-free ethanol and purged with nitrogen gas for 2 h at 25 °C. Compound **6** (30 mmol) was added dropwise to the solution *via* syringe with constant stirring at 25 °C. The reaction was complete in 1 h, as monitored by ^{31}P NMR spectroscopy. Removal of the solvent *in vacuo* afforded compound **7** in 95% yield (10.9 g) as a colorless, viscous oil. Low-resolution FAB/MS: calcd for $C_{13}H_{30}O_4P_2S_2$ 376.1, found [M + H$^+$], *m/z* 409.1. ^{31}P NMR (D_2O): δ −25.6 (s). For characterization purposes, the (hydroxymethyl)phosphine **7** was converted into its corresponding phosphonium chloride salt by addition of 3 N HCl. The reaction mixture was concentrated *in vacuo* and loaded onto a Waters Sep-Pak 35 cm^{-3} (10 g) C18 cartridge. The pure phosphonium salt was isolated as a clear, viscous oil. ^{1}H NMR (D_2O): δ 1.78 (m, 2H, $SCH_2CH_2CH_2S$), 1.94 (m, 4H, $PCH_2CH_2CH_2$), 2.41 (m, 4H, $PCH_2CH_2CH_2$), 2.63 (m, 8H, $PCH_2CH_2CH_2$, $SCH_2CH_2CH_2$), 4.60 (m, 12H, PCH_2OH). ^{13}C NMR (D_2O): δ 13.2 (d, $^1J_{PC}$ = 40.8 Hz, $PCH_2CH_2CH_2$), 21.5 (d, $^3J_{PC}$ = 4.5 Hz, $PCH_2CH_2CH_2$), 29.1 (s, $SCH_2CH_2CH_2S$), 30.2 (s, $SCH_2CH_2CH_2S$), 32.2 (d, $^2J_{PC}$ = 15.9 Hz, $PCH_2CH_2CH_2$), 50.6 (d, $^1J_{PC}$ = 54.3 Hz, PCH_2OH). ^{31}P NMR (D_2O): δ 28.8 (s).

Synthesis of $[ReO_2(HOH_2C)_2P(CH_2)_2S(CH_2)_3S(CH_2)_2P(CH_2OH)_2]_2(Cl)_2$ (8). An aqueous solution (10 mL) of $(HOH_2C)_2P(CH_2)_2S(CH_2)_3S(CH_2)_2P(CH_2OH)_2$ (1.8 mmol) was added dropwise to an aqueous solution (50 mL) of $[ReO_2(C_5H_5N)_4](Cl)$ (1.7 mmol) at 25 °C with constant stirring. The reaction mixture was heated to ∼80 °C for 30 min, upon which the color changed from bright orange to light brown. The reaction mixture was concentrated *in vacuo* and loaded onto a Waters Sep-Pak Vac 35 cm^{-3} (10 g) C18 cartridge. The pure reaction product was isolated as a green microcrystalline solid. The product was reconstituted in methanol/diethyl ether (4:1) and allowed to evaporate slowly at room temperature to afford **8** as a green crystalline solid in 84% yield (1.72 g). Anal. Calcd for $C_{22}H_{52}O_{12}P_4S_4Re_2Cl_2$: C, 21.93; H, 4.35. Found: C, 22.65; H, 4.24. ^{1}H NMR (D_2O): δ 2.44 (m, 12H, $SCH_2CH_2CH_2S$, PCH_2CH_2), 3.19 (m, 16H, PCH_2CH_2, $SCH_2CH_2CH_2S$), 4.46 (m, 16H, PCH_2OH). ^{13}C NMR (D_2O): δ 22.1 (d, $^1J_{PC}$ = 33.8 Hz, PCH_2CH_2), 24.9 (s, $CH_2CH_2CH_2$), 33.7 (s, PCH_2CH_2), 34.5 (s, $SCH_2CH_2CH_2S$), 56.0 (d, $^1J_{PC}$ = 37.7 Hz, PCH_2OH). ^{31}P NMR (D_2O): δ 38.6 (s).

Synthesis of $[ReO_2(HOH_2C)_2P(CH_2)_2S(CH_2)_4S(CH_2)_2P(CH_2OH)_2]_2(ReO_4^-)_2$ (9). A solid sample of $(HOH_2C)_2P(CH_2)_2S(CH_2)_4S(CH_2)_2P(CH_2OH)_2$ (1.32 mmol) was added to an aqueous solution (50 mL) of $[ReO_2(C_5H_5N)_4](Cl)$ (1.2 mmol) at 25 °C with constant stirring. The reaction mixture was heated to ∼80 °C for 30 min, upon which the color changed from bright orange to light brown. The reaction mixture was concentrated *in vacuo* and loaded onto a Waters Sep-Pak Vac 35 cm^{-3} (10 g) C18 cartridge. The pure reaction product was isolated as a green microcrystalline solid. The product was reconstituted in water/methanol (4:1) and allowed to evaporate slowly at room temperature

to afford **9** as a green microcrystalline solid in 40% yield (0.8 g). Anal. Calcd for $C_{24}H_{56}O_{20}P_4S_4Re_4$: C, 17.35; H, 3.40. Found: C, 17.34; H, 3.31. ^{1}H NMR (D_2O): δ 2.05 (bs, 8H, PCH_2CH$_2$), 2.42 (m, 8H, SCH$_2$CH_2CH_2CH$_2$S), 3.05 (m, 16H, PCH$_2$CH_2, SCH_2CH$_2$CH$_2$CH_2S), 4.41 (m, 16H, PCH_2OH). ^{13}C NMR (D_2O): δ 21.9 (d, $^1J_{PC}$ = 34.0 Hz, PCH$_2$CH$_2$), 26.2 (s, SCH$_2$CH$_2$CH$_2$CH$_2$S), 34.5 (s, PCH$_2$CH$_2$), 37.0 (s, SCH$_2$CH$_2$CH$_2$CH$_2$S), 55.9 (d, $^1J_{PC}$ = 37.7 Hz, PCH$_2$OH). ^{31}P NMR (D_2O): δ 37.5 (s).

Synthesis of [ReO$_2$(HOH$_2$C)$_2$P(CH$_2$)$_3$S(CH$_2$)$_3$S(CH$_2$)$_3$P(CH$_2$OH)$_2$](Cl) (10). An aqueous solution (10 mL) of (HOH$_2$C)$_2$P(CH$_2$)$_3$S(CH$_2$)$_3$S(CH$_2$)$_3$P(CH$_2$OH)$_2$ (1.06 mmol) was added dropwise to an aqueous solution (50 mL) of [ReO$_2$(C$_5$H$_5$N)$_4$](Cl) (0.926 mmol) at 25 °C with constant stirring. The reaction mixture was heated to ∼80 °C for 30 min, upon which the color changed from bright orange to light brown. The reaction mixture was concentrated *in vacuo* and loaded onto a Waters Sep-Pak Vac 35 cm^{-3} (10 g) C18 cartridge. The pure reaction product was isolated as a green microcrystalline solid. The product was reconstituted in methanol/diethyl ether (4:1) and allowed to evaporate slowly at room temperature to afford **10** as a green microcrystalline solid in 80% yield (0.47 g). Anal. Calcd for $C_{13}H_{30}O_6P_2S_2ReCl$: C, 24.76; H, 4.80. Found: C, 24.77; H, 4.73. ^{1}H NMR (D_2O): δ 2.53 (m, 10H, PCH_2CH$_2$CH$_2$, PCH$_2$CH_2CH$_2$, SCH$_2$CH_2CH$_2$S), 3.18 (bs, 4H, PCH$_2$CH$_2$CH_2), 3.47 (m, 4H, SCH_2CH$_2$CH_2), 4.43 (m, 8H, PCH_2OH). ^{13}C NMR (D_2O) δ 17.5 (d, $^1J_{PC}$ = 37.7 Hz, PCH$_2$CH$_2$CH$_2$), 20.4 (s, PCH$_2$CH$_2$CH$_2$), 23.6 (s, SCH$_2$CH$_2$CH$_2$S), 36.3 (s, PCH$_2$CH$_2$CH$_2$), 37.0 (s, SCH$_2$CH$_2$CH$_2$S), 58.3 (d, $^1J_{PC}$ = 37.7 Hz, PCH$_2$OH). ^{31}P NMR (D_2O): δ −8.56 (s).

HPLC Analysis of 8−10. Complexes **8**−**10** were dissolved in deionized water and prefiltered through a 0.22 μm Cameo syringe filter. High-performance liquid chromatography (HPLC) analysis was performed using an analytical PRP-1 column (Hamilton poly(styrene−divinylbenzene), 100 Å). The mobile phase consisted of a gradient system with solvent A corresponding to water with 0.1% trifluoroacetic acid and B corresponding to acetonitrile with 0.1% trifluoroacetic acid. The mobile phase started with 100% A for 2 min followed by a linear gradient from 0% B to 100% B from 2 to 7 min. The gradient remained at 100% B for an additional 2 min before being ramped to 0% B at time 20 min for column equilibration. The flow rate of the mobile phase was 1.5 mL/min. The chart speed of the integrator was 0.5 cm/min. Detection was accomplished using an in-line Waters 486 tunable absorbance detector preset to 380 nm.

X-ray Data Collection and Processing. The crystal data and the details of data collection for complexes **8**−**10** are listed in Tables 1−5. Clear, yellowish green crystals of **8**−**10** suitable for X-ray diffraction were obtained by slow evaporation from the appropriate solvent systems as described in the Experimental Section. Intensity data were collected on a Siemens SMART CDD system using the ω-scan mode. Data were corrected for absorption using the program SADABS, which is based on the method of Blessing.[37] Crystal decay was less than 1%, and a correction was deemed unnecessary. The structures were solved by direct methods using SHELXS-86[38] and refined by the full-matrix least-squares method on F^2 using SHELXL-93.[39]

For compound **8**, all non-hydrogen atoms, with the exception of the lattice water oxygen atom, were refined anisotropically. Ethylenic hydrogen atoms were placed in calculated positions with their thermal parameters fixed at values of 1.2 times those of their parent atoms. The hydroxyl hydrogen atoms were located in difference Fourier maps and refined with their O−H distances constrained to 1.0 ± 0.02 Å and with independent isotropic thermal parameters. The water hydrogen atoms were similarly located and refined with O−H distances constrained to 1.0 ± 0.02 Å and the H−H distance to 1.62 ± 0.02 Å (the hydrogen thermal parameters were fixed at a value of 1.2 times that of their parent oxygen atom).

For compound **9**, all non-hydrogen atoms, with the exception of the perrhenate oxygen atoms, were refined anisotropically. Ethylenic and hydroxyl hydrogen atoms were placed in calculated positions with their thermal parameters fixed at values of 1.2 times those of their parent atoms. The hydroxyl hydrogen atoms were placed by modeling the hydroxyl moieties as rigid groups, maximizing the electron density at the calculated hydrogen positions. The oxygen atoms of both of the perrhenate anions were disordered, and the Re−O distances were restrained to 1.71(2) Å.[40] In addition, all of the perrhenate O−O distances were restrained to 2.79(2) Å in order to impart tetrahedral geometry to the anions, and, the oxygen atoms were assigned a common isotropic thermal parameter.

For compound **10**, all non-hydrogen atoms were refined anisotropically and C-H hydrogen atoms were placed in calculated positions. Hydroxyl hydrogen atoms belonging to the ligand were located in difference electron density maps and refined with their O−H distances restrained to 1.0 ± 0.01 Å. For hydrogen atoms placed in calculated positions, all isotropic thermal parameters were fixed at values of 1.2 those of their parent atoms. The methanolic hydroxyl hydrogen atom was not located and thus omitted from the structure refinement.

Other pertinent details relating to data collection, structure solution, and refinement are given in Tables 1−5.

***In Vitro* Stability Studies of 8−10.** Appropriate sample sizes of complexes **8**−**10** were dissolved in 10 mL of deionized water to afford solution concentrations of ∼0.01 M. To these solutions was added 15 mL of a 1.0 M cysteine solution also in water. The solutions were allowed to stir at room temperature overnight. The reaction progress for potential ligand displacement was monitored by ^{31}P NMR spectroscopy at various time points over a 24 h study period.

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Supporting Information Available: Tables giving complete crystallographic experimental details, distances and angles, positional parameters for all atoms, anisotropic thermal parameters, and hydrogen atom coordinates of **8**−**10** (26 pages). Ordering information is given on any current masthead page.

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