Novel Six-Coordinate Oxorhenium "3 + 2" Mixed-Ligand Complexes Carrying the SNS/PO Donor Atom Set: Synthesis and Characterization

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Replacing the monothiolate group of the so-called "3 + 1" mixed-ligand oxorhenium(V) complexes with the bidentate phosphinophenolate ligand produces novel "3 + 2" mixed-ligand complexes carrying the SNS/PO donor atom set. Thus, reactions of either $[ReOCl_3(L)]^-$ or $[ReOCl_2(L)(PPh_3)]$ (HL = *o*-$HOC_6H_4P(C_6H_5)_2$) with aminedithiol (H_2L^n) in dichloromethane methanol solutions lead to six-coordinate mixed-ligand oxo−Re(V) complexes of the type $[ReO(L^n)(L)]$, where $H_2L^1 = CH_3CH_2N(CH_2CH_2SH)_2$ (**1**), $H_2L^2 = (CH_3CH_2)_2NCH_2CH_2N(CH_2CH_2SH)_2$ (**2**), and $H_2L^3 = CH_3CH_2SCH_2CH_2N(CH_2CH_2SH)_2$ (**3**). The coordination geometry around rhenium is distorted octahedral with the SNS donors of the aminedithiolate and the phosphorus of the phosphinophenolate ligand defining the equatorial plane, while the apical positions are occupied by the oxo group and the oxygen atom of the HL ligand, as shown by single-crystal X-ray analyses of **1** and **3**. The strong metal−phosphorus bonds together with the chelating properties of both ligands contribute to the stability of 18-electron $[ReO(L^n)(L)]$ complexes. In fact, these six-coordinate species appear to be much more substitution inert than the "3 + 1" analogous complexes vs excess thiolate, such as cysteine or glutathione, during appropriate challenge reactions.

Introduction

The widespread use of the metastable ^{99m}Tc isomer in diagnostic nuclear medicine[1−4] and the recent advent of ^{186}Re and ^{188}Re agents in radiotherapy[5−7] still offer the possibility for chemists actively involved in technetium and rhenium coordination chemistry to propose new model molecules as potential radiopharmaceuticals. In this connection, the continuous efforts to find efficient chelating systems for the $[MO]^{3+}$ cores (M = Tc, Re) recently produced several examples in which the oxometal center is surrounded by variable ligand combinations displaying different donor sets and denticities.[8−10]

Among these chelating frameworks, the so-called "3 + 1" system[11−14] has been extensively investigated and several examples of ^{99m}Tc−oxo complexes incorporating biologically active fragments, such as tropane[15,16] or ketanserin mimetics,[17,18] have been proposed as receptor-binding tracers. All of these "3 + 1" complexes contain a dianionic tridentate ligand carrying the SSS, SOS, SN(R)S, or SNN(R) donor atom set (R = various alkyl or aryl-substituted pendant groups) and a monodentate thiol, to which the pharmacophore is usually attached. The oxo group completes the coordination sphere of a neutral five-coordinate compound of a geometry varying between square pyramidal and trigonal bipyramidal. Although there are numerous examples of stable five-coordinate technetium and rhenium

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complexes,[19] a tendency to expand the coordination sphere to six, especially for the third-row congener, can be predicted. In fact, a simple formal valence electron count[20,21] for a "3 + 1" complex of the type [MO(SN(R)S)(SR′)] reveals a maximum electron count (MEC) value of 16, deficient from the ideal value of 18. On the other hand, the neutral bis(amino) (or bis(amido)) bis(thiolato) (BAT or DADS) derivatives [MO(SNN(R)S)] and $[MO(SNNS)]^-$ achieve a closed shell, and indeed, they are known to be very stable compounds. For this reason, the N_2S_2 donor set has represented, and still represents, the most investigated framework in oxo−M(V) technetium and rhenium chemistries, and since the early 1990s these backbones have been modified with appropriate linkers for coupling to peptides and antibodies.[22−25] Also, tridentate aminedithiolate ligands may be efficiently used as chelating agents to produce rather stable $[MO(SN(R)S)]^+$ moieties, that easily undergo further reaction with monothiols. These "3 + 1" systems can also carry biologically active fragments, usually inserted onto the monodentate thiol. This approach simplifies to some extent the organic synthesis as compared to that followed for the conjugation of a tetradentate chelate to a pharmacophore group. However, recent evidence has revealed, that "3 + 1" systems may undergo further substitution reactions, presumably to achieve a closed shell. Thus, the monothiolate ligand is easily and reversibly substituted by excess thiolate in organic and aqueous media. Of particular interest is the rapid in vivo nucleophilic substitution of these complexes by the native thiols cysteine and glutathione, which eventually leads to hydrophilic metabolic products of these compounds in thiolate-rich tissues such as the liver.[26−29] The rate of this metabolism can be properly tuned by choosing the correct combination of tridentate/monodentate ligands with the aim of trapping the radioactivity in organs of interest, e.g. the brain. However, the in vivo instability of the "3 + 1" system constitutes a serious handicap when the application is aimed at the in vivo imaging of high-specificity low-capacity receptor systems with ^{99m}Tc-labeled bioactive molecules.[26,27]

In an effort to increase stability, we decided to replace the monodentate thiol with the bidentate phosphinophenol, thereby achieving a six-coordination. Thus, we report herein on the synthesis, characterization, and relative stability of the resulting complexes of the general formulation [ReO(L^n)(L)] (HL = *o*-$HOC_6H_4P(C_6H_5)_2$; $H_2L^1 = CH_3CH_2N(CH_2CH_2SH)_2$ (**1**); $H_2L^2 = (CH_3CH_2)_2NCH_2CH_2N(CH_2CH_2SH)_2$ (**2**); $H_2L^3 = CH_3CH_2SCH_2CH_2N(CH_2CH_2SH)_2$ (**3**) against the nucleophilic attack of glutathione.

Experimental Section

Materials. All chemicals were of reagent grade and were used as such without further purification. Synthesis and purification of H_2L^1 ($CH_3CH_2N(CH_2CH_2SH)_2$), H_2L^2 ($(CH_3CH_2)_2NCH_2CH_2N(CH_2CH_2SH)_2$), H_2L^3 ($CH_3CH_2SCH_2CH_2N(CH_2CH_2SH)_2$)[30−33] and HL (*o*-$HOC_6H_4P(C_6H_5)_2$)[34,35] were performed according to published methods. Rhenium was purchased from Aldrich as $KReO_4$ and was converted to either the $Re^VOCl_3(PPh_3)_2$ or the $[(n\text{-}Bu)_4N][ReOCl_4]$ precursor as described previously.[36] Solvents for high-performance liquid chromatography (HPLC) were of HPLC grade; they were filtered through membrane filters (0.22 μm, Millipore, Milford) and degassed by helium flux before use. Column chromatography was performed on silica gel packing material from Merck, whereas thin-layer chromatography (TLC) was conducted on 0.25 mm silica gel coated aluminum F_{254} plates also from Merck.

Instrumentation. IR spectra were recorded on KBr pellets by using a Perkin-Elmer 1600FT-IR spectrophotometer in the region 500−4000 cm^{-1} with polystyrene as a reference. Proton, ^{13}C, and ^{31}P NMR spectra were collected on a Bruker AC-200 instrument, using $SiMe_4$ (^{1}H, ^{13}C) and 85% aqueous H_3PO_4 (^{31}P) as external references. Samples were dissolved in deuterated chloroform at a concentration of ca. 1−2%. Chemical shifts are given as δ in ppm. Elemental analyses for C, H, N, and S were conducted on a Perkin-Elmer 2400/II automatic elemental analyzer. Chemical ionization mass spectra were recorded on a direct-probe DCI Micromass Platform II instrument using methane as the reagent gas. Analysis by HPLC was performed on a Waters Chromatograph having with a 600E solvent delivery system and coupled to a Waters 991 photodiode array detector. An NP Porasil (10 μm, 3.9 mm × 300 mm) column from Waters was eluted at a 1 mL/min flow rate with CH_2Cl_2/MeOH mixtures of varying composition.

Synthesis of ReO(L^n/L) Complexes. (i) ReO{$[C_2H_5N(CH_2CH_2S)_2]$-[*o*-$OC_6H_4P(C_6H_5)_2$]}, ReO(L^1/L), 1. Method A: From [$(n$-$Bu)_4N$]-[$ReOCl_3$(L)]. The $[(n\text{-}Bu)_4N][ReOCl_3(L)]$ precursor was prepared by reaction of the HL ligand with an equimolar quantity of $[(n\text{-}Bu)_4N][ReOCl_4]$ in MeCN, as described previously.[37] The emerald green $[(n\text{-}Bu)_4N][ReOCl_3(L)]$ complex (100 mg, 0.12 mmol) was then dissolved in CH_2Cl_2 (5 mL), and a solution of H_2L^1 (19.9 mg, 0.12 mmol) in 1/1 CH_2Cl_2/MeOH (2 mL) was added under stirring. The mixture was refluxed for 15 min, whereupon the color changed from emerald green to orange and was left to cool at ambient temperature. An orange solid precipitated upon standing. The supernate was decanted and the solid rinsed with EtOH and Et_2O. Orange needle crystals separated by slow evaporation from CH_2Cl_2/MeOH. The product is soluble in CH_2Cl_2 and $CHCl_3$ and insoluble in MeOH, EtOH, and Et_2O.

Yield: 80%. R_f (SiO_2; 99/1 CH_2Cl_2/MeOH): 0.3. t_R (HPLC Porasil; CH_2Cl_2): 4.64 min. Anal. Calcd (found) for $C_{24}H_{27}NO_2PReS_2$: C, 44.75 (44.78); H, 4.30 (4.23); N, 1.98 (2.18); S, 10.00 (9.94). CI: *m*/*z* 644.08 (M^+, 100%). UV/vis (CH_2Cl_2; λ/nm): 325, 361, 400. IR (KBr; ν/cm^{-1}): 3446, 1584, 1457, 1444, 1435, 1329, 1097, 948 (Re═O str), 859. ^{1}H NMR (200 MHz, Me_4Si, $CDCl_3$): 2.95 (2H, exo, H-1, H-4), 3.60 (2H, endo, H-1, H-4), 3.20 (2H, exo, H-2, H-3), 3.79 (2H, endo, H-2, H-3), 3.92 (2H, H-5), 1.29 (3H, H-6), 6.32 (1H, H-8′), 7.14 (1H, H-9′), 6.66 (1H, H-10′), 7.31 (1H, H-11′), 7.40−7.85 (10H, H-14′−H18′). ^{13}C NMR (200 MHz, Me_4Si, $CDCl_3$): 38.1 (C-1, C-4), 62.8 (C-2, C-3), 47.5 (C-5), 6.9 (C-6), 117.2, 119.6, 123.6, 128.5, 131.0, 131.7, 132.2, 133.4, 133.7, 169.2 (C-7′−C18′). ^{31}P NMR (200 MHz, 85% H_3PO_4, $CDCl_3$): 16.3.

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Table 1. Summary of Crystal, Intensity Collection, and Refinement Data

	1	**1′**	**3**
formula	$C_{24}H_{27}NO_2PS_2Re\cdot0.4C_2H_5OH\cdot0.3CH_3OH$	$C_{24}H_{27}NO_2PS_2Re\cdot0.5CH_3OH$	$C_{26}H_{31}NO_2PS_3Re$
fw	670.83	658.81	702.87
a, Å	14.960(7)	16.14(1)	9.013(3)
b, Å	10.187(4)	10.384(7)	29.03(1)
c, Å	17.910(8)	15.66(1)	10.186(4)
α, deg		100.11(2)	
β, deg	93.36(1)	102.71(2)	93.69(1)
γ, deg		100.89(2)	
V, Å^3	2725(2)	2449(1)	2659(2)
Z	4	4	4
D_{calcd}/D_{measd}, Mg/m^3	1.635/1.61	1.787/1.76	1.755/1.73
space group	$P2_1/c$	$P\bar{1}$	$P2_1/n$
temp, K	298	298	298
radiation; *λ*, Å	Mo Kα; 0.710 730	Mo Kα; 0.710 730	Mo Kα; 0.710 730
abs coeff (*μ*), cm^{-1}	4.696	5.223	4.889
octants collected	$\pm h,k,-l$	$\pm h,-k,\pm l$	$-h,k,\pm l$
GOF on F^2	1.104	1.138	1.102
R1	0.0335[a]	0.0389[b]	0.0449[c]
wR2	0.0855[a]	0.0901[b]	0.1196[c]

[a] For 2173 reflections with $I > 2\sigma(I)$. [b] For 5562 reflections with $I > 2\sigma(I)$. [c] For 4211 reflections with $I > 2\sigma(I)$.

NMR data for the HL ligand are as follows. ^{1}H NMR (200 MHz, Me_4Si, $CDCl_3$): 6.80−7.35 (10H, H-14′−H18′). ^{13}C NMR (200 MHz, Me_4Si, $CDCl_3$): 115.6, 120.6, 121.1, 128.4, 128.7, 131.4, 133.1, 134.5, 134.7, 159.6 (C-7′−C18′). ^{31}P NMR (200 MHz, 85% H_3PO_4, $CDCl_3$): −31.2.

Method B: From [ReOCl$_2$(L)(PPh$_3$)]. The [$ReOCl_2$(L)(PPh_3)] intermediate was synthesized by reacting the HL ligand with the $ReOCl_3(PPh_3)_2$ precursor in refluxing benzene, as previously reported.[37] It was then dissolved (110 mg, 0.188 mmol) in 1/1 CH_2Cl_2/MeOH (8 mL), and a solution of H_2L^1 (31.2 mg, 0.188 mmol) in MeOH (2 mL) was added under stirring. This reaction mixture was refluxed for 30 min and left to cool at room temperature. An orange solid precipitated, and the supernate was decanted. The solid was rinsed with EtOH and Et_2O and then purified by crystallization from EtOH/CH_2Cl_2. Orange needle crystals were collected. Yield: 65%.

(ii) ReO{[(C$_2$H$_5$)$_2$NCH$_2$CH$_2$N(CH$_2$CH$_2$S)$_2$][*o*-HOC$_6$H$_4$P(C$_6$H$_5$)$_2$]}, ReO(L^2/L), 2. The [(*n*-Bu)$_4$N][$ReOCl_3$(L)] precursor (100 mg, 0.12 mmol) was dissolved in a 1/1 CH_2Cl_2/MeOH mixture (8 mL), and a solution of H_2L^2 (28.5 mg, 0.12 mmol) in CH_2Cl_2 (2 mL) was added under stirring. The emerald green reaction mixture was refluxed for 30 min, while the color changed gradually to brown. The mixture was left to cool at ambient temperature, and Et_2O was added. The formed precipitate was redissolved in a small portion of CH_2Cl_2 and purified over a SiO_2 column using 98/2 CH_2Cl_2/MeOH as eluent. The orange product was crystallized by slow evaporation from a CH_2Cl_2/MeOH mixture. It is soluble in chlorinated solvents, sparingly soluble in alcohols, and insoluble in Et_2O.

Yield: 75%. R_f (SiO_2; 99/1 CH_2Cl_2/MeOH): 0.3. t_R (HPLC Porasil; 99/1 CH_2Cl_2/MeOH): 6.28 min (0→7 min CH_2Cl_2, then 98/2 CH_2Cl_2/MeOH); 15.86 min. Anal. Calcd (found) for $C_{28}H_{36}N_2O_2PReS_2$: C, 46.95 (47.05); H, 4.95 (5.08); N, 4.03 (3.92); S, 9.02 (8.95). CI: *m*/*z* 714.15 (M^+, 100%). UV/vis (CH_2Cl_2; *λ*/nm): 325, 361, 400. IR (KBr; *ν*/cm^{-1}): 2967, 2926, 2815, 1582, 1457, 1443, 1326, 1268, 1097, 950 (Re═O str), 858. ^{1}H NMR (200 MHz, Me_4Si, $CDCl_3$): 3.02 (2H, exo, H-1, H-4), 3.83 (2H, endo, H-1, H-4), 3.22 (2H, exo, H-2, H-3), 3.88 (2H, endo, H-2, H-3), 3.94 (2H, H-5), 2.87 (2H, H-6), 2.55 (4H, H-7, H-9), 1.04 (6H, H-8, H-10), 6.31 (1H, H-8′), 7.15 (1H, H-9′), 6.66 (1H, H-10′), 7.31 (1H, H-11′), 7.40−7.85 (10H, H-14′−H18′). ^{13}C NMR (200 MHz, Me_4Si, $CDCl_3$): 38.4 (C-1, C-4), 64.2 (C-2, C-3), 46.3 (C-5), 49.9 (C-6), 47.3 (C-7, C-9), 12.0 (C-8, C-10), 117.6, 119.5, 123.9, 128.5, 131.1, 131.9, 132.2, 133.4, 133.8, 169.0 (C-7′−C18′). ^{31}P NMR (200 MHz, 85% H_3PO_4, $CDCl_3$): 16.3.

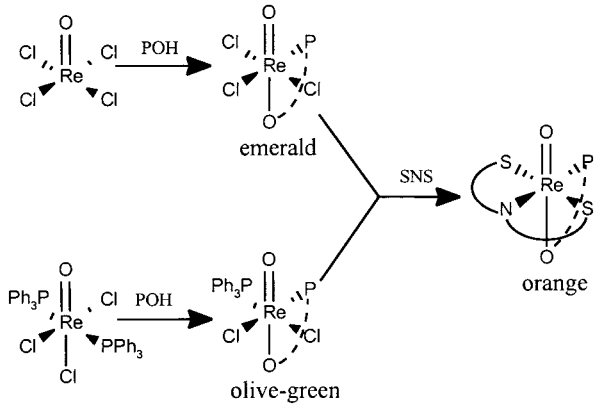
(iii) ReO{[CH$_3$CH$_2$SCH$_2$CH$_2$N(CH$_2$CH$_2$S)$_2$][*o*-HOC$_6$H$_4$P(C$_6$H$_5$)$_2$]}, ReO(L^3/L), 3. Complex **3** was obtained in a similar manner by reacting the [(*n*-Bu)$_4$N][$ReOCl_3$(L)] precursor (100 mg, 0.12 mmol) with the H_2L^3 ligand (27.18 mg, 0.12 mmol) in a refluxing CH_2Cl_2/MeOH (10 mL + 3 mL) medium for 3 h. An orange solid precipitated when the reaction mixture was left to cool at room temperature. This was redissolved in a small portion of $CHCl_3$ and purified over a silica gel column, using $CHCl_3$ and 95/5 $CHCl_3$/MeOH as the eluent. A small portion of MeOH was added to the component containing the product, which by slow evaporation afforded orange needles suitable for X-ray analysis. Complex **3** is soluble in chlorinated solvents, sparingly soluble in alcohols, and insoluble in Et_2O.

Yield: 85%. R_f (SiO_2; 99/1 CH_2Cl_2/MeOH): 0.3. t_R (HPLC Porasil; CH_2Cl_2): 4.28 min. Anal. Calcd (found) for $C_{26}H_{31}NO_2PReS_3$: C, 44.50 (44.38); H, 4.39 (4.44); N, 2.02 (1.99); S, 13.72 (13.64). CI: *m*/*z* 703.08 (M^+, 100%). UV/vis (CH_2Cl_2, *λ*/nm): 322, 361, 403. IR (KBr; *ν*/cm^{-1}): 3446, 2923, 2852, 1582, 1456, 1309, 1270, 1097, 1020, 950 (Re═O str), 856. ^{1}H NMR (200 MHz, Me_4Si, $CDCl_3$): 3.02 (2H, exo, H-1, H-4), 3.62 (2H, endo, H-1, H-4), 3.23 (2H, exo, H-2, H-3), 3.81 (2H, endo, H-2, H-3), 4.04 (2H, H-5), 2.87 (2H, H-6), 2.57 (2H, H-7), 1.25 (3H, H-8), 6.34 (1H, H-8′), 7.15 (1H, H-9′), 6.66 (1H, H-10′), 7.30 (1H, H-11′), 7.40−7.85 (10H, H-14′−H18′). ^{13}C NMR (200 MHz, Me_4Si, $CDCl_3$): 38.4 (C-1, C-4), 63.7 (C-2, C-3), 52.9 (C-5), 23.5 (C-6), 26.3 (C-7), 14.5 (C-8), 117.5, 119.4, 123.6, 128.5, 131.0, 131.8, 132.2, 133.4, 133.8, 168.6 (C-7′−C18′). ^{31}P NMR (200 MHz, 85% H_3PO_4, $CDCl_3$): 16.2.

Interaction of ReO(L^n/L) Complexes with GSH. In a penicillin vial, a 1 mM solution of the respective ReO(L^n/L) complex in CH_2Cl_2 (1 mL) was reduced to a minimum volume (≈20 *μ*L) under a gentle stream of nitrogen at 25 °C and then diluted with EtOH (1 mL). To this was added an aqueous solution of GSH (200 mM, 500 *μ*L) followed by 0.2 M phosphate buffer, pH 7.4 (500 *μ*L). The pH was adjusted to 7.4 by addition of a 1 M NaOH solution (≈300 *μ*L), and the vial was sealed under nitrogen and incubated at 37 °C. All above solutions were purged with nitrogen prior to use. Aliquots of the incubate were withdrawn at several time intervals and tested by TLC on SiO_2 plates developed by the CH_2Cl_2/MeOH mixtures reported above. For detection of decomposition products, the plates were also checked under UV light.

X-ray Crystal Structure Determinations of ReO(L^n/L) Complexes. Diffraction measurements were performed on a Crystal Logic dual-goniometer diffractometer using graphite-monochromated Mo Kα radiation. Unit cell dimensions were determined and refined by using the angular settings of 25 automatically centered reflections in the range $11 < 2\theta < 23°$, and they appear in Table 1. Intensity data were recorded using a $\theta-2\theta$ scan. Three standard reflections monitored every 97 reflections showed less than 3% variation and no decay. Lorentz, polarization, and *ψ*-scan absorption corrections were applied using Crystal Logic software. The structures were solved by direct methods using SHELXS-86[38] and refined by full-matrix least-squares techniques on F^2 with SHELXL-93.[39]

Scheme 1. Alternative Routes for the Two-Step Synthesis of [ReO(L^n)(L)] Complexes



ReO{[$C_2H_5NCH_2CH_2N(CH_2CH_2S)_2$][*o*-$HOC_6H_4P(C_6H_5)_2$]}, ReO(L^1/L), 1. Slow crystallization from CH_2Cl_2/MeOH/EtOH yielded two different kinds of red crystals for **1**. A hexagonal crystal of **1** and a prismatic crystal of **1′**, with dimensions 0.10 × 0.30 × 0.30 mm and 0.10 × 0.35 × 0.60 mm, respectively, were each mounted in a capillary.

Conditions for **1**: $2\theta_{max} = 42°$, scan speed 2.0°/min, scan range 2.4° plus $\alpha_1\alpha_2$ separation, reflections collected/unique/used = 2771/2666 (R_{int} = 0.0382)/2666, 310 parameters refined, R1/wR2 (for all data) = 0.0485/0.0951, $[\Delta\rho]_{max}/[\Delta\rho]_{min}$ = 0.772/−0.609 e/Å^3, $[\Delta/\sigma]_{max}$ = 0.506. All hydrogen atoms were introduced at calculated positions as riding on bonded atoms. All non-hydrogen atoms were refined anisotropically. In the final stages of refinement, five peaks were found in the difference map which were modeled as C_2H_5OH and CH_3OH because of the crystallization solvents. The solvent molecules were refined isotropically with occupation factors fixed at 10.4 and 10.3 for ethanol and methanol, respectively.

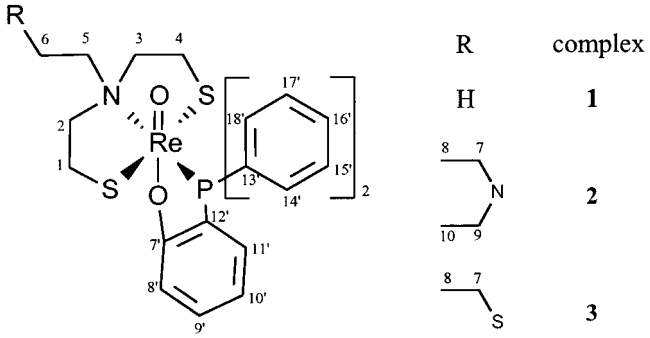
Conditions for **1′**: $2\theta_{max} = 46°$, scan speed 1.2°/min, scan range 2.1° plus $\alpha_1\alpha_2$ separation, reflections collected/unique/used = 7265/6821 (R_{int} = 0.0232)/6821, 718 parameters refined, R1/wR2 (for all data) = 0.0525/0.01011, $[\Delta\rho]_{max}/[\Delta\rho]_{min}$ = 1.719/−1.297 e/Å^3 in the vicinity of the heavy metals, $[\Delta/\sigma]_{max}$ = 0.183. The asymmetric unit contained two crystallographically independent molecules of **1′** and one methanol. More than the half of the hydrogen atoms were located by difference maps and refined isotropically; the rest were introduced at calculated positions as riding on bonded atoms. All non-hydrogen atoms were refined anisotropically.

ReO{[$CH_3CH_2SCH_2CH_2N(CH_2CH_2S)_2$][*o*-$HOC_6H_4P(C_6H_5)_2$]}, ReO(L^3/L), 3. A red crystal of **3** (0.10 × 0.10 × 0.50 mm) was mounted in air. Conditions: $2\theta_{max} = 50°$, scan speed 3.2°/min, scan range 2.4° plus $\alpha_1\alpha_2$ separation, reflections collected/unique/used = 4978/4665 (R_{int} = 0.0285)/4663, 318 parameters refined, R1/wR2 (for all data) = 0.0501/0.1257, $[\Delta\rho]_{max}/[\Delta\rho]_{min}$ = 1.825/−2.342 e/Å^3 in the vicinity of the heavy metal, $[\Delta/\sigma]_{max}$ = 0.002. All hydrogen atoms were introduced at calculated positions as riding on bonded atoms. All non-hydrogen atoms were refined anisotropically.

Results

Synthesis. [ReO(L^n)(L)] complexes **1**−**3** were prepared using a two-step synthesis, as shown in Scheme 1. In the first step, the labile precursors $[ReOCl_4]^-$ and $[ReOCl_3(PPh_3)_2]$ were reacted with equimolar amounts of HL to give monosubstituted compounds of the type $[ReOCl_3(L)]^-$ and $[ReOCl_2(L)(PPh_3)]$.[37] These derivatives were then treated with equimolar amounts of the relevant aminedithiol (H_2L^n) in refluxing dichloromethane/methanol solutions until the original green color turned orange-brown. Purification of the raw material via column chromatography on silica yielded neutral six-coordinate complexes.

Chart 1



Characterization. Elemental analyses, as given in the Experimental Section, were in good agreement with the proposed formulations. The IR spectra exhibit the characteristic Re═O stretching vibration around 950 cm^{-1}. Additional absorptions typical of the phosphinophenolato ligand are present in the range 750−690 cm^{-1}, whereas coordination of the aminedithiolato moiety is indirectly indicated by the absence of the thiol bands of the free ligand around 2550 cm^{-1}. Mass spectra show the parent molecules with no significant fragmentation peaks, reflecting the stability of the six-coordinate environments. UV/vis spectra show maxima at 325, 365, and 400 nm.

Proton, ^{13}C, and ^{31}P chemical shifts for compounds **1**−**3** are given in the Experimental Section, and the numbering of atoms used in the study is shown in Chart 1. Proton and carbon assignments were based on selected homonuclear decoupling experiments (^{1}H) and on comparison with similar "3 + 1" technetium and rhenium complexes containing identical N-substituted aminedithiolato systems (^{1}H, ^{13}C),[40,41] which were previously and exhaustively investigated using a battery of two-dimensional experiments, including COSY, NOESY, and HETCOR. Due to the symmetry of complexes **1**−**3** (vide infra), the corresponding protons and carbons of the two ethanethiolato arms and of the unsubstituted phenyl rings attached at the phosphine phosphorus resonate at the same frequency at room temperature. In addition, protons of the tridentate NS_2 backbone are distinguished as endo (facing toward the oxo oxygen) and exo (remote from the oxo oxygen).[11−14,40,41] Proton resonances of the aromatic ring interposed between the P and O donors of the phosphinophenolato fragment fall outside (upfield shifted) the narrow range observed for unsubstituted phenyl protons and are easily distinguished on the basis of their multiplicity and two-dimensional experiments. The ^{31}P NMR singlet of free HL (δ = −31.2 ppm) moves significantly downfield upon coordination, as $[ReO]^{3+}$ is a strong-acid center.[37]

Description of the Structures. ORTEP diagrams of complexes **1** and **3** are given in Figures 1 and 2, respectively, and selected bond distances and angles are collected in Table 2. Complexes **1** and **1′** have the same molecular structure but crystallize in different space groups and contain different amounts of crystallization solvents. In particular, **1** crystallizes in the monoclinic space group $P2_1/c$ as red hexagonal crystals holding 0.4 C_2H_5OH and 0.3 CH_3OH per oxorhenium complex and **1′** crystallizes in the triclinic space group $P\bar{1}$ as red

(38) Sheldrick, G. M. SHELXS-86: Structure Solving Program. University of Goettingen, Germany, 1986.
(39) Sheldrick, G. M. SHELXL-93: Crystal Structure Refinement Program. University of Goettingen, Germany, 1993.
(40) Papadopoulos, M. S.; Pelecanou, M.; Pirmettis, I. C.; Spyriounis, D. M.; Raptopoulou, C. P.; Terzis, A.; Stassinopoulou, C. I.; Chiotellis, E. *Inorg. Chem.* **1996**, *35*, 4478−4483.
(41) Papadopoulos, M. S.; Pirmettis, I. C.; Pelecanou, M.; Raptopoulou, C. P.; Terzis, A.; Stassinopoulou, C. I.; Chiotellis, E. *Inorg. Chem.* **1996**, *35*, 7377−7383.

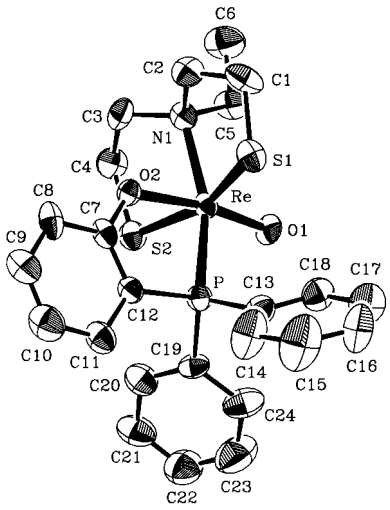


Figure 1. ORTEP diagram of complex **1** with 50% thermal probability ellipsoids showing the atomic labeling scheme.

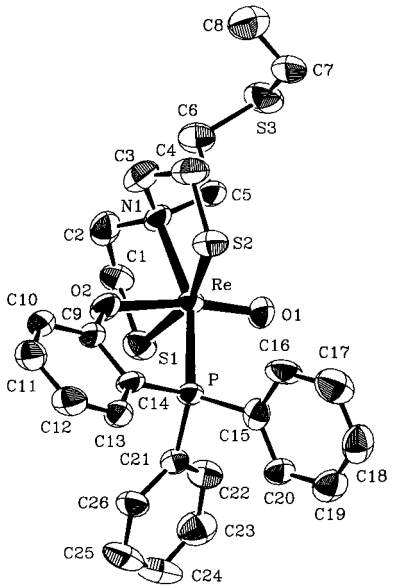


Figure 2. ORTEP diagram of complex **3** with 50% thermal probability ellipsoids showing the atomic labeling scheme.

parallelepiped crystals. The asymmetric unit of **1′** contains two crystallographically independent oxorhenium complexes and one methanol. As a result, small differences in the geometrical characteristics of **1** and **1′** are observed and will be discussed later.

The coodination environment of rhenium, in all complexes, is distorted octahedral with the SNS donor atom set of the tridentate ligand and the phosphorus of the HL ligand defining the equatorial plane while the apical positions are occupied by the oxo ligand and the oxygen atom of the HL ligand. The Re═O, Re−S, Re−N, and Re−$O_{phenolate}$ bond distances are in the ranges observed for analogous compounds. The Re−P bond lengths (∼2.40 Å) are close to the value observed (2.422(2) Å) in the precursor compound [*n*-Bu_4N][$ReOCl_3$(L)].[37] Rhenium lies ∼0.38 Å out of the equatorial plane toward the oxo ligand in all complexes. The Re−O_{oxo} axis is inclined at 81.9, 82.1, 78.4, and 82.9° in **1**, **1′A**, **1′B**, and **3**, respectively, with respect to the equatorial plane.

The N-substituent of the tridentate ligand is in cis configuration with respect to the oxo ligand. The closest C···O_{oxo} interatomic distances are 3.11 Å (C(5)···O(1)) in **1**, 3.11 and 3.19 Å (for C(5)···O(1) and C(35)···O(11), respectively) in **1′**, and 3.14 Å (C(5)···O(1)) in **3**.

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

	1	**1′**		**3**
		mol 1	mol 2	
		Distances		
Re−S(1)	2.372(3)	2.369(3)	2.389(3)	2.369(2)
Re−S(2)	2.375(3)	2.370(3)	2.348(3)	2.393(2)
Re−P	2.405(3)	2.397(3)	2.402(3)	2.409(2)
Re−N(1)	2.190(9)	2.176(7)	2.184(8)	2.191(6)
Re−O(1)	1.697(6)	1.686(6)	1.671(6)	1.693(6)
Re−O(2)	2.117(6)	2.093(6)	2.098(6)	2.099(6)
		Angles		
O(1)−Re−O(2)	168.7(3)	167.7(3)	166.1(3)	167.8(3)
O(1)−Re−N(1)	109.2(3)	109.5(3)	111.2(4)	108.0(3)
O(2)−Re−N(1)	82.1(3)	82.8(2)	82.6(3)	84.1(2)
O(1)−Re−S(1)	99.5(3)	100.0(3)	97.4(2)	100.0(2)
O(2)−Re−S(1)	80.9(2)	81.6(2)	82.1(2)	82.1(2)
N(1)−Re−S(1)	84.5(2)	83.6(2)	83.9(2)	83.6(2)
O(1)−Re−S(2)	99.3(3)	98.8(3)	100.3(3)	97.6(2)
O(2)−Re−S(2)	81.9(2)	81.4(2)	82.1(2)	82.2(2)
N(1)−Re−S(2)	83.8(2)	84.6(2)	83.9(2)	84.0(2)
S(1)−Re−S(2)	160.4(1)	160.4(1)	161.2(1)	161.0(1)
O(1)−Re−P	90.9(2)	90.7(2)	88.6(3)	92.1(2)
O(2)−Re−P	77.8(2)	76.9(2)	77.5(2)	75.8(2)
N(1)−Re−P	159.9(2)	159.7(2)	159.7(2)	159.9(2)
S(1)−Re−P	92.2(1)	92.1(1)	89.6(1)	93.6(1)
S(2)−Re−P	93.4(1)	93.5(1)	96.9(1)	93.1(1)

The dihedral angles defined by the atoms of the tridentate chelating backbone, i.e. S1−C1−C2−N1 and N1−C3−C4−S2, range from 52.4 to 57.8°. In particular, these angles are −54.3(1) and 53.3(1)° in **1**, −53.8(1) and 53.5(1)° in **1′A**, −53.8(1) and 52.4(1)° in **1′B**, and 55.1(1) and −57.8(1)° in **3**.

The three five-membered rings around the coordination sphere, i.e. the two Re−S−C−C−N rings and the Re−O−C−C−P ring, exist in the envelope form. In the first case, where the five-membered rings refer to the tridentate ligand, the carbon atoms C(2) and C(3) adjacent to the coordinated nitrogen are the "flap" atoms. In particular, the displacements of C(2) and C(3) are 0.57 and 0.62 Å in **1**, 0.64 and 0.58 Å in **1′A**, 0.62 and 0.59 Å in **1′B**, and 0.63 and 0.67 Å in **3**. In the five-membered ring involving rhenium and the atoms of the chelating HL ligand, the metal is the "flap" atom (0.07, 0.19, 0.38, and 0.70 Å for **1′B**, **1**, **1′A**, and **3**, respectively).

The dihedral angles between the S−N−S−P equatorial plane and the O−C−C−P chelating plane are 88.5, 85.7, 80.7, and 71.8° for **1′B**, **1**, **1′A**, and **3**, respectively, which leads to the following observed trend: as the displacement of rhenium out of the O−C−C−P chelating plane increases, the dihedral angle between the above plane and the S−N−S−P equatorial plane decreases.

The major differences between the two crystallographically independent molecules in **1′** are (i) the displacement of the "flap" atom rhenium in the five-membered chelating ring Re−O−C−C−P, (ii) the dihedral angle between the equatorial plane and the chelating atoms of the HL ligand, and (iii) the inclination of the Re−O_{oxo} axis with respect to the equatorial plane.

Stability against GSH Substitution. All three [ReO(L^n)(L)] complexes remain intact after 24 h incubation with a 100 molar excess of GSH in an aqueous medium at pH 7.4 and 37 °C. None of the respective "3 + 1" [ReO(L^n)(S)] complexes containing the same aminedithiolate ligand and various benzenethiolate derivatives as coligands survive the above conditions longer than 2 h, but they are converted to the corresponding hydrophilic daughter [ReO(L^n)(GS)] species.

Discussion

The syntheses of five-coordinate "3 +1" [MO(SN(R)S)(SR′)] complexes usually lead to mixtures of two isomers depending upon the relative orientation (cis or trans) of the pendant R group attached at the nitrogen atom of the aminedithiolate ligand with respect to the oxo core. The above syn and anti isomers exhibit trigonal-bipyramidal and square-pyramidal geometries, respectively.[11−14] The different molecular arrangements lead to remarkably different biological behaviors when we transfer this chemistry at the "carrier-free level" utilizing the ^{99m}Tc isomer. Generally, the formation of the syn isomer is favored. In the case of the complexes incorporating the (diethylamino)ethyl pendant group at nitrogen, the syn isomer accumulates in brain tissue, whereas the more rigid anti isomer crosses reversibly the blood brain barrier (BBB) without being retained in the brain.[26,27] The brain retention of the syn [^{99m}Tc] isomer has been attributed to the nucleophilic attack of intracerebral glutathione (GSH, 2 mM) on the complex metal center. This attack is followed by rearrangement to the [^{99m}TcO(SN(R)S)(SG)] hydrophilic species, which cannot cross the BBB back into the bloodstream.[26,27] In vitro challenge reactions of GSH with homologous "cold" Re complexes have demonstrated the existence of the hydrophilic [ReO(SN(R)S)(GS)] species by NMR and mass spectroscopies.[28,29] Thus, the "3 + 1" syn isomers are not substitution inert in the biological milieu. This behavior appears to be related to the electron vacancy (16-electron species) of five-coordinate complexes. However, anti isomers do not rearrange to hydrophilic species and retain their configurations intact.

In our "3 + 2" approach, the replacement of the monothiolate group for the phosphinophenolate fragment allows the generation of quite stable six-coordinate 18-electron species, wherein the pendant N-substituted arm of the aminedithiolate chelate is always cis-oriented with respect to the oxo core, leading exclusively to neutral *syn*-[ReO(L^n)(L)] complexes. The neutrality is achieved by deprotonation of the two thiol groups of the tridentate ligand and by deprotonation of the phosphinophenol. Both tridentate aminedithiolato and bidentate phosphinophenolato ligands are tightly bonded to the metal, as indicated by the absence of fragmentation of the parent molecule in the mass spectrum. The metal−phosphorus bond is very strong, given that the average value is 2.40 Å as compared to the corresponding value of 2.47 Å encountered in other oxo−rhenium PO complexes.[37] In addition, the ^{31}P NMR chemical shift suggests that the lone pair at P is solidly engaged in the metal bond, as demonstrated by the pertinent signal which is dramatically deshielded from δ −31.2 ppm in the uncoordinated ligand to δ +16.3 ppm in the complexes. This value is at the longer end of the range (−9.0 to +15.0 ppm) so far observed for other oxo−rhenium PO complexes. The replacement of the thiolato sulfur for the phosphinophenolato phosphorus does not seriously affect the magnetic environment at the aminedithiolato proton and carbon network. As expected, the only detectable variations occur at H-2 (and H-3) and at C-5.

As expected, the above characteristics are suggestive of the high stability imparted by the SNS/PO system, a property further demonstrated during GSH challenge reactions. All three complexes survive exposure to a high excess of GSH at physiological pH up to 24 h incubation at 37 °C, as opposed to the respective SNS/S compounds that are all rapidly converted to GS−X hydrophilic species.

Acknowledgment. We thank the General Secretariat of Research & Development of Greece as well as the Italian Ministry of Foreign Affairs for partial financial support of this work provided by the grant Sapfo. We also thank Mr. John Boutaris for financial support of A.T. The contribution of Dr. S. Boyatzis to the MS measurements is greatly appreciated.

Supporting Information Available: X-ray crystallographic files in CIF format and listings of structure determination details, fractional atomic coordinates and isotropic thermal parameters, anisotropic thermal parameters, and complete bond lengths and angles for all three structures. This material is available free of charge via the Internet at http://pubs.acs.org.

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