Synthesis and Characterization of Six-Coordinate "3 + 2" Mixed-Ligand Oxorhenium Complexes with the *o*-Diphenylphosphinophenolato Ligand and Tridentate Coligands of Different N and S Donor Atom Combinations

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A series of octahedral six-coordinate oxorhenium(V) mixed ligand complexes containing the common $[ReO(L)]^{2+}$ fragment (L = *o*-$OC_6H_4P(C_6H_5)_2$] have been synthesized and characterized. Hence, it was shown that the $[ReO(L)]^{2+}$ moiety can accommodate a variety of tridentate ligands containing a central amine group amenable to deprotonation and different combinations of lateral groups, such as ethylamine, substituted ethylamine, ethylthiol, and ethylthioether arms. In particular, by reaction of equimolar amounts of the pertinent HL^n ligands with the $[(n\text{-}C_4H_9)_4N][ReOCl_3(L)]$ precursor in refluxing acetonitrile/methanol or dichloromethane/methanol mixtures, the following series of $[ReO(L^n)(L)]^{+/0}$ oxorhenium(V) complexes has been generated: ReO{$[N(CH_2CH_2NH_2)_2][o\text{-}OC_6H_4P(C_6H_5)_2]$}Cl (**1**); ReO{$[(C_2H_5)_2NCH_2CH_2NCH_2CH_2S][o\text{-}OC_6H_4P(C_6H_5)_2]$} (**2**); ReO{$[(CH_2)_4NCH_2CH_2\text{-}NCH_2CH_2S][o\text{-}OC_6H_4P(C_6H_5)_2]$} (**3**); and ReO{$[C_2H_5SCH_2CH_2NCH_2CH_2S][o\text{-}OC_6H_4P(C_6H_5)_2]$} (**4**). The complexes are closed-shell 18-electron oxorhenium species, which adopt octahedral geometries both in solution and in the solid state, as established by conventional physicochemical techniques including multinuclear NMR and single-crystal X-ray diffraction analyses.

Introduction

Despite the large number of technetium radiopharmaceuticals already utilized as diagnostic tools in clinical practice,[1−5] the search for new compounds that exhibit in vivo stability continues to remain a challenge in the design of improved radiotracers. As far as the safe use of radiotherapeutic compounds based on rhenium radionuclides (^{186}Re or ^{188}Re) is concerned, stability in the biological milieu consists of an important prerequisite. In this respect, the chemistry of technetium, and its nonradioactive surrogate rhenium, is rapidly growing today while very often relevant stability issues are seriously considered. Thus, new donor atom sets for these two group VII elements are continuously emerging, designed mainly to provide a higher thermodynamic and/or kinetic stability at the metal center. Molecular structures involving electron-rich d^6 configurations, such as $[M^I(CNR)_6]^+$ and $[M^I(CO)_3(L{-}L)]^{+/0}$ (M = Tc, Re; CNR = various isonitriles; (L−L) = tridentate ligand) are illustrative examples in which the use of a common chemical property, the extremely high kinetic stability of these octahedral species, has a tremendous impact in their application in vivo.[6−9]

By decrease of the electron density at the metal center, other concepts have to be applied in order to guarantee sufficient stability for the resulting compounds. This is the case of d^2 configurations (Tc^V and Re^V), where a distinctive core (mono-oxo, di-oxo, nitrido, imido, etc.) usually confers distinct properties to the associated molecule, and the denticity of appropriate ligand(s) and the nature of the donor atoms engaged in coordination determine overall stability. [TcO(HMPAO)] and [TcO(ECD)] (HMPAO = hexamethylpropyleneamineoxime, ECD = ethylenecysteinate dimer), utilized as cerebral perfusion agents, are two representative examples of this category, as neutral and five-coordinate complexes in which the oxo−metal moiety is surrounded by tetradentate N_4 or N_2S_2.[10−13] A more flexible molecular structure known as the "3 + 1" system,[14−17] which retains the mono-oxo group but utilizes a combination

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of tridentate and monodentate ligands, has provided a series of potential brain perfusion agents. Recent evidence has shown that retention in brain cells exhibited by many of these "3 + 1" technetium chelates is based on their susceptibility against nucleophilic substitution by intracerebral glutathione.[18,19]

In a recent contribution we have established that the substitution of the monothiolate ligand in 16-electron *syn*-[ReO(SNS)(SR)] complexes by the bidentate phosphinophenolate [L = *o*-$OC_6H_4P(C_6H_5)_2$] chelate allows the generation of more stable 18-electron [ReO(SNS)(L)] octahedral structures.[20] In the present study we confirm that the $[ReO(L)]^{2+}$ fragment constitutes an efficient moiety to which several tridentate ligands can bind. In detail, we have considered the coordination of tridentate chelates having a central secondary amine function amenable to deprotonation and different combinations of lateral groups including ethylamine, substituted ethylamine, ethylthiol, and ethylthioether arms. The following octahedral monooxo Re(V) complexes of the general formula $[ReO(L^n)(L)]^{+/0}$ have been accordingly obtained: ReO{[$N(CH_2CH_2NH_2)_2$][*o*-$OC_6H_4P(C_6H_5)_2$]}Cl (**1**); ReO{[$(C_2H_5)_2NCH_2CH_2NCH_2CH_2S$][*o*-$OC_6H_4P(C_6H_5)_2$]} (**2**); ReO{[$(CH_2)_4NCH_2CH_2NCH_2CH_2S$][*o*-$OC_6H_4P(C_6H_5)_2$]} (**3**); and ReO{[$C_2H_5SCH_2CH_2NCH_2CH_2S$][*o*-$OC_6H_4P(C_6H_5)_2$]} (**4**). The molecular structure of the above oxorhenium(V) species has been authenticated by X-ray diffraction analysis and multinuclear NMR spectroscopy.

Experimental Section

Materials. All chemicals were reagent grade and used without further purification. Ligand HL, *o*-$HOC_6H_4P(C_6H_5)_2$ was prepared according to a reported protocol,[20−23] whereas HL^1, $NH(CH_2CH_2NH_2)_2$, was purchased from Aldrich. Synthesis and purification of ligands H_2L^2, $(C_2H_5)_2NCH_2CH_2NHCH_2CH_2SH$, H_2L^3, $(CH_2)_4NCH_2CH_2NHCH_2CH_2SH$, and H_2L^4, $C_2H_5SCH_2CH_2NHCH_2CH_2SH$, were performed according to published methods.[24,25] Rhenium was purchased from Aldrich as $KReO_4$ and was converted to the [(n-$C_4H_9)_4N$][$ReOCl_4$] precursor as reported previously.[26] Solvents for high-performance liquid chromatography (HPLC) were HPLC grade; they were filtered through membrane filters (0.22 μm, Millipore, Milford) and degassed by helium flux before use. Silica gel packing material from Merck was applied for column chromatography. Thin-layer chromatography (TLC) was performed on 0.25 mm silica gel coated aluminum F_{254} plates from Merck.

Instrumentation. IR spectra were recorded on KBr pellets on a Perkin-Elmer 1600 FT-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 $(CH_3)_4Si$ as an internal reference (for ^1H and ^{13}C) and 85% aqueous H_3PO_4 as an external reference (for ^{31}P). Complexes were dissolved in deuterated solvents 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. HPLC analyses were performed on a Waters chromatograph efficient with a 600 solvent delivery system and coupled to a Waters 996 photodiode array UV detector. The Millennium software by Waters was applied to control the HPLC system and to process the data. For analyses a RP C18 column from Merck (Lichrospher 100, 10 μm, 4.6 mm × 250 mm) was eluted at a 1 mL/min flow rate with MeOH and aqueous buffer mixtures of varying composition.

Synthesis of ReO(L^n/L) Complexes. (a) ReO{[$N(CH_2CH_2NH_2)_2$][*o*-$OC_6H_4P(C_6H_5)_2$]}Cl (ReO(L^1/L), 1). The [(n-$C_4H_9)_4N$][$ReOCl_3$(L)] precursor was first prepared by reacting the HL ligand with an equimolar amount of [(n-$C_4H_9)_4N$][$ReOCl_4$] in MeCN according to published methods.[20,21] Then the emerald [(n-$C_4H_9)_4N$][$ReOCl_3$(L)] complex (200 mg, 0.24 mmol) was dissolved in MeCN (10 mL) and a solution of $HN(CH_2CH_2NH_2)_2$ (24.8 mg, 0.24 mmol) in MeOH (10 mL) was added under stirring. This mixture was refluxed under stirring for 60 min while its color was slowly turning from emerald-green to dark-wine-red. The solvent was then expelled by rotary evaporation, leaving an aubergine oily residue behind. This was redissolved in a small portion of CH_2Cl_2 and placed on top of a silica gel column (20 cm × 1.5 cm). The column was eluted with a CH_2Cl_2/MeOH 4/1 mixture, and the fraction containing the major product was collected and concentrated to a small volume. By addition of a small amount of MeOH and petroleum ether (60−80 °C), the product was left to crystallize slowly, affording aubergine crystals.

Yield: 55%. R_f (SiO_2; CH_2Cl_2/MeOH 10/3): 0.5. t_R (HPLC RP C18 Merck Lichrospher 100, 10 μm, 4.6 mm × 250 mm, A = MeOH/B = 2% Et_3N/H_3PO_4, pH 7.1, 100% A to 10% A from 1 to 10 min): 15.57 min. t_R (HPLC RP C18 Merck Lichrospher 100, 10 μm, 4.6 mm × 250 mm, MeOH/10 mM CH_3COONH_4 isocratic 90/10): 11.7 min. Anal. Calcd (found) for $C_{22}H_{26}N_3O_2PReCl$: C, 42.82 (42.90); H, 4.25 (4.11); N, 6.81 (6.76). UV/vis (MeOH/2% Et_3N/H_3PO_4, pH 7.1, λ/nm): 255, 303, 368, 551. IR (KBr, ν/cm^{-1}): 3407, 3195, 1587, 1444, 1309, 1271, 1163, 1089, 933 (Re═O str), 854. ^1H NMR (200 MHz, Me_4Si, CD_3OD): δ 3.23 (2H, dt, *exo*-$H_2NCH_2CH_2N$), 3.48 (2H, dd, *exo*-$H_2NCH_2CH_2N$), 3.63 (2H, m, *endo*-$H_2NCH_2CH_2N$), 4.24 (2H, dd, *endo*-$H_2NCH_2CH_2N$), 6.57 (1H, dd, *o*-C_6H_4ORe), 6.71 (1H, t, *p*-C_6H_4ORe), 7.16 (1H, dd, *p*-C_6H_4PRe), 7.43 (1H, t, *o*-C_6H_4PRe), 7.45−7.70 (10H, $(C_6H_5)_2P$). ^{13}C NMR (200 MHz, Me_4Si, CD_3OD): δ 55.13 (C-1, C-4), 64.55 (C-2, C-3), 120.32, 121.05, 130.29, 132.08, 133.15, 133.72, 133.96, 134.77, 135.22, 147.01 (aromatic C). ^{31}P NMR (200 MHz, 85% H_3PO_4, CD_3OD): 0.05 (s).

(b) ReO{[$(C_2H_5)_2NCH_2CH_2NCH_2CH_2S$][*o*-$OC_6H_4P(C_6H_5)_2$]} (ReO($L^2$/L), 2). To an emerald solution of [(n-$C_4H_9)_4N$][$ReOCl_3$(L)] (200 mg, 0.24 mmol) in CH_2Cl_2 (5 mL) a solution of $(C_2H_5)_2NCH_2CH_2NHCH_2CH_2SH$ (42.27 mg, 0.24 mmol) in MeOH (5 mL) was added under stirring, and the mixture was refluxed for 30 min while the color changed to orange-red. The solvent was expelled by rotary evaporation, and the residue redissolved in a small quantity of CH_2Cl_2. Purification was conducted on a silica gel column (20 cm × 1.5 cm) eluted with a CH_2Cl_2/MeOH 99/1 solvent mixture. The fraction containing the orange-red compound was collected and concentrated to a small volume, and MeOH was added. By slow evaporation from this dark-red mixture, red needlelike crystals separated.

Yield: 75%. R_f (SiO_2; CH_2Cl_2/MeOH 10/0.3): 0.4. t_R (HPLC RP C18 Merck Lichrospher 100, 10 μm, 4.6 mm × 250 mm, MeOH/10 mM CH_3COONH_4 isocratic 80/20): 12.58 min. Anal. Calcd (found) for $C_{26}H_{32}N_2O_2PReS$: C, 47.70 (47.59); H, 4.93 (5.03); N, 4.28 (4.50);

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Table 1. Summary of Crystal Data for **1**−**4**

	1·Cl·0.5EtOH	**2**	**3**	**4**·0.25MeOH
formula	$C_{23}H_{29}ClN_3O_{2.5}PRe$	$C_{26}H_{32}N_2O_2PReS$	$C_{26}H_{30}N_2O_2PReS$	$C_{24.25}H_{28}NO_{2.25}PReS_2$
fw	640.11	653.77	651.75	650.80
a, Å	19.132(7)	11.806(2)	14.328(2)	24.00(1)
b, Å	11.188(4)	10.067(2)	18.603(2)	24.00(1)
c, Å	23.666(9)	21.332(5)	18.948(2)	8.693(4)
β, deg	98.77(1)			
V, Å^3	5007(1)	2535.4(9)	5050.2(9)	5009(1)
Z	8	4	8	8
D_{calcd}/D_{measd}, Mg m^{-3}	1.698/1.67	1.713/1.69	1.714/1.69	1.726/1.70
space group	*I*2/*a*	*P*2$_1$*cn*	*Pcab*	*I*4
temp, K	298	298	298	298
radiation λ, Å	Mo Kα, 0.710 73	Cu Kα, 1.5418	Cu Kα, 1.5418	Mo Kα, 0.710 73
abs coeff μ, mm^{-1}	5.051	10.943	10.987	5.105
octants collected	$h, -k, \pm l$	$\pm h, -k, l$	$h, k, -l$	$h, -k, \pm l$
GOF on F^2	1.078	1.052	1.143	1.076
R1	0.0279[a]	0.0300[b]	0.0398[c]	0.0378[d]
wR2	0.0710[a]	0.0795[b]	0.1125[c]	0.0899[d]

[a] For 3947 refs with $I > 2\sigma(I)$. [b] For 3867 refs with $I > 2\sigma(I)$. [c] For 3254 refs with $I > 2\sigma(I)$. [d] For 2944 refs with $I > 2\sigma(I)$.

S, 4.89 (5.00). UV/vis (MeOH/10 mM CH_3COONH_4, λ/nm): 298, 320. IR (KBr, ν/cm^{-1}): 3453, 2918, 2817, 1582, 1454, 1444, 1310, 1260, 1123, 1091, 1012, 915 (Re═O str), 854. ^{1}H NMR (200 MHz, Me_4Si, $CDCl_3$): δ 0.52 (3H, t, CH_2CH_3-*exo*), 0.84 (3H, t, CH_2CH_3-*endo*), 2.41 and 2.80 (2H, m, *endo*-, *exo*-NCH_2CH_3-*exo*), 2.79 and 3.30 (2H, m, *endo*-, *exo*-NCH_2CH_3-*endo*), 2.91 (1H, m, *exo*-$SCH_2CH_2NCH_2$), 3.07 (2H, m, *endo*-$SCH_2CH_2NCH_2$ and *exo*-SCH_2CH_2N), 3.48 (1H, dd, *endo*-SCH_2CH_2N), 3.67 (1H, m, *exo*-$SCH_2CH_2NCH_2CH_2N$), 3.99 (1H, m, *exo*-SCH_2), 4.44 (1H, m, *endo*-$SCH_2CH_2NCH_2CH_2N$), 4.67 (1H, dd, *endo*-SCH_2), 6.50 (1H, dd, *o*-C_6H_4ORe), 6.71 (1H, t, *p*-C_6H_4ORe), 7.16 (1H, dd, *p*-C_6H_4PRe), 7.43 (1H, t, *o*-C_6H_4PRe), 7.30−7.95 (10H, $(C_6H_5)_2P$). ^{13}C NMR (200 MHz, Me_4Si, $CDCl_3$): δ 9.31, 9.44, 47.39, 49.89, 53.29, 62.62, 63.23, 68.81 (aliphatic C), 114.21, 115.35, 117.31, 117.43, 119.60, 119.69, 127.82, 128.02, 128.20, 128.38, 129.78, 129.85, 132.33, 132.53, 133.24, 133.37, 133.59, 134.31, 135.34, 136.10 (aromatic C). ^{31}P NMR (200 MHz, 85% H_3PO_4, $CDCl_3$): δ −6.18 (s).

(c) ReO{[$(CH_2)_4NCH_2CH_2NCH_2CH_2S$][*o*-$OC_6H_4P(C_6H_5)_2$]} (ReO-($L^3$/L), 3). The emerald [($n$-$C_4H_9)_4N$][$ReOCl_3$(L)] complex (200 mg, 0.24 mmol) was dissolved in CH_2Cl_2 (5 mL), and a solution of $(CH_2)_4$-$NCH_2CH_2NHCH_2CH_2SH$ (41.8 mg, 0.24 mmol) in MeOH was added under stirring. The mixture was refluxed under stirring for 30 min, while the color changed from emerald to orange-red. The solvent was expelled by rotary evaporation, and the oily residue redissolved in a small amount of CH_2Cl_2 and mounted on a silica gel column (20 cm × 1.5 cm). When the column was eluted with a CH_2Cl_2/MeOH 99/1 mixture, the fraction containing the major complex was collected and concentrated to a small volume by N_2 flux, and MeOH (∼3 mL) was added. By slow evaporation of the dark-red CH_2Cl_2/MeOH mixture at ambient temperature, red crystals of **3** separated.

Yield: 73%. R_f (SiO_2; CH_2Cl_2/MeOH 10/0.3): 0.4. t_R (HPLC RP C18 Merck Lichrospher 100, 10 μm, 4.6 mm × 250 mm, MeOH/10 mM CH_3COONH_4 isocratic 80/20): 13.27 min. Anal. Calcd (found) for $C_{26}H_{30}N_2O_2PReS$: C, 47.84 (47.90); H, 4.64 (4.55); N, 4.29 (4.30); S, 4.90 (4.94). UV/vis (MeOH/10 mM CH_3COONH_4, λ/nm): 300, 325. IR (KBr, ν/cm^{-1}): 3448, 2961, 2904, 2811, 1585, 1456, 1441, 1313, 1259, 1123, 1095, 1027, 957, 915 (Re═O str), 856. ^{1}H NMR (200 MHz, Me_4Si, $CDCl_3$): δ 1.21 (2H, m, $-CH_2CH_2CH_2CH_2N$-*exo*), 1.69 (2H, m, $-CH_2CH_2CH_2CH_2N$-*endo*), 2.38 and 2.77 (2H, m, *endo*-, *exo*-$NCH_2CH_2CH_2CH_2$-*endo*), 2.78 and 2.87 (2H, m, *endo*-, *exo*-NCH_2CH_2-CH_2CH_2-*exo*), 2.75 (1H, m, *exo*-$SCH_2CH_2NCH_2$), 2.94 (1H, m, *endo*-$SCH_2CH_2NCH_2$), 3.22 (1H, dt, *endo*-SCH_2CH_2N), 3.44 (1H, dd, *exo*-SCH_2CH_2N), 3.76 (1H, m, *exo*-$SCH_2CH_2NCH_2CH_2N$), 3.83 (1H, m, *endo*, SCH_2), 4.15 (1H, m, *endo*-$SCH_2CH_2NCH_2CH_2N$), 4.66 (1H, dd, *exo*, SCH_2), 6.45 (1H, dd, *o*-C_6H_5ORe), 6.66 (1H, t, *p*-C_6H_5ORe), 7.15 (1H, t, *p*-C_6H_5PRe), 7.39 (1H, m, *o*-C_6H_5PRe), 7.30−7.95 (10H, $(C_6H_5)_2P$). ^{13}C NMR (200 MHz, Me_4Si, $CDCl_3$): δ 20.49, 22.39, 47.26, 47.40, 57.39, 63.72, 64.20, 64.78, 68.39 (aliphatic C), 117.22, 117.37, 119.51, 119.62, 127.56, 128.05, 128.29, 128.40, 128.57, 129.96, 130.19, 132.33, 132.50, 132.96, 133.17, 133.43, 133.89, 134.09 (aromatic C). ^{31}P NMR (200 MHz, 85% H_3PO_4, $CDCl_3$): δ 0.32 (s).

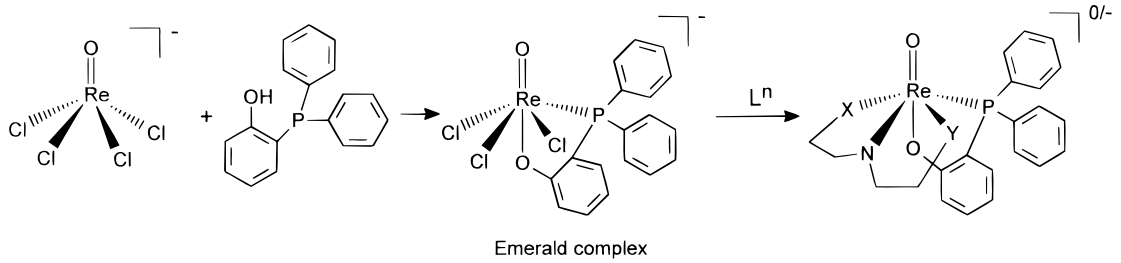
(d) ReO{[$C_2H_5SCH_2CH_2NCH_2CH_2S$][*o*-$OC_6H_5P(C_6H_5)_2$]} (ReO-($L^4$/L), 4). The emerald [($n$-$C_4H_9)_4N$][$ReOCl_3$(L)] precursor (200 mg, 0.24 mmol) was dissolved in CH_2Cl_2 (5 mL), and a solution of C_2H_5-$SCH_2CH_2NHCH_2CH_2SH$ ligand (39.67 mg, 0.24 mmol) in MeOH (4 mL) was added under stirring. The color of the reaction mixture changed from emerald-green to olive-green within 5 min. When the mixture was refluxed under stirring for 30 min, the color turned orange-red. The solvent was expelled under rotary evaporation, and the brown residue redissolved in a small quantity of CH_2Cl_2 and was purified further on a silica gel column (20 cm × 1.5 cm) by using a CH_2Cl_2/MeOH 100/1.5 solvent mixture as the eluent. The fraction containing the product was collected and concentrated to a small volume. After addition of MeOH (∼3 mL), the mixture was left to stand at ambient temperature, affording complex **4** as orange-red needlelike crystals.

Yield: 80%. R_f (SiO_2; CH_2Cl_2/MeOH 10/0.3): 0.5. t_R (HPLC RP C18 Merck Lichrospher 100, 10 μm, 4.6 mm × 250 mm, MeOH/10 mM CH_3COONH_4 isocratic 80/20): 11.29 min. Anal. Calcd (found) for $C_{24}H_{27}NO_2PReS_2$: C, 44.85 (44.79); H, 4.23 (4.32); N, 2.18 (2.21); S, 9.98 (10.03). UV/vis (MeOH/10 mM CH_3COONH_4, λ/nm): 300, 350. IR (KBr, ν/cm^{-1}): 3522, 2913, 2817, 1583, 1457, 1442, 1433, 1314, 1267, 1099, 910 (Re═O str), 897, 858, 845. ^{1}H NMR (200 MHz, Me_4Si, $CDCl_3$, at 240 K): δ 0.86 (3H, m), 2.22 (1H, m), 2.75 (1H, m), 3.16 (1H, m), 3.36 (2H, dt), 3.54 (1H, m) 3.91 (2H, m), 4.50 (1H, dd), 4.75 (1H, dd), 6.41 (1H, *o*-C_6H_5ORe), 6.66 (1H, *p*-C_6H_5ORe), 7.12 (1H, *p*-C_6H_5PRe), 7.32 (1H, *o*-C_6H_5PRe), 7.35−8.10 (10H, $(C_6H_5)_2P$). ^{13}C NMR (200 MHz, Me_4Si, $CDCl_3$): δ 12.35, 12.50, 26.52, 34.35, 34.46, 39.67, 41.81, 44.69, 45.51, 65.23, 69.66, 70.32 (aliphatic C), 117.45, 117.96, 119.40, 120.19, 128.47, 130.20, 130.55, 132.17, 132.43, 133.42, 133.91 (aromatic C). ^{31}P NMR (200 MHz, 85% H_3PO_4, $CDCl_3$): δ 3.20 (s), 2.75 (s).

(e) X-ray Crystal Structure Determination of ReO(L^n/L) Complexes. Diffraction measurements for **1** and **4** were performed on a Crystal Logic dual goniometer−diffractometer using graphite monochromated Mo Kα radiation, while compounds **2** and **3** were measured on a P2$_1$ Nicolet upgraded by crystal logic using Ni-filtered Cu radiation. Unit cell dimensions were determined and refined by using the angular settings of 25 automatically centered reflections in the range $11 < 2 < 23°$ (for **1** and **4**) and $24 < 2 < 54°$ (for **2** and **3**), and they appear in Table 1. Intensity data were recorded using $\omega-2\theta$ 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[27] and refined by full-matrix least-squares techniques on F^2 with SHELXL-93.[28] Further crystallographic details for compounds **1**−**4** are given in the Supporting

(27) Sheldrick, G. M. *SHELXS-86: Structure Solving Program*; University of Göttingen: Göttingen, Germany, 1986.
(28) Sheldrick, G. M. *SHELXL-93: Crystal Structure Refinement*; University of Göttingen: Göttingen, Germany, 1993.

Scheme 1. Two-Step Synthesis of ReO(L^n/L) Complexes



Emerald complex

Complex	*L^n*	*X*	*Y*
1	$N(CH_2CH_2NH_2)_2$	NH_2	NH_2
2	$(C_2H_5)_2NCH_2CH_2NCH_2CH_2S$	$(C_2H_5)_2N$	S
3	$(CH_2)_4NCH_2CH_2NCH_2CH_2S$	$(CH_2)_4N$	S
4	$C_2H_5SCH_2CH_2NCH_2CH_2S$	C_2H_5S	S

Information. All hydrogen atoms of **1** and **3** were located by difference maps and were refined isotropically, while those of **4** were introduced at calculated positions as riding on bonded atoms. Hydrogen atoms on methyl groups C6 and C8 as well as those of the phenyl ring C22−C26 of **2** were introduced at calculated positions as riding on bonded atoms; the rest were located by difference maps and refined isotropically. All non-hydrogen atoms of **1**−**4** were refined anisotropically (except from the ethanolic atoms in **1** and the methanolic atoms in **4**, which were refined isotropically).

Results and Discussion

Synthesis and Characterization. The ReO(L^n/L) complexes **1**−**4** were prepared in a facile two-step synthesis, as outlined in Scheme 1. Analytical data, given in the Experimental Section, confirm the formulas assigned to ReO(L^n/L) complexes **1**−**4**. All the complexes except for **1**, which is monocationic, are neutral oxorhenium species as a result of coordination of the respective doubly deprotonated $[(R)_2NNS]^{2-}$/$[(R)SNS]^{2-}$ tridentate ligands to the common $[ReO(L)]^{2+}$ fragment. The IR spectra of ReO(L^n/L) complexes exhibit characteristic bands at 933 (for **1**), 915 (for **2** and **3**), and 910 cm^{-1} (for **4**) assigned to the Re═O stretching vibration, values in good agreement with those reported for similar oxorhenium(V) species.[20,21] Additional bands in the 750−690 cm^{-1} region indicate the coordination of the phosphinophenolato chelate spanning an equatorial and the *trans*-oxo positions.[21] The UV/vis spectra show maxima at 368 (for **1**), 320, 325 (for **2** and **3**), and 350 nm (for **4**) that fall within the range of values reported for similar compounds.[20,21]

The NMR spectra reveal that these oxorhenium mixed complexes are diamagnetic, consistent with a d^2 electronic configuration in a distorted octahedral environment. Proton, ^{13}C, and ^{31}P chemical shifts for **1**−**4** are given in the Experimental Section. 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 tridentate-like systems (^{1}H, ^{13}C),[20,24] which were recently and exhaustively investigated using a battery of two-dimensional experiments, including COSY, NOESY, and HETCOR.

Because of the symmetry of the HL^1 ligand, the cationic complex **1** has a mirror plane, which makes the corresponding protons and carbons of the two ethaneamine arms resonate at the same frequency at room temperature. Such a symmetry is removed in complexes **2**−**4**, resulting in more complicated signal patterns. For all the complexes the protons of the coordinated tridentate L^n ligand are distinguished as *endo* (those facing toward the oxo oxygen) and *exo* (those remote from the oxo oxygen). As an example, taking into account both the symmetry of the ligand and the asymmetry introduced in the molecule by the oxo oxygen, the methylene protons of the ethaneamine arms in complex **1** display four distinct signals of identical integration and of various multiplicity (two doublets of doublets, a doublet of triplets, and a multiplet), depending on the different coupling constants induced by the dihedral angles formed between vicinal protons. In addition, proton resonances of the aromatic ring interposed between the P and O donors of the phosphinophenolato fragment are upfield-shifted in the range 6.40−7.40 ppm with respect to those observed for unsubstituted phenyl protons (7.30−8.10 ppm) and are easily distinguished on the basis of their multiplicity and two-dimensional experiments (see the proton network of the P,O-substituted ring in the aromatic region of Figure 1). In complexes **2** and **3**, the protons of the distal diethylamine arms and pyrrolidine ring are further distinguished as *endo* (those facing toward the oxo oxygen) and *exo* (those remote from the oxo oxygen), as depicted in the aliphatic region of Figure 1 for the ethyl substitutents in complex **2**.

The ^{31}P NMR singlet of free HL ($\delta = -31.2$ ppm) moves downfield to the $\delta = -6.2$ to $+3.2$ ppm region upon coordination. Contrasting behavior is shown by complex **4**, in which two singlets are observed. Also, proton NMR and ^{13}C NMR indicate the presence of two compounds in solution (also lowering the temperature to 240 K), giving a series of unresolved multiplets in the aliphatic portion of the proton spectra and 12 carbon signals (instead of the expected 6) in the aliphatic region of the carbon spectra. Despite the unique anti isomer isolated and X-ray authenticated in the solid state (vide infra), the solution state most likely allows the thioether ethyl arm to be both cis- and trans-oriented with respect to the oxo moiety, thereby generating a mixture of syn and anti isomers.

Description of the Structures. ORTEP diagrams of the cation of **1** and of the neutral compounds **2**−**4** are shown in Figures 2−5, respectively, and selected bond distances and

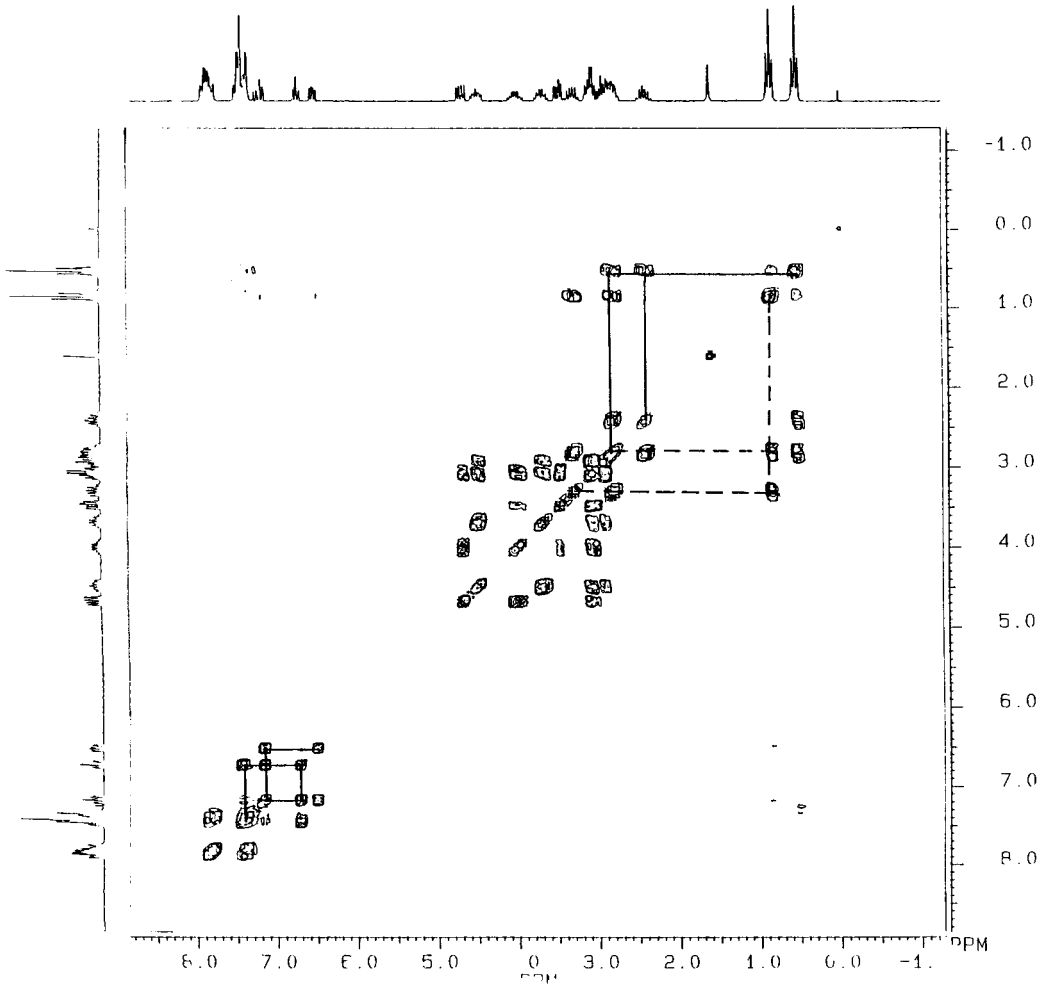


Figure 1. Two-dimensional COSY-90 ^{1}H NMR contour plot of complex **2** in chloroform-*d* over the −1.3 to 8.9 ppm region. In the aliphatic region, solid lines and dotted lines indicate the couplings arising from the ethyl arm oriented *exo* and *endo*, respectively, toward the oxo group. In the aromatic region, the coupling of the four protons of the phenyl ring interposed between the P and O donors is evidenced.

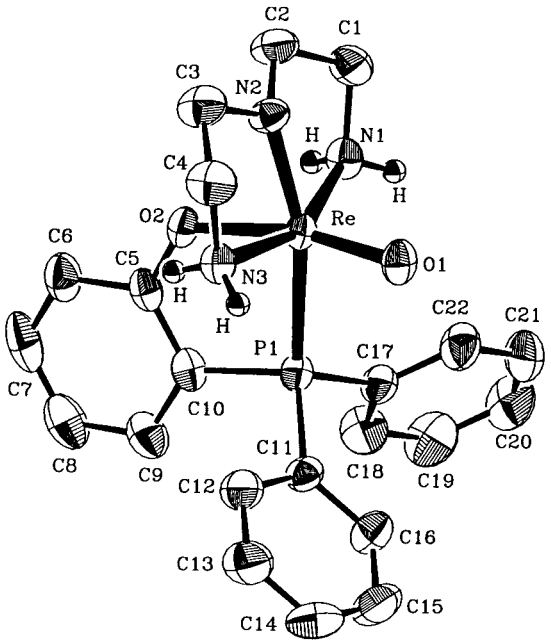


Figure 2. ORTEP diagram of the cation of complex **1**, showing the atomic labeling scheme.

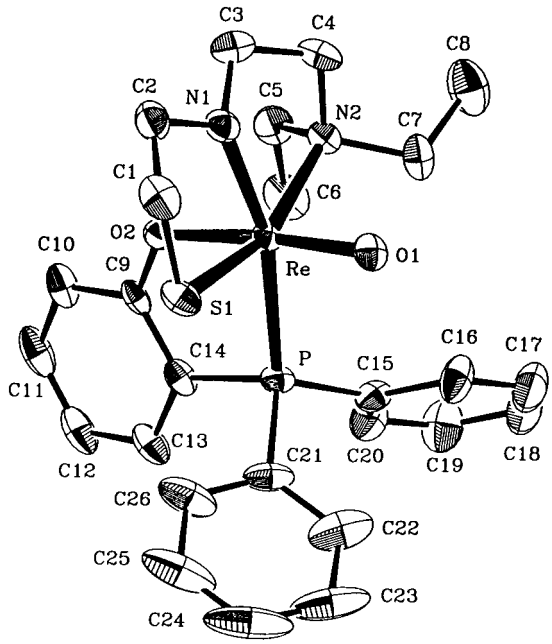


Figure 3. ORTEP diagram of complex **2**, showing the atomic labeling scheme.

angles are listed in Tables 2−4. All compounds present distorted octahedral coordination geometry about rhenium consisting of the tridentate [NNN]/[SNN]/[SNS] ligand, the bidentate PO ligand, and the oxo group. In all four compounds, the coordinate secondary amine nitrogen of the tridentate ligand has lost its proton. In all cases rhenium lies above the equatorial plane,

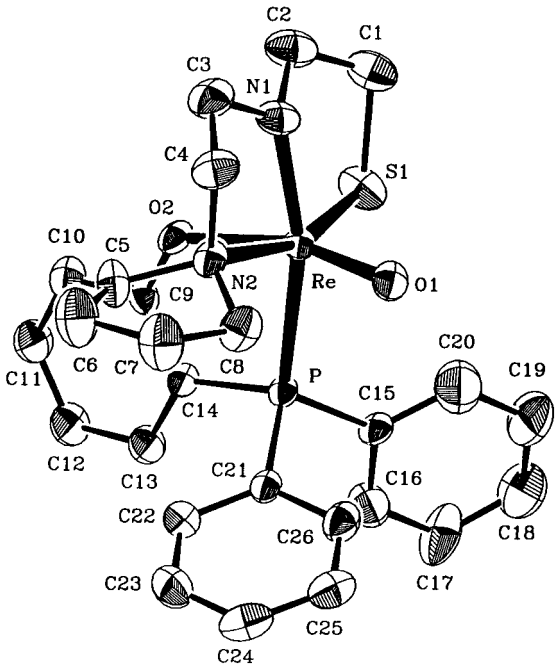


Figure 4. ORTEP diagram of complex **3**, showing the atomic labeling scheme.

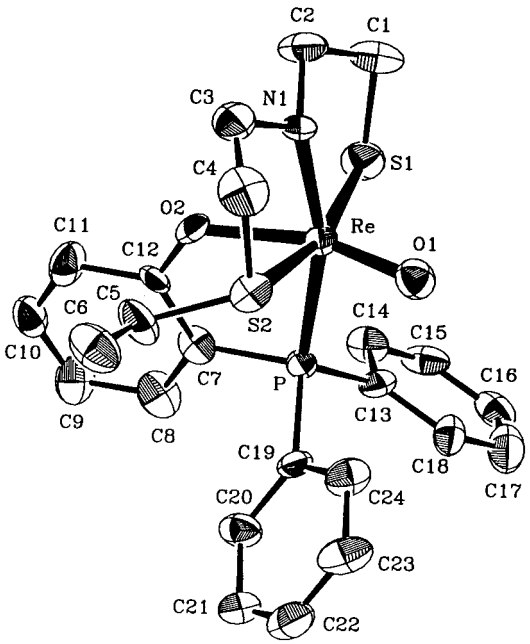


Figure 5. ORTEP diagram of complex **4**, showing the atomic labeling scheme.

defined by the donor atoms of the tridentate ligand and the phosphorus of the bidentate one, toward the oxo group (0.33 Å for **1**, 0.27 Å for **2**, and ∼0.30 Å for **3** and **4**). The Re═O_{oxo} axis is inclined at 79.6°, 78.7°, and 78.2° for **1**−**2**, **3**, and **4**, respectively, with respect to the equatorial plane, which is almost perpendicular to the O−C−C−P chelating plane of the bidentate ligand (88.8, 88.0, 86.2, and 87.7° for **1**−**4**, respectively).

The dihedral angles of the tridentate chelating backbone range from 45.2 to 55.6° (N1−C1−C2−N2 = 46.4° and N2−C3−C4−N3 = −46.8° in **1**; S1−C1−C2−N1 = −45.2° and N1−C3−C4−N2 = 55.6° in **2**; S1−C1−C2−NA = 46.4° and N1−C3−C4−N2 = −49.9° in **3**; S1−C1−C2−N1 = 46.9° and N1−C3−C4−S2 = −48.6° in **4**). The two five-membered rings in the coordination sphere, formed by the metal and the chelating backbone of the tridentate ligand, exist in the stable envelope form. The displacement of the "flap" atom, C1, is 0.54, 0.61, and 0.57 Å in **1**, **2**, and **3,** respectively, while C4 is displaced by 0.57, 0.55, and 0.57 Å in **1**, **2,** and **3,** respectively, out of the mean plane defined by the metal and the remaining three atoms of the chelating backbone. In **4**, C1 and C3 are displaced by 0.57 and 0.58 Å, respectively, out the mean plane of the remaining four atoms. On the other hand, the metal is the "flap" atom of the third five-membered ring in the coordination sphere (Re−O−C−C−P) and is displaced by 0.17, 0.11, 0.24, and 0.26 Å in **1**, **2**, **3**, and **4**, respectively.

Table 2. Selected Bond Distances (Å) and Angles (deg) for **1**

Distance			
Re−O(1)	1.708(3)	Re−N(3)	2.135(4)
Re−N(1)	2.132(4)	Re−P(1)	2.470(2)
Re−O(2)	2.048(3)	Re−N(2)	1.937(4)
Angle			
O(1)−Re−N(2)	110.7(2)	O(2)−Re−N(3)	83.3(2)
O(1)−Re−O(2)	165.1(2)	N(1)−Re−N(3)	156.6(2)
N(2)−Re−O(2)	84.1(2)	O(1)−Re−P(1)	88.6(1)
O(1)−Re−N(1)	100.3(2)	N(2)−Re−P(1)	160.6(1)
N(2)−Re−N(1)	79.8(2)	O(2)−Re−P(1)	76.6(1)
O(2)−Re−N(1)	82.3(2)	N(1)−Re−P(1)	94.9(1)
O(1)−Re−N(3)	98.4(2)	N(3)−Re−P(1)	99.5(1)
N(2)−Re−N(3)	80.5(2)		

Table 3. Selected Bond Distances (Å) and Angles (deg) for **2** and **3**

Distance		
	2	**3**
Re−O(1)	1.707(3)	1.716(4)
Re−N(2)	2.381(7)	2.262(5)
Re−O(2)	2.080(4)	2.101(4)
Re−S(1)	2.298(2)	2.312(2)
Re−N(1)	1.942(5)	1.960(5)
Re−P	2.469(1)	2.461(1)
Angle		
	2	**3**
O(1)−Re−N(1)	107.9(2)	109.3(2)
O(1)−Re−O(2)	161.6(2)	162.8(2)
N(1)−Re−O(2)	86.0(2)	85.2(2)
O(1)−Re−S(1)	102.4(2)	103.5(1)
N(1)−Re−S(1)	84.1(2)	84.4(2)
O(2)−Re−S(1)	90.6(1)	86.7(1)
O(1)−Re−N(2)	89.4(2)	90.9(2)
N(1)−Re−N(2)	79.5(2)	80.0(2)
O(2)−Re−N(2)	81.3(2)	82.3(2)
S(1)−Re−N(2)	162.1(2)	161.6(1)
O(1)−Re−P	89.7(1)	88.9(1)
N(1)−Re−P	162.3(2)	161.8(1)
O(2)−Re−P	77.1(1)	76.7(1)
S(1)−Re−P	91.1(1)	92.3(1)
N(2)−Re−P	102.5(1)	99.4(1)

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

Distance			
Re−O(1)	1.69(1)	Re−S(1)	2.319(3)
Re−N(1)	1.98(1)	Re−P	2.449(4)
Re−O(2)	2.107(9)	Re−S(2)	2.492(3)
Angle			
O(1)−Re−N(1)	109.2(4)	O(2)−Re−P	77.0(4)
O(1)−Re−O(2)	162.8(4)	S(1)−Re−P	90.8(1)
N(1)−Re−O(2)	82.9(4)	O(1)−Re−S(2)	87.5(4)
O(1)−Re−S(1)	103.7(4)	N(1)−Re−S(2)	83.0(4)
N(1)−Re−S(1)	84.5(4)	O(2)−Re−S(2)	81.9(3)
O(2)−Re−S(1)	89.2(4)	S(1)−Re−S(2)	165.4(1)
O(1)−Re−P	91.4(4)	P−Re−S(2)	98.3(1)
N(1)−Re−P	159.4(4)		

The Re═O_{oxo} and Re−$O_{phenolate}$ bond distances are ∼1.70 and ∼2.08 Å, as observed in analogous compounds, while the Re−P distances (∼2.46 Å) are slightly longer than those found in the precursor compound [*n*-$(C_4H_9)_4N$][$ReOCl_3(PO)$][21] (2.422(2) Å) and in [ReO{$(CH_3CH_2)N(CH_2CH_2S)_2$}(PO)] and [ReO-{$(CH_3CH_2SCH_2CH_2)N(CH_2CH_2S)_2$}(PO)] (∼2.40 Å).[22] The lengthening of the Re−P bond distances is reflected in the shortening (ca. 0.24 Å) of the trans Re−$N_{deprotonated}$ bond lengths with respect to analogous compounds.[22] The angles around the deprotonated nitrogens are close to the ideal 120°, as expected for the sp^2 hybridization of these atoms, and the Re, $N_{deprotonated}$, and the carbon atoms adjacent to the nitrogen are nearly coplanar. The metal to sp^3-hybridized nitrogens bond distances fall in the range 2.132(4)−2.381(7) Å depending on the N substitution. Thus, the Re−NH_2 distances in **1** are the shortest ones [Re−N(1) = 2.132(4), Re−N(3) = 2.135(4) Å] followed by the Re−$N_{pyrrolidino}$ in **3** [Re−N(2) = 2.262(5) Å], while the two ethyl substituents on N(2) in **2** result in the longest bond distance of 2.381(7) Å. The Re−S bond distances in compounds **2**−**4** (mean value of 2.309 Å) fall in the range observed for analogous compounds, but a lengthening is found in **4** where the sulfur atom is ethyl-substituted [Re−S(2) = 2.492(3) Å].

The presence of primary amine hydrogens in the cation of **1** is responsible for the formation of hydrogen bonds with the chlorine counterion and the oxo group [HN(1A)···Cl′ (1 − *x*, −0.5 + *y*, 1.5 − *z*) = 2.458 Å, N1···Cl′ = 3.223 Å, N1−HN-(1A)···Cl′ = 144.6°; HN(1B)···O(1′) (1 − *x*, −0.5 + *y*, 1.5 − *z*) = 2.152 Å, N1···O(1′) = 2.938 Å, N1−HN(1B)···O(1′) = 169.0°; HN(3A)···Cl′ (0.5 − *x*,1.5 − *y*, 1.5 − *z*) = 2.563 Å, N3···Cl′ = 3.206 Å, N3−HN(3A)···Cl′ = 141.9°; HN(3B)··· Cl (*x*, *y*, *z*) = 2.358 Å, N3···Cl = 3.190 Å, N3−HN(3B)···Cl = 157.2°].

In conclusion, in this work novel 18-electron octahedral "3 + 2" oxorhenium complexes have been synthesized and characterized. The "3 + 2" approach was followed for enhancing the stability of these metal chelates in the biological milieu compared to the well-known "3 + 1" oxotechnetium and oxorhenium complexes that undergo in vivo substitution/ decomposition reactions. Given that nonradioactive rhenium is often used as a surrogate for technetium and also because of the expanding use of the renium radionuclides ^{186}Re and ^{188}Re in radiotherapy, this study provides preliminary data on new donor atom sets with potential radiopharmaceutical application. Experiments on technetium analogues at the carrier level (^{99g}Tc) as well as both technetium (^{99m}Tc) and rhenium tracer (^{188}Re) levels for exploring the practical applicability of this system are planned.

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Supporting Information Available: Listings of crystal data, fractional atomic coordinates for all atoms, anisotropic thermal parameters for non-H atoms, and full bond lengths and angles. This material is available free of charge via the Internet at http://pubs.acs.org.

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