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Technetium and Rhenium in Five-Coordinate Symmetrical and Dissymmetrical Nitrido Complexes with Alkyl Phosphino-thiol Ligands. Synthesis and Structural Characterization

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The reactivity of bulky alkylphosphino-thiol ligands (PSH) toward nitride-M(V, VI) (M = Tc/Re) precursors was investigated. Neutral five-coordinate monosubstituted complexes of the type $[M(N)(PS)Cl(PPh_3)]$ (**Tc1**−**4**, **Re1**−**2**) were prepared in moderate to high yields. It was found that these $[M(N)(PS)Cl(PPh_3)]$ species underwent ligand-exchange reactions under mild conditions when reacted with bidentate mononegative ligands having soft donor atoms such as dithiocarbamates (NaL^n) to afford stable dissymmetrical mixed-substituted complexes of the type $[M(N)(PS)(L^n)]$ (**Tc5**,**8**−**10**, **Re5**−**9**) containing two different bidentate chelating ligands bound to the $[M{\equiv}N]^{2+}$ moiety. In these reactions, the dithiocarbamate replaced the two labile monodentate ligands (Cl and PPh_3) leaving the $[M(N)(PS)]^+$ building block intact. In the above reactions, technetium and rhenium were found to behave in a similar way. Instead, under more drastic conditions, reactions of PSH with $[M(N)Cl_2(PPh_3)_2]$ gave a mixture of monosubstituted $[M(N)(PS)Cl(PPh_3)]$ and bis-substituted species $[M(N)(PS)_2]$ (**Tc11**−**14**) in the case of technetium, whereas only monosubstituted $[M(N)(PS)Cl(PPh_3)]$ complexes were recovered for rhenium. All isolated products were characterized by elemental analysis, IR and multinuclear (^1H, ^{13}C, and ^{31}P) NMR spectroscopies, ESI MS spectrometry, and X-ray crystal structure determination of the representative monosubstituted $[Tc(N)(PS\textit{tbu})Cl(PPh_3)]$ (**Tc4**) and mixed-substituted $[Re(N)(PS\textit{cy})(L^3)]$ (**Re7**) and $[Re(N)(PS\textit{iso})(L^4)]$ (**Re9**) complexes. The latter rhenium complexes represent the first example of a square-pyramidal nitrido Re species with the basal plane defined by a PS_3 donor set. Monosubstituted $[M(N)(PS)Cl(PPh_3)]$ species bearing the substitution-inert $[M(N)(PS)]^+$ moieties act as suitable building blocks proposed for the construction of new classes of dissymmetrical nitrido compounds with potential application in the development of essential and target specific ^{99m}Tc and ^{188}Re radiopharmaceuticals for imaging and therapy, respectively.

Introduction

Despite the introduction of efficient new technologies based on Tc chemistry (Tc-HYNIC, $[Tc(CO)_3]^+$, and $[Tc(N)(PNP)]^{2+}$), there is an apparent stagnation in introducing novel ^{99m}Tc radiopharmaceuticals due to scientific and economic factors, such as the difficulties in designing Tc-labeled biologically active compounds, the high cost of development, the limited return on the investment, and the increasing performance and competition of other imaging modalities, in particular of positron emission tomography (PET) techniques.[1] Positron-emitting radionuclides currently have an advantage over single-photon-emitting radionuclides in the resolution of the human image, but in the small-animal imaging field, single-photon emission computed tomography (SPECT) is becoming increasingly competitive with PET by exhibiting higher resolution and comparable sensitivity.[2−4]

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In addition, the ability to monitor two emission energies and, therefore, two radiopharmaceuticals simultaneously give SPECT another advantage. It appears that, for human studies, SPECT will be following this trend in instrumentation as well, and thus, ^{99m}Tc should be competitive in all situations as long as the biological half-life of the targeted molecule is consistent with the physical half-life of ^{99m}Tc.

An analysis of the recent literature shows that the number of papers focusing on in vivo evaluation by using small-animal SPECT of new ^{99m}Tc-based compounds has increased reflecting a renewed interest in the research of SPECT compounds.[5]

Considering the ^{99m}Tc radiopharmaceuticals scenario, at present it appears that the commercially available ^{99m}Tc tracers, used in routine clinical practice as myocardial or brain perfusion imaging agents, are far from ideal, while the introduction in the clinical field of receptor-specific radiopharmaceuticals still remains in infancy. Hence, efforts addressed to devise new strategies useful to find more efficient ^{99m}Tc perfusion and new receptor imaging agents continue.

In past years, the chemistry of potential ^{99m}Tc radiopharmaceuticals has been expanded due to the introduction of an efficient method for the production, at tracer level, of ^{99m}Tc species containing the terminal Tc≡N multiple bond, in sterile and pyrogen-free conditions. It was found that the resulting $[Tc{\equiv}N]^{2+}$ core could be viewed as a true inorganic functional group exhibiting very high stability under a wide range of experimental conditions.[6] Based on these considerations, extensive studies have been carried out on the synthesis and biological evaluation of different classes of symmetrical and dissymmetrical five-coordinate nitrido technetium complexes of the type $[^{99m}Tc(N)(L)_2]$, $[^{99m}Tc(N)(Ar_2PS)_2]$ (where L is a dithiocarbamate and Ar_2PS an arylphosphino-thiolate ligand), and $[^{99m}Tc(N)(YZ)(PNP)]^{+/0}$ (where YZ is a π-donor bidentate ligand and PNP a polydentate aminodiphosphine).[7,8] Biodistribution profiles in rats of some of these different compounds displayed promising biological properties.[9] In particular, the monocationic $[^{99m}Tc(N)(DBODC)(PNP5)]^+$ complex [DBODC = bis-(*N*-ethoxyethyl)dithiocarbamato; PNP5 = bis-*N*,*N*-(dimethoxypropylphosphinoethyl)ethoxyethylamine] showed high and persistent myocardial uptake with favorable target-to-not-target ratios, and it is currently under investigation as potential myocardial imaging agent.[10]

Over the past few years, we reported an extensive study on the reactivity of different bidentate mixed phosphino-thiol (R_2PSH) ligands (R = phenyl, tolyl, cyclohexyl) toward both pertechnetate and prereduced technetium compounds such as oxo-$Tc^{(V)}$ and nitride-$Tc^{(V/VI)}$ precursors.[7,11] Reaction of $[Tc(N)Cl_2(PPh_3)_2]$ with the bulky 2-(dicyclohexylphosphino)-ethanethiol (PS*cy*H) ligand afforded a rare example of monosubstituted species $[Tc(N)(PScy)Cl(PPh_3)]$.[12] This complex was produced at tracer level with the metastabile isotope ^{99m}Tc.

^{99m}Tc studies aimed to evaluate the role of the PPh_3 in the formation of monosubstituted complexes, with respect to the use of other tertiary phosphines [TPPS = tris(3-sulfonatophenyl)phosphine; PCN = tris(2-cyanoethyl)phosphine; $P(CH_2OH)_3$ = tris(hydroxymethyl)phophine], which were selected according to their electronic and steric properties, showed the key role of the PPh_3 unit in controlling the formation and stabilization of reactive monosubstituted entity characterized by the $[^{99m}Tc(N)(PS)]^+$ building block.[13]

Furthermore, it was found that $[^{99m}Tc(N)(PS)Cl(PPh_3)]$ reacted almost quantitatively with mononegative bidentate ligands, such as dithiocarbamates (NaL^n), to provide another class of neutral species, assigned as mixed-substituted $[^{99m}Tc(N)(PS)(L^n)]$ compounds. Preliminary biodistribution studies of representative $[^{99m}Tc(N)(PS)(L^n)]$ tracers revealed an initial brain uptake followed by a rapid washout, indicating their ability to cross in and out of the blood−brain barrier (BBB).[13]

The purpose of this investigation was to elucidate the chemical structure of these mixed-substituted ^{99m}Tc agents. This was achieved through the comparison of their chemical and physical properties with those of the corresponding compounds prepared at macroscopic level with the long-lived isotope Tc and with the naturally occurring mixture of cold Re isotopes and characterized by standard analytical and spectroscopic methods.

The elucidation of the molecular structure of this new class of complexes could be essential to (i) clarify the chemical behavior and the reactivity of this new class of complexes,

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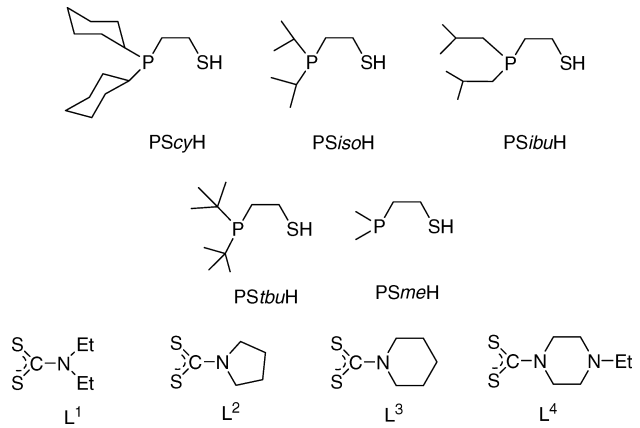

Figure 1. Phosphino-thiol and dithiocarbamate ligands.

(ii) understand the mechanism responsible of their biodistribution profile, and (iii) provide an important design strategy aimed at improving the biological properties of these molecules through rational modification of their chemical structure.

Hence, this study describes the synthesis and the solution- and solid-state determination of the molecular structure of three series of Tc and Re compounds: monosubstituted [M(N)(PS)Cl(PPh$_3$)] (**Tc1**−**4**, **Re1**−**2**), dissymmetric mixed-substituted [M(N)(PS)(L^n)] (**Tc5**,**8**−**10**, **Re5**−**9**), and symmetric bis-substituted [Tc(N)(PS)$_2$] (**Tc11**−**14**), where PS and L^n indicate the deprotonated form of alkyl phosphino-thiolate and of dithiocarbamate ligands, respectively.

Bidentate phosphino-thiol (PSH) and dithiocarbamate (NaL^n) ligands utilized in our experiments are depicted in Figure 1.

Experimental Section

Caution! *Tc is a weak β-emitter (E_β = 0.292 MeV, $t_{1/2}$ = 1.12 × 10^5 years). All manipulations were carried out in laboratories approved for low-level radioactivity use. Handling milligram amounts of Tc does not present a serious health hazard, since common laboratory glassware provides adequate shielding and all work is performed in approved and monitored hoods and glove-boxes. Bremsstrahlung is not a significant problem due to the low energy of the β-particles; however, proper radiation safety procedures must be followed at all times, and particular care should be taken when handling solid samples.*

Materials. All chemicals and reagents were purchased from Aldrich Chemicals. The solvents were reagent grade and were used without further purification. Due to the tendency of the phosphine thiol ligands to oxidize, all the solvents used in reactions with PSH were previously degassed to remove dissolved trace dioxygen.

Commercially available [(NH$_4$)TcO$_4$] (Oak Ridge National Laboratories) was purified from a black contaminant (TcO$_2$·nH$_2$O) by addition of H$_2$O$_2$ and NH$_4$OH solutions followed by recrystallization as [(NH$_4$)TcO$_4$] from hot water.

[(AsPh$_4$)Tc(N)Cl$_4$] and [Tc(N)Cl$_2$(PPh$_3$)$_2$] were prepared as previously described.[14] The phosphine thiol ligands were purchased from Argus Chemicals (Prato, Italy). Dithiocarbamates NaL^1 and NaL^2 were purchased from Sigma Aldrich. The remaining dithiocarbamates were synthesized according to literature methods.[6,9]

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Physical Measurements. Elemental analyses (C, H, N, S) were performed on a Carlo Erba 1106 elemental analyzer. FT IR spectra were recorded on a Nicolet 510P Fourier transform spectrometer in the range 4000−200 cm^{-1} and in KBr mixture using a Spectra-Tec diffuse-reflectance collector accessory. ^{1}H, ^{13}C, and ^{31}P NMR spectra were acquired at room temperature in CDCl$_3$ on a Brucker 300 instrument, using SiMe$_4$ as internal reference (^{1}H and ^{13}C) and 85% aqueous H$_3$PO$_4$ as external reference (^{31}P).

Mass spectrometric measurements (ESI MS) were performed with a LCQ DECA (Thermo Finnigan, San Jose, CA) ion trap instrument operating in the positive ion mode.

Chromatographic separations were accomplished on a SiO$_2$ column (30 cm × 2 cm, 70−230 mesh, Aldrich). TLC analyses were carried out using C18 F$_{254S}$ or SiO$_2$ F$_{254S}$ plates (Merck) eluted with a mixture of CH$_3$CN/H$_2$O (90/10) or EtOH/CHCl$_3$/C$_6$H$_6$ (0.1/2/1.5), respectively. Tc radioactivity on TLC plates was detected and measured using a Cyclone Instrument equipped with a phosphorus imaging screen and OptiQuant image analysis software (Packard, Meridian, CT).

Synthesis of Monosubstituted Complexes. [Tc(N)(PS*cy*)Cl(PPh$_3$)] (**Tc1**) was prepared as previously reported.[12]

[Tc(N)(PS)Cl(PPh$_3$)] (PS = PS*iso*, PS*ibu*, PS*tbu*) (Tc2−4). To 0.092 mmol of [Tc(N)Cl$_2$(PPh$_3$)$_2$] suspended in CH$_2$Cl$_2$ (5 mL) was added 0.140 mmol of the selected PSH ligand dissolved in EtOH (5 mL). The mixture was stirred at reflux for 30 min during which the solution became clear and the color changed to yellow. The solvents were removed, and the residue was treated with EtOH. A yellow precipitate was collected by filtration and washed with EtOH followed by *n*-hexane. The solid was dissolved in CHCl$_3$, loaded onto a silica column previously conditioned, and eluted with CHCl$_3$. A yellow band was separated and collected. The eluate was evaporated, and the residue was treated with Et$_2$O to yield the pure [Tc(N)(PS)Cl(PPh$_3$)] compound (yields 80−85%).

[Tc(N)(PS*iso*)Cl(PPh$_3$)] (Tc2): Yield 80%. Anal. Calcd for C$_{26}$H$_{33}$NP$_2$SClTc (MW 588.06): C 53.10, H 5.65, N 2.39, S 5.45. Found: C 53.24, H 5.69, N 2.32, S 5.22.

FT-IR (KBr, cm^{-1}): [1065 (ν Tc≡N)], [3054 ν(H−Ar)], [2955−2870 ν(H−alkyl)], [746−693 ν(H−Ar)].

^{31}P NMR (CDCl$_3$ ppm): δ 96.9 (bs), 40.7 (bs). ^{1}H NMR (CDCl$_3$ ppm): δ 7.95−7.28 (m, 15H, C$_6$*H*$_5$P), 2.96 and 2.75 (m, 1H + 1H, SC*H*$_2$CH$_2$P), 2.72 and 2.41 (m, 1H + 1H, PC*H*(CH$_3$)$_2$), 2.39 and 1.79 (m, 1H + 1H, SCH$_2$C*H*$_2$P), 1.48, 1.24, and 0.70 (dd, 3H + 6H + 3H, PCH(C*H*$_3$)$_2$).

[Tc(N)(PS*ibu*)Cl(PPh$_3$)] (Tc3): Yield 82%. Anal. Calcd for C$_{28}$H$_{37}$NP$_2$SClTc (MW 616.06): C 54.59, H 6.05, N 2.27, S 5.20. Found: C 54.84, H 6.44, N 2.09, S 5.22.

FT-IR (KBr, cm^{-1}): [1052 (ν Tc≡N)], [3055 ν(H−Ar)], [2956−2867 ν(H−alkyl)], [749−695 ν(H−Ar)]. ^{31}P NMR (CDCl$_3$ ppm): δ 65.3 (bs), 38.4 (bs). ^{1}H NMR (CDCl$_3$ ppm): δ 7.80−7.36 (m, 15H, C$_6$*H*$_5$P), 3.08−1.75 (2H + 2H + 2H + 2H + 1H + 1H, (SC*H*$_2$CH$_2$P), PCH$_2$C*H*(CH$_3$)$_2$, (SCH$_2$C*H*$_2$P), and PC*H*$_2$CH(CH$_3$)$_2$), 1.18−0.81 (12H, PCH$_2$CH(C*H*$_3$)$_2$).

ESI MS (*m*/*z*): 580.2 [M − Cl]$^+$.

[Tc(N)(PS*tbu*)Cl(PPh$_3$)] (Tc4): Yield 85%. Yellow crystals of **Tc4** suitable for X-ray studies were obtained by slow diffusion of *n*-hexane into a CH$_2$Cl$_2$ solution of the compound.

Anal. Calcd for C$_{28}$H$_{37}$NP$_2$SClTc (MW 616.06): C 54.59, H 6.05, N 2.27, S 5.20. Found C 54.62, H 6.09, N 2.22, S 5.25.

FT-IR (KBr, cm^{-1}): [1066 (ν Tc≡N)], [3049 ν(H−Ar)], [2957−2868 ν(H−alkyl)], [749−692 ν(H−Ar)]. ^{31}P NMR (CDCl$_3$ ppm): δ 102.6 (bs), 40.4 (bs). ^{1}H NMR (CDCl$_3$ ppm): δ 7.83−7.33 (m, 15H, C$_6$*H*$_5$-P), 3.13 [m, 1H, SC*H*$_2$CH$_2$P], 2.48

[m, 1H + 1H, SCH_2CH$_2$P and SCH$_2$CH_2P], 1.86 [m, 1H, SCH$_2$CH_2P], 1.58 [d, $^3J_{HP}$ = 13 Hz, 9H, C(CH_3)$_3$], 1.17 [d, $^3J_{HP}$ = 13 Hz, 9H, C(CH_3)$_3$].

[Re(N)(PS)Cl(PPh$_3$)] (PS = PS*cy*, PS*iso*) (Re1,2). The reactions were carried out as indicated for the Tc complexes. Column chromatography was not necessary to obtain pure Re products. After cooling, the solvents were completely removed by gentle dinitrogen stream, and the residue was treated with EtOH. A yellow precipitate was collected by filtration and washed with EtOH followed by Et$_2$O and *n*-hexane.

[Re(N)(PS*cy*)Cl(PPh$_3$)] (Re1): Yield 90%. Anal. Calcd for $C_{32}H_{41}NP_2SClRe$ (MW 755.33): C 50.88, H 5.47, N 1.85, S 4.24. Found: C 50.84, H 5.44, N 1.81, S 4.32.

FT-IR (KBr, cm^{-1}): [1075 ν(Re≡N)], [3055 ν(H−Ar)], [2926−2851 ν(H−Cy)], [746−694 ν(H−Ar)].

^{31}P NMR (CDCl$_3$ ppm): δ 82.7 (d, $^2J_{PP}$ = 170 Hz, *P*CH$_2$CH$_2$S), 35.9 (d, $^2J_{PP}$ = 170 Hz, *P*Ph$_3$). ^{1}H NMR (CDCl$_3$ ppm): δ 7.86−7.29 (m, 15H, C$_6H_5$P), 2.91 and 2.63 (m + m, 1H + 1H, SCH_2CH$_2$P), 2.02−1.03 (22H, *Cy*P), 1.93 and 1.46 (m + m, 1H + 1H, (SCH$_2$CH_2P)).

[Re(N)(PS*iso*)Cl(PPh$_3$)] (Re2): Yield 85%. Anal. Calcd for $C_{26}H_{33}NP_2SClRe$ (MW 675.26): C 46.24, H 4.92, N 2.07, S 4.75. Found: C 46.29, H 4.93, N 2.10, S 4.80.

FT-IR (KBr, cm^{-1}): [1075 ν(Re≡N)], [3052 ν(H−Ar)], [2957−2870 ν(H−alkyl)], [747−694 ν(H−Ar)].

^{31}P NMR (CDCl$_3$ ppm): δ 92.0 (d, $^2J_{PP}$ = 170 Hz, *P*CH$_2$CH$_2$S), 35.2 (d, $^2J_{PP}$ = 170 Hz, *P*Ph$_3$). ^{1}H NMR (CDCl$_3$ ppm): δ 7.90−7.28 (m, 15H, C$_6H_5$P), 2.95 and 2.63 (m + m, 1H + 1H, SCH_2CH$_2$P), 2.75 and 2.42 (m + m, 1H + 1H, PCH(CH$_3$)$_2$), 1.96 and 1.44 (m + m, 1H + 1H, SCH$_2$CH_2P), 1.51, 1.25, and 0.62 (dd, 3H + 6H + 3H, PCH(CH_3)$_2$).

Monosubstituted [M(N)(PS)Cl(PPh$_3$)] compounds are soluble in chlorinated solvents, benzene, and toluene and insoluble in alcohols, MeCN, Et$_2$O, and *n*-hexane.

Synthesis of Mixed-Substituted Dissymmetrical Complexes. [M(N)(PS)(L^n)] (M = Tc5,8−10, Re5−9). To 0.051 mmol of the selected intermediate complex (**M1−4**) dissolved in 5 mL of CH$_2$Cl$_2$, 0.06 mmol of the appropriate dithiocarbamate ligand (L$^{1-4}$) was added. The reaction mixture was stirred at room temperature for 30 min. Rapidly the solution became clear, and the color changed to yellow-green.

The reaction mixture was concentrated by gentle dinitrogen stream and a white powder was removed by filtration. The solvent was completely evaporated and the yellow-green residue was treated with *n*-hexane to remove the PPh$_3$.

[Tc(N)(PS*cy*)(L^1)] (Tc5): The final product was isolated as pure yellow powder upon treatment of the residue with Et$_2$O. Yield 85%. Anal. Calcd for $C_{19}H_{36}N_2PS_3Tc$ (MW = 516.06): C 44.22, H 7.03, N 5.42, S 12.42. Found: C 43.65, H 7.12, N 5.56, S 13.20.

FT IR (cm^{-1}): [1059 ν(Tc≡N)], [2928−2851 ν(H−Cy)].

^{31}P NMR (CDCl$_3$ ppm): δ 92.5 (bs). ^{1}H NMR (CDCl$_3$ ppm): δ 4.02−3.67 (4H, NCH_2CH$_3$), 2.89 (m, 2H, SCH_2CH$_2$P), 2.16−1.16 (22H + 2H + 6H, *Cy*P, SCH$_2$CH_2P and NCH$_2$CH_3).

ESI-MS(+) (*m*/*z*): 1058 [2 M + Na]$^+$ (60%), 541 [M + Na]$^+$ (26%), 519 [M + H]$^+$ (100%).

[M(N)(PS)(L^n)] (M6−10). Column chromatography was necessary to separate pure species from the corresponding bis-substituted [Tc(N)(L^n)$_2$] and other unidentified side products. The residue was dissolved in CHCl$_3$ (1 mL) and loaded onto a silica column previously conditioned with CHCl$_3$. The column was eluted with CHCl$_3$. Evaporation by a dinitrogen stream of the eluate led to the isolation of a pure yellow solid. A different eluant was utilized for the purification of **Tc9** (CHCl$_3$/MeOH 98/2).

[Tc(N)(PS*iso*)(L^2)] (Tc8): Yield 81%. Anal. Calcd for $C_{13}H_{26}N_2PS_3Tc$ (MW 436.51): C 35.77, H 6.00, N 6.41, S 22.03. Found: C 35.79, H 6.04, N 6.40, S 22.23.

FT IR (cm^{-1}): [1062 ν(Tc≡N)], [2956−2870 ν(H−alkyl)], [1510 ν(S$_2$CN<)].

^{31}P NMR (CDCl$_3$ ppm): δ 102.7 (bs). ^{1}H NMR (CDCl$_3$ ppm): δ 3.83 [m, 4H, NCH_2CH$_2$], 2.92 [m, 2H, SCH_2CH$_2$P], 2.32 [m, 1H + 1H, PCH(CH$_3$)$_2$], 2.06 [m, 4H, NCH$_2$−CH_2], 2.06 and 2.00 [m, 1H + 1H, SCH$_2$CH_2P], 1.22 [m, 9H, PCH(CH_3)$_2$], 0.93 [dd, 3H, PCH(CH_3)$_2$]. ^{13} C NMR (CDCl$_3$ ppm): δ 211.05 (*C*S$_2$), 50.28 and 50.06 (s + s, N*C*H$_2$CH$_2$), 31.16 [d, $^2J_{PC}$ = 7.5 Hz, S*C*H$_2$CH$_2$P], 26.09 [d, $^1J_{PC}$ = 30.1 Hz, SCH$_2$*C*H$_2$P], 24.95−24.64 [NCH$_2$*C*H$_2$], 23.82 and 23.55 [s + s, P*C*H(CH$_3$)$_2$], 19.42, 18.88, 17.42 and 17.21 [4s, PCH(*C*H$_3$)$_2$].

ESI-MS(+) (*m*/*z*): 459 [M + Na]$^+$ (54%), 437 [M + H]$^+$ (36%), 367 [M + H − pyr]$^+$ (100%).

[Tc(N)(PS*iso*)(L^4)] (Tc9): Yield 75%. Anal. Calcd for $C_{15}H_{31}N_3PS_3Tc$ (MW 479.58): C 37.56, H 6.51, N 8.76, S 20.05. Found: C 37.62, H 6.53, N 8.71, S 20.22.

FT-IR (KBr, cm^{-1}): [1062 ν(Tc≡N)], [2959−2821 ν(H−alkyl)], [1517 ν(S$_2$CN<)].

^{31}P NMR (CDCl$_3$ ppm): δ 102.3 (bs). ^{1}H NMR (CDCl$_3$ ppm): δ 4.15 and 3.92 [m + m, 2H + 2H, NCH_2CH$_2$NCH$_2$CH$_3$], 2.93 [m, 2H, SCH_2CH$_2$P], 2.57 [m, 4H, NCH$_2$CH_2NCH$_2$CH$_3$], 2.47 [q, 2H, NCH_2CH$_3$], 2.31 and 2.25 [m + m, 1H + 1H, PCH(CH$_3$)$_2$], 2.08 and 1.93 [m + m, 1H + 1H, SCH$_2$CH_2P], 1.36−0.94 [4 dd, 12H, PCH(CH_3)$_2$], 1.11 [t, 3H, NCH$_2$CH_3]. ^{13}C NMR (CDCl$_3$ ppm): δ 210.5 (s, *C*S$_2$), 51.9 [s, NCH$_2$*C*H$_2$NCH$_2$CH$_3$], 51.71 (s, N*C*H$_2$CH$_3$), 47.7 and 47.1 (s + s, N*C*H$_2$CH$_2$NCH$_2$CH$_3$], 31.08 [d, $^2J_{PC}$ = 7.3 Hz, S*C*H$_2$CH$_2$P], 26.12 [d, $^1J_{PC}$ = 29.6 Hz, 1C, SCH$_2$*C*H$_2$P], 24.82 [d, $^1J_{PC}$ = 24.3 MHz, P*C*H(CH$_3$)$_2$], 23.66 [d, $^1J_{PC}$ = 23.6 Hz, P*C*H(CH$_3$)$_2$], 19.42, 18.86, 17.41, and 17.24 [4s, PCH(*C*H$_3$)$_2$], 11.90 (s, NCH$_2$*C*H$_3$).

[Tc(N)(PS*tbu*)(L^3)] (Tc10): Yield 84%. Anal. Calcd for $C_{16}H_{32}N_2PS_3Tc$ (MW 478.60): C 40.15, H 6.74, N 5.85, S 20.09. Found: C 40.22, H 6.51, N 5.71, S 21.05.

FT-IR (KBr, cm^{-1}): [1063 (ν Tc≡N)], [2957−2868 ν(H−alkyl)], [1512 ν(S$_2$CN<)].

^{31}P NMR (CDCl$_3$ ppm): δ 115.9 (bs). ^{1}H NMR (CDCl$_3$ ppm): δ 4.14 and 3.88 [m, 2H + 2H, NCH$_2$CH_2CH$_2$], 2.96 [m, 2H, SCH_2CH$_2$P], 2.12 [m, 2H, SCH$_2$CH_2P], 1.75 [bs, 4H + 2H, NCH$_2$CH_2CH$_2$ and NCH$_2$CH$_2$CH_2], 1.45 and 1.19 [d, $^3J_{HP}$ = 13 Hz, 9H + 9H, PC(CH_3)$_3$].

[Re(N)(PS*cy*)(L^1)] (Re5): Yield 60%. Anal. Calcd for $C_{19}H_{36}N_2PS_3Re$ (MW 606.13): C 37.65, H 5.98, N 4,62, S 15.86. Found: C 37.22, H 6.01, N 4.65, S 16.98.

FT-IR (KBr, cm^{-1}): [1072 ν(Re≡N)] [2940−2850 ν(H−Cy)], [1522 ν(S$_2$CN<)].

^{31}P NMR (CDCl$_3$ ppm): δ 84.6 (s). ^{1}H NMR (CDCl$_3$ ppm): δ 4.05−3.53 (4H, NCH_2CH$_3$), 2.81 (m, 2H, SCH_2CH$_2$P), 2.15−1.12 (22H + 2H + 6H, *Cy*P, SCH$_2$CH_2P and NCH$_2$CH_3).

[Re(N)(PS*cy*)(L^2)] (Re6): Yield 70%. Anal. Calcd for $C_{19}H_{34}N_2PS_3Re$ (MW 604.11): C 37.77, H 5.67, N 4,63, S 15.92. Found: C 36.48, H 5.37, N 4.51, S 16.24.

FT-IR (KBr, cm^{-1}): [1072 ν(Re≡N)], [2924−2850 ν(H−Cy)], [1508 ν(S$_2$CN<)].

^{31}P NMR (CDCl$_3$ ppm): δ 84.3 (s). ^{1}H NMR (CDCl$_3$ ppm): δ 3.82 (m, 4H, N[CH_2CH$_2$]$_2$), 2.81 (m, 2H, SCH_2CH$_2$P), 2.18−1.12 (22H + 2H + 4H, *Cy*P, SCH$_2$CH_2P and N[CH$_2$CH_2]$_2$). ^{13} C NMR (CDCl$_3$

ppm): δ 218.77 (*C*S$_2$), 50.26 and 49.88 (s + s, N*C*H$_2$CH$_2$), 35.95 [d, $^2J_{PC}$ = 6.8 Hz, S*C*H$_2$CH$_2$P], 34.76, 34.36, 33.95, 33.59 29.68, 29.21, 27.99, 27.48, 27.05, 26.92, 26.52, 26.00, 25.73, 24.86, 24.72.

[Re(N)(PS*cy*)(L^3)] (Re7): Yellow crystals of **Re7**·$^1/_2$H$_2$O suitable for X-ray studies were obtained by slow diffusion of *n*-hexane into a CH_2Cl_2 solution of the compound. Yield 73%. Anal. Calcd for $C_{20}H_{36}N_2PS_3Re$ (MW 618.13): C 38.86, H 5.87, N 4,55, S 15.56. Found: C 38.67, H 6.01, N 4.60, S 15.85.

FT-IR (KBr, cm^{-1}): [1073 ν(Re≡N)], [2913−2849 ν(H−Cy)], [1522 ν(S$_2$CN<)].

^{31}P NMR ($CDCl_3$ ppm): δ 84.6 (s). ^{1}H NMR ($CDCl_3$ ppm): δ 4.08 and 3.76 (m + m, 2H + 2H, N[C*H*$_2$CH$_2$]$_2$CH$_2$), 2.91 (m, 2H, SC*H*$_2$CH$_2$P), 2.21−1.04 (22H + 2H + + 2H + 4H, *Cy*P, SCH$_2$C*H*$_2$P and N[CH$_2$C*H*$_2$]$_2$C*H*$_2$). ^{13} C NMR ($CDCl_3$ ppm): δ 224.08 (*C*S$_2$), 49.07 and 48.24 (s + s, N*C*H$_2$CH$_2$), 35.80 [d, $^2J_{PC}$ = 6.8 Hz, S*C*H$_2$CH$_2$P], 34.72, 34.31, 33.88, 33.53 29.26, 29.21, 27.88, 27.44, 27.03, 26.92, 26.56, 26.00, 25.73, 25.66, 24.48, 23.91.

[Re(N)(PS*iso*)(L^2)] (Re8): Yield 65%. Anal. Calcd for $C_{13}H_{26}N_2PS_3Re$ (MW 524.05): C 29.79, H 5.00, N 5,34, S 18.35. Found: C 29.07, H 5.07, N 5.40, S 18.80.

FT-IR (KBr, cm^{-1}): [1072 ν(Re≡N)], [2952−2868 ν(H−alkyl)], [1508 ν(S$_2$CN<)].

^{31}P NMR ($CDCl_3$ ppm): δ 94.0(s). ^{1}H NMR ($CDCl_3$ ppm): δ 3.83 (m, 4H, N[C*H*$_2$CH$_2$]$_2$), 2.85 (m, 2H, S*CH*$_2$CH$_2$P), 2.30 (m, 1H + 1H, PC*H*(CH$_3$)$_2$), 2.08 (m, 4H, N[CH$_2$C*H*$_2$]$_2$), 1.91 and 1.52 (m+m, 1H+1H, SCH$_2$C*H*$_2$P), 1.30−0.91 (6H+6H, PCH(C*H*$_3$)$_2$). ESI-MS(+) (*m*/*z*): 547 [M + Na]$^+$ (100%), 525 [M + H]$^+$ (20%).

[Re(N)(PS*iso*)(L^4)] (Re9): Yellow crystals of **Re9** suitable for X-ray studies were obtained by slow diffusion of *n*-hexane into a CH_2Cl_2 solution of the compound. Anal. Calcd for $C_{15}H_{31}N_3PS_3Re$ (MW 567.09): C 31.77, H 5.51, N 7,41, S 16.96. Found: C 31.27, H 5.50, N 7.49, S 17.32.

FT-IR (KBr, cm^{-1}):[1072 ν(Re≡N)], [2958−2810 ν(H−alkyl)], [1524 ν(S$_2$CN<)].

^{31}P NMR ($CDCl_3$ ppm): δ 94.1 (s). ^{1}H NMR (CCl_3 ppm): δ 4.11 and 3.84 (m + m, 2H + 2H, N[C*H*$_2$CH$_2$]$_2$NCH$_2$CH$_3$), 2.85 (m, 2H, S*CH*$_2$CH$_2$P), 2.58 (m, 4H, N[CH$_2$C*H*$_2$]$_2$NCH$_2$CH$_3$), 2.48 (q, 2H, N[CH$_2$CH$_2$]$_2$NC*H*$_2$CH$_3$), 2.32 (m, 1H + 1H, PC*H*(CH$_3$)$_2$), 1.92 and 1.53 (m + m, 1H + 1H, SCH$_2$C*H*$_2$P), 1.39−0.89 (6H + 6H + 3H, PC*H*(CH$_3$)$_2$ and N[CH$_2$C*H*$_2$]$_2$NCH$_2$C*H*$_3$).

^{13}C NMR ($CDCl_3$ ppm): δ 228.26 (*C*S$_2$), 51.86, 51.79, 51.62, 47.77, 46.92, 36.26 [d, $^2J_{PC}$ = 6.6 Hz, S*C*H$_2$CH$_2$P], 27.55, 27.11, 25.73, 25.33, 24.36, 23.99, 19.33, 17.56, 11.93.

ESI-MS(+) (*m*/*z*): 590 [M + Na]$^+$ (26%), 568 [M + H]$^+$ (52%), 547 [M + Na − CH(CH$_3$)$_2$]$^+$ (100%).

Mixed-substituted complexes are soluble in chlorinated solvents, MeCN, and alcohols and insoluble in *n*-hexane, Et_2O, and water.

Synthesis of Bis-substituted Complexes. [Tc(N)(PS)$_2$] (Tc11−14) (PS = PSme, PS*iso*, PS*ibu*, PS*tbu*) and [Tc(N)(PS*ibu*)(OPS*ibu*)] (Tc13a). For method a, to 0.194 mmol of the selected PSH ligand dissolved in degassed EtOH (5 mL) were added ten drops of TFA (10% v/v) followed by 0.05 mmol of [(AsPh$_4$)Tc(N)Cl$_4$] dissolved in CH_2Cl_2 (2 mL). The reaction mixture was stirred at reflux under dinitrogen atmosphere for 2 h during which the solution became yellow-brown. The solvents were removed by gentle dinitrogen stream, and the crude product was treated with Et_2O. Column chromatography was necessary to separate pure species. The residue was dissolved in $CHCl_3$ and loaded onto a silica column previously conditioned with $CHCl_3$. The column was eluted with $CHCl_3$ and two yellow bands were separated and collected. The eluate was evaporated, and the residues were treated with Et_2O to yield the complexes. The first yellow product was identified as the pure [Tc(N)(PS)$_2$] compound (yield ≈ 80%) and the second yellow complex as the oxidized derivative (yield < 10%).

For method b, to 0.092 mmol of [Tc(N)Cl$_2$(PPh$_3$)$_2$] suspended in CH_2Cl_2 (5 mL) was added 0.928 mmol of the selected PSH ligand dissolved in EtOH (5 mL). The reaction mixture was stirred at reflux under dinitrogen atmosphere overnight. After cooling, the solvents were removed by gentle dinitrogen stream, and the residue was treated with *n*-hexane. A yellow precipitate was collected by filtration. The solid was dissolved in $CHCl_3$ and loaded onto a silica column previously conditioned with $CHCl_3$. The column was eluted with $CHCl_3$, and two yellow bands were separated and collected. The eluate was evaporated, and the residues were treated with Et_2O to yield the complexes. The first yellow product was identified as [Tc(N)(PS)Cl(PPh$_3$)] (vide infra) and the second yellow complex as [Tc(N)(PS)$_2$] (yields 60−80%).

[Tc(N)(PSme)$_2$] (Tc11): Yield 60%. Anal. Calcd for $C_8H_{20}P_2S_2NTc$ (M.W 354.95): C 27.07, H 5.67, N 3.94, S 9.03. Found: C 27.92, H 5.40, N 3.51, S 9.50. FT-IR (KBr, cm^{-1}): [1066 (ν Tc≡N)], [2950−2867 ν(H−alkyl)].

^{31}P NMR ($CDCl_3$ ppm): δ 48.9 (bs). ^{1}H NMR ($CDCl_3$ ppm): δ 1.57 [m, 12H P(C*H*$_3$)$_2$], 2.08 and 2.01 [m, 2H + 2H, SCH$_2$C*H*$_2$P], 2.89 [m, 4H, SC*H*$_2$CH$_2$P].

^{13}C NMR ($CDCl_3$ ppm): δ 35.90 [SCH$_2$*C*H$_2$P], 28.79 [S*C*H$_2$CH$_2$P], 17.15 and 11.11 [P(*C*H$_3$)$_2$].

[Tc(N)(PS*iso*)$_2$] (Tc12): Yield 81%. Anal. Calcd for $C_{16}H_{36}NP_2S_2Tc$ (MW 467.59): C 41.10, H 7.76, N 3.01, S 13.71. Found C 40.84, H 7.44, N 2.81, S 13.92.

FT-IR (KBr, cm^{-1}): [1065 (ν Tc≡N)], [2928−2869 ν(H−alkyl)].

^{31}P NMR ($CDCl_3$ ppm): 98.8 (bs). ^{1}H NMR ($CDCl_3$ ppm): δ 0.82 [m, 6H, PCH(C*H*$_3$)$_2$], 1.25 [m, 12H, PCH(C*H*$_3$)$_2$], 1.44 [m, 6H, PCH(C*H*$_3$)$_2$], 1.89 and 2.10 (2H + 2H, PC*H*(CH$_3$)$_2$], 2.47 (m, 4H, (SCH$_2$C*H*$_2$P)], 2.94 [m, 4H, SC*H*$_2$CH$_2$P].

[Tc(N)(PS*ibu*)$_2$] (Tc13): Yield 76%. Anal. Calcd for $C_{20}H_{44}NP_2S_2Tc$ (MW 523.70): C 45.87, H 8.68, N 2.68, S 12.24. Found C 46.97, H 8.98, N 2.56, S 13.24.

FT-IR (KBr, cm^{-1}): [1048 (ν Tc≡N)], [2954−2867 ν(H−alkyl)].

^{31}P ($CDCl_3$ ppm): 66.7 (bs). ^{1}H NMR ($CDCl_3$ ppm): δ 2.99 and 2.67 [m, 2H + 2H, (SC*H*$_2$CH$_2$P)], 2.32 and 2.05 [m, 2H + 2H, PCH$_2$C*H*(CH$_3$)$_2$], 2.25 and 2.01 [m, 2H + 2H, SCH$_2$C*H*$_2$P], 1.95 and 1.55 [m, 4H + 4H, PC*H*$_2$CH(CH$_3$)$_2$], 1.15, 1.08, 1.05 and 0.96 [4d, 6H + 6H + 6H + 6H, (*CH*$_3$)$_2$CHCH$_2$P]. ^{13}C NMR ($CDCl_3$ ppm): δ 35.56 and 32.54 [SCH$_2$*C*H$_2$P], 33.15 [P*C*H$_2$CH(CH$_3$)$_2$], 28.37 [S*C*H$_2$CH$_2$P], 26.58 and 25.04 [PCH$_2$*C*H(CH$_3$)$_2$], 25.61- 24.54 [PCH$_2$CH(*C*H$_3$)]. ESI-MS(+) (*m*/*z*): 1069 [2M + Na]$^+$ (52%), [(2M + H) - PS*ibu*]$^+$ (72%), 524 [M + H]$^+$ (100%).

[Tc(N)(PS*ibu*)(OPS*ibu*)] (Tc13a): Yield < 10%. Anal. Calcd for $C_{20}H_{44}NP_2S_2Tc$ (MW 668.203): C 57.52, H 6.18, N 2.1, S 5.22. Found C 53.84, H 6.44, N2.81, S 5.22.

FT-IR (KBr, cm^{-1}): [1053 (ν Tc≡N)], [2957−2869 ν(H−alkyl)].

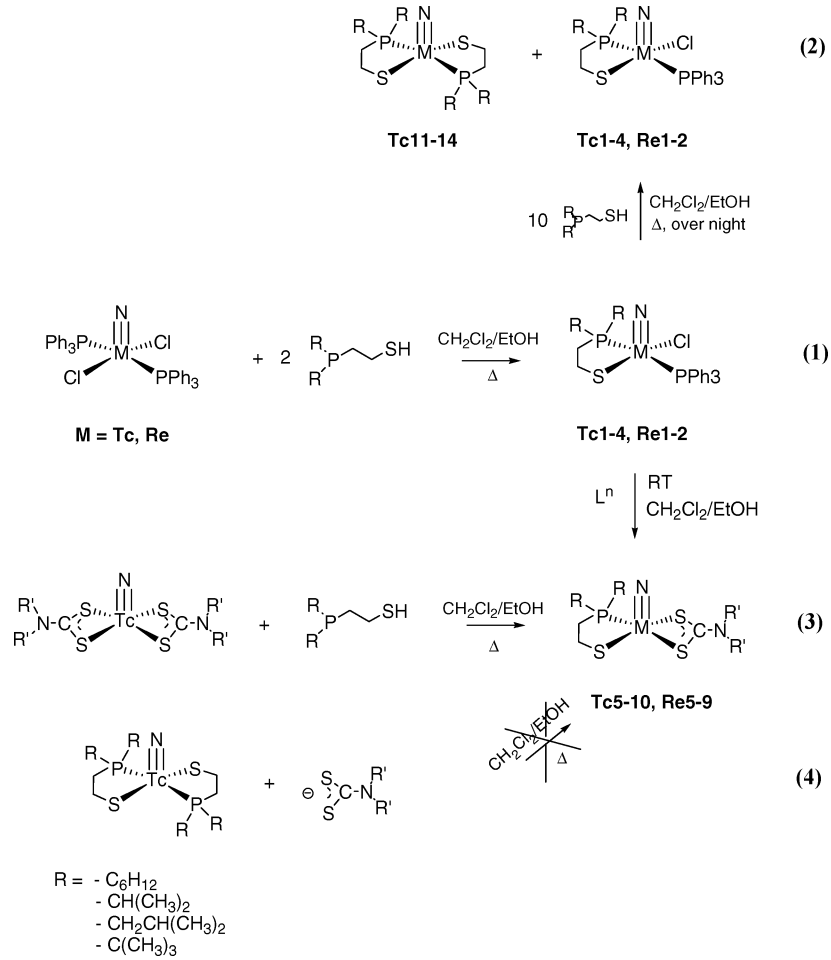
^{31}P NMR ($CDCl_3$ ppm): δ 65.5 (bs), 46.3 (d, $^2J_{PP}$ = 134 Hz). ^{1}H NMR ($CDCl_3$ ppm): δ 3.62 (m, 1H), 2.96 (m, 1H), 2.75 (m, 1H + 1H), 2.32−1.70 [8H], 2.20 (m, 2H + 1H), 2.13 (m, 1H), 1.93 (m, 1H), 1.77 (m, 1H + 1H), 1.41 (dt, 1H), 1.10 (m, 18H), 1.00 (dd, 6H).

[Tc(N)(PS*tbu*)$_2$] (Tc14): Yield 80%. Anal. Calcd for $C_{20}H_{44}NP_2S_2Tc$ (MW 523.70): C 45.87, H 8.68, N 2.68, S 12.24. Found: C 45.97, H 8.83, N 2.60, S 13.11.

FT-IR (KBr, cm^{-1}): [1062 (ν Tc≡N)], [2967−2863 ν(H−alkyl)].

^{31}P NMR ($CDCl_3$ ppm): δ 109.0 (bs). ^{1}H NMR ($CDCl_3$ ppm): δ 3.12−2.87 [4H, (SC*H*$_2$CH$_2$P)], 2.26−2.02 [4H, (SC*H*$_2$CH$_2$P)], 1.51 and 1.22 [m, 18H, PC(C*H*$_3$)$_3$]. ^{13}C NMR ($CDCl_3$ ppm): δ 34.96

Scheme 1



[P*C*(CH$_3$)$_3$], 32.45 [SCH$_2$*C*H$_2$P], 29.58 and 29.37 [PC(*C*H$_3$)$_3$], 27.19 [S*C*H$_2$CH$_2$P].

X-ray Crystallography. The measurements were collected at room temperature on a Philips PW1100 diffractometer with graphite-monochromated Mo Kα radiation. The structures of **Tc4**, **Re7**·$^1/_2$H$_2$O, and **Re9** were solved by heavy-atom methods expanded using Fourier techniques and refined by full-matrix least-squares method on F^2.[15] The non-hydrogen atoms (excluding the water oxygens in **Re7**·$^1/_2$H$_2$O) were refined anisotropically; the hydrogen atoms were placed in idealized positions and allowed to ride with the parent atoms to which each were bonded. The final difference maps were featureless. Supplementary crystallographic data files for complexes **Tc4**, **Re7**·$^1/_2$H$_2$O and **Re9** have been deposited at Cambridge Crystallographic Data Centre (www.ccdc.cam.ac.uk), numbers CCDC 689602, 689603, and 689604, respectively.

Results

Synthesis, Characterization and Reactivity of Monosubstituted [M(N)(PS)Cl(PPh$_3$)] Complexes (M = Tc1−4, Re1,2). According to the synthetic pathway outlined in Scheme 1, monosubstituted nitrido M(V) complexes of the type [M(N)(PS)Cl(PPh$_3$)] were prepared by reaction of the [M(N)Cl$_2$(PPh$_3$)$_2$] precursors with the appropriate bulky alkylphosphinothiol ligand in refluxing CH$_2$Cl$_2$/EtOH mixtures, eq 1.

In the case of Tc, accurate control of the metal/ligand stoichiometric ratio and heating time (30 min) allowed the collection of monosubstituted [Tc(N)(PS)Cl(PPh$_3$)] species in high yield. In contrast, less restricted reaction conditions were required to obtain the analogous monosubstituted Re compounds in high yield. In this case, even the use of a large excess of ligand, conditions generally met in radiopharmaceuticals preparations, produced only the monosubstituted Re complexes, while the corresponding bis-substituted Re compounds were never observed.

As exceptions of this general behavior, in Tc synthesis the use of the less sterically hindered PS*me*H ligand led to the formation of the bis-substituted compound [Tc(N)(PS-*me*)$_2$], and when the bulkiest PS*tbu*H ligand was used, the monosubstituted [Re(N)(PS)Cl(PPh$_3$)] was never formed under a wide range of reaction conditions.

The reactivity of [M(N)(PS)Cl(PPh$_3$)] complexes toward different mononegative bidentate ligands, such as PSH and NaL^n was investigated. In particular, [Tc(N)(PS)Cl(PPh$_3$)] was treated in refluxing CH$_2$Cl$_2$/EtOH with 2−10-fold excess of the selected alkylphosphino-thiol ligand, eq 2. TLC analysis showed that, when the reactions were carried out with 5-fold molar excess of PSH at reflux for 8 h, a 6:4 mixture of symmetric bis-substituted [Tc(N)(PS)$_2$] and monosubstituted [Tc(N)(PS)Cl(PPh$_3$)] was recovered. When the amount of the PS-ligand (10-fold molar excess) was increased and the bis-substituted/monosubstituted mixture was refluxed overnight, the ratio was enriched in the bis-

(15) Sheldrick, G. M. *Acta Crystallogr.* **2008**, *A64*, 112–122.

Table 1. ^{31}P NMR ($CDCl_3$) Spectral Data of Five-Coordinate Phosphino Thiolato Complexes

compounds	δ ^{31}P (ppm)	Δ ($\delta_{complex} - \delta_{free}$)	compounds	δ ^{31}P (ppm)	Δ ($\delta_{complex} - \delta_{free}$)
PS*cy*H	5.1				
PS*iso*H/P(O)S*iso*H	+3.6/+46.0				
P*sibu*H/P(O)S*ibu*H	−38.6/+46.0				
PS*tbu*H/P(O)S*tbu*H	+26.2/+77.3				
[Tc(N)(PS*cy*)Cl(PPh_3)] **Tc1***	86.3 (d, cy_2P, $^2J_{PP}$ 162 Hz), 39.3 (d, Ph_3P, $^2J_{PP}$ 162 Hz)	91.9	[Re(N)(PS*cy*)Cl(PPh_3)] **Re1**	82.7 (d,cy_2P, $^2J_{PP}$ 170 Hz), 35.9 (d, Ph_3P, $^2J_{PP}$ 170 Hz)	88.5
[Tc(N)(PS*iso*)Cl(PPh_3)] **Tc2**	96.9 (d b, iso_2P)), 40.7 (d b, Ph_3P)	93.3	[Re(N)(PS*iso*)Cl(PPh_3)] **Re2**	92.7 (d,iso_2P, $^2J_{PP}$ 170 Hz), 35.9 (d, Ph_3P, $^2J_{PP}$ 170 Hz)	89.1
[Tc(N)(PS*ibu*)Cl(PPh_3)] **Tc3**	65.3 (d b, ibu_2P), 38.4 (d b, Ph_3P)	103.9			
[Tc(N)(PS*tbu*)Cl(PPh_3)] **Tc4**	102.6 (d b,tbu_2P), 40.5 (d, Ph_3P)	76.4			
[Tc(N)(PS*cy*)(L^1)] **Tc5**	92.5 (s)	97.6	[Re(N)(PS*cy*)(L^1)] **Re5**		
			[Re(N)(PS*cy*)(L^2)] **Re6**	84.34	79.24
			[Re(N)(PS*cy*)(L^3)] **Re7**	84.61	79.61
[Tc(N)(PS*iso*)(L^2)] **Tc8**	102.7 (s)	99.1	[Re(N)(PS*iso*)(L^2)]**Re8**	94.01	90.41
[Tc(N)(PS*iso*)(L^4)] **Tc9**	102.3 (s)	98.7	[Re(N)(PS*iso*)(L^4)] **Re9**	94.11	90.51
[Tc(N)(PS*tbu*)(L^3)] **Tc10**	115.96 (s)	89.7			
[Tc(N)(PS*cy*)$_2$]*	85.9 (s)	91			
[Tc(N)(PS*me*)$_2$] **Tc11**					
[Tc(N)(PS*iso*)$_2$] **Tc12**	98.8 (s)	95.2			
[Tc(N)(PS*ibu*)$_2$] **Tc13**	66.7 (s)	105.3			
[Tc(N)(PS*ibu*)(OPS*ibu*)]**Tc13a**	65.55 (s), 46.81−45.70 (d)				
[Tc(N)(PS*tbu*)$_2$] **Tc14**	109.08 (s) (273 K)	82.9			

substituted species (8:2) without reaching quantitative conversion. This behavior indicates that steric and electronic effects due to the presence of two different P donors provided an efficient stabilization of the [Tc(N)(PS)Cl(PPh_3)] arrangement making difficult the substitution of the second monodentate ligand by an additional bulky alkylphosphinothiolate ligand. Under similar reaction conditions monosubstituted [Re(N)(PS)Cl(PPh_3)] did not convert into bis-substituted complexes at all.

In contrast, chloride and PPh_3 were promptly replaced by dithiocarbamate ligand at room temperature allowing the preparation of a new class of neutral, dissymmetrical mixed-substituted complexes, eq 3 (*vide infra*).

Elemental analyses of complexes **M1**−**4** were in agreement with the proposed formulation. FT-IR spectra exhibited a medium to intense vibration in the range 1075−1052 cm^{-1} typical of the ν(M≡N) stretching, along with vibrations characteristics of both the aliphatic groups of the PS ligand (2957−2851 cm^{-1}) and coordinated triphenylphosphine (3055−3049 cm^{-1}; 749−692 cm^{-1}).

ESI(+) mass spectra of the representative **Tc3** compound did not show the molecular ion peak but the only attributable signal at *m*/*z* 580.2 corresponding to the [M(N)(PS)(PPh_3)]$^+$ fragment ion. Monosubstituted complexes were characterized in the solution state by means of ^{31}P NMR spectroscopy. The presence of two magnetically nonequivalent P donors resulted in two sharp doublet signals in the case of rhenium derivatives (**Re1**,**2**) (see Table 1 and in Supporting Information, Figure S1a). The $^2J_{PP}$ coupling constant of 170 Hz is consistent with a reciprocal *trans* orientation of triphenylphosphine and phosphinothiolate P donors. In **Tc1**−**4** derivatives, such signals appeared as two broad singlets at room temperature (Figure S1c, Supporting Information), which narrowed on lowering the temperature to 250 K. The downfield signal (in the range 102.6−65.3 ppm) was assigned to the phosphinothiolate P atom by comparison with the signals of the bis-substituted and mixed-substituted species (*vide infra*). The other signal (in the range 40.7−35.9 ppm) corresponded to coordinated PPh_3. Both signals are significantly downfield shifted (see Table 1) compared with the corresponding ones in uncoordinated ligands by ca. 100 and 45 ppm for phosphinothiolate and triphenylphosphine, respectively, indicating the better donor properties of PSH compared with PPh_3. The magnitude of the coordination chemical shifts (Δ) value for phosphinothiolate P (see Table 1) is a function of the phosphine Tolman cone angle. Small cone angles determine larger shifts as for [Tc(N)(PS*ibu*-)Cl(PPh_3)], and larger cone angles determine smaller shifts as for [Tc(N)(PS*tbu*)Cl(PPh_3)].[16]

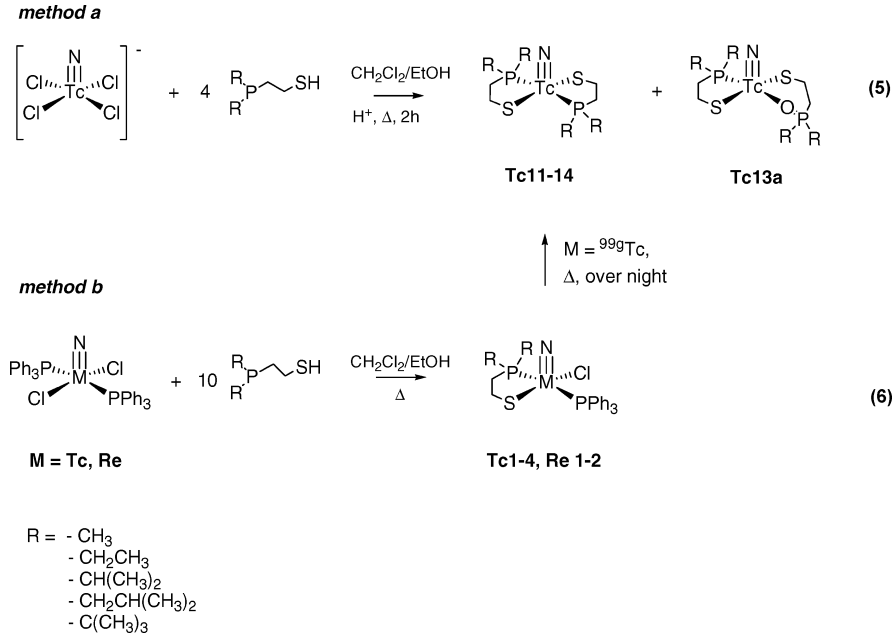
This behavior was also observed in mixed-substituted [Tc(N)(PS)(L^n)] and bis-substituted [Tc^V(N)$(PS)_2$] compounds.

^{1}H NMR spectra of [M(N)(PS)Cl(PPh_3)] showed signals in the 7.9−7.3 ppm range due to aromatic PPh_3 protons and a series of signals in the aliphatic region corresponding to the alkyl substituents and ethylene bridging chain of the PS ligand. As an example, the two-dimensional ^{1}H−^{1}H COSY map of the [Tc(N)(PS*iso*)Cl(PPh_3)] complex (**Tc2**) in the aliphatic region is sketched in Figure S2 (Supporting Information). The analysis provides evidence that geminal protons of the ethylene bridging chain are diastereotopic (four different proton signals) and that the two isopropyl substituents at P are magnetically nonequivalent (dotted lines in the map).

The description of the structure of the monosubstituted [Tc(PS*tbu*)Cl(PPh_3)] complex (**Tc4**) is reported below.

Synthesis and Characterization of Dissymmetrical Mixed-Substituted [M(N)(PS)(L^n)] Complexes. As outlined in Scheme 1, dissymmetrical nitrido M(V) complexes [M(N)(PS)(L^n)] (**M5**−**10**) were prepared via ligand exchange reaction treating monosubstituted [M(N)(PS)Cl(PPh_3)] derivatives with a dithiocarbamate ligand in CH_2Cl_2/MeOH solutions at room temperature, eq 3. In these reactions, the monosubstituted species selectively and instantaneously reacted with the mononegative ligand irrespective of the nature of the PS coligand to afford novel five-coordinate mixed-substituted compounds, characterized by the presence of two different bidentate ligands around the [M≡N] group, in nearly quantitative yields.

Scheme 2



Identical mixed-substituted compounds were obtained by reacting the corresponding symmetrical bis-substituted $[Tc(N)(L^n)_2]$ species with a large excess of the selected phosphinothiol ligand. In this case, the reaction yield decreased considerably (<30%) (Scheme 1, eq 4). TLC studies showed the presence of three spots of comparable intensity, attributable to the following products: the dissymmetrical mixed-substituted $[Tc(N)(PS)(L^n)]$ compound and two bis-substituted species identified as $[Tc(N)(PS)_2]$ and $[Tc(N)(L^n)_2]$ compounds. In contrast, no formation of $[Tc(N)(PS)(L^n)]$ was observed when the reaction was carried out using $[Tc(N)(PS)_2]$ as starting material. This behavior underlines the superior coordination ability of bidentate phosphino-thiolate with respect to dithiocarbamate toward the $[Tc{\equiv}N]^{2+}$ core and the remarkable kinetic inertness and stability of the symmetrical $[Tc(N)(PS)_2]$ complexes.

Physical and chemical characterization of the isolated mixed-substituted compounds indicated that all contain the $[M(N)(PS)]^+$ fragment. In detail, elemental analyses were in agreement with the proposed formulations. FT-IR spectra exhibited the characteristic $\nu(Tc{\equiv}N)$ stretching vibration in the range 1073−1059 cm^{-1}, along with typical absorption of coordinated alkyl phosphine in the region 2959−2810 cm^{-1}.

ESI(+) mass spectra of mixed-substituted compounds showed the protonated ($[M + H]^+$) and the cationized $[M + Na]^+$ molecular ion peaks. Under collision experiments, $[M + H]^+$ exhibited fragmentation processes mainly related to the dithiocarbamate moiety.[17]

The appearance of a singlet in the ^{31}P NMR spectra, (Figure S1b,d, Supporting Information) was diagnostic for the formation of mixed-substituted complexes. As observed in monosubstituted complexes, the ^{31}P signal was significantly broadened as well as slightly downfield shifted for technetium species compared with the corresponding signal in rhenium analogs.

Both ^1H and ^{13}C NMR spectra showed complicated patterns consistent with coordination of the phosphinothiolate and the dithiocarbamate ligands. For illustrative purposes, the $^1H-^1H$ COSY and $^1H-^{13}C$ HMQC maps of $[Tc(N)(PS_{iso})(L^4)]$ (**Tc9**) are reported in Figure S3 (Supporting Information).

Synthesis and Characterization of Symmetric Bis-Substituted $[Tc(N)(PS)_2]$ Complexes. As previously reported,[7] symmetric bis-substituted nitrido Tc(V) complexes $[Tc(N)(PS)_2]$ (**Tc11−14**) were easily prepared in high yield (ca. 80%) by reacting the prereduced precursor Tc(VI) $[(AsPh_4)Tc(N)Cl_4]$ in acidic media with a 3-fold molar excess of the appropriate PSH. In these reduction−substitution reactions, PSH acts both as reducing and as coordinating agent, giving neutral five-coordinate bis-substituted Tc(V) complexes.

When the reactions were carried out without the addition of a proton source, the yield of $[Tc(N)(PS)_2]$ was lowered to <50% because of the formation of several byproducts, among which **Tc13a**, containing an oxophosphine−thiolate ligand, was characterized by multinuclear NMR spectroscopy (Scheme 2, eq 5).

Bis-substituted $[Tc(N)(PS)_2]$ compounds can be also obtained via ligand exchange reaction of PSH onto the Tc(V) precursor $[Tc(N)Cl_2(PPh_3)_2]$ using 10-fold molar excess of PSH at reflux overnight (Scheme 2, eq 6). In these reactions, the yield of $[Tc(N)(PS)_2]$ was significantly lowered because of the competitive formation of the corresponding monosubstituted $[Tc(N)(PS)Cl(PPh_3)]$ compounds.

Complexes **Tc11−14** were characterized by elemental analysis, IR and NMR spectroscopies, and ESI-MS. FT-IR spectra exhibited the characteristic ν (Tc≡N) stretching vibration in the range 1065−1048 cm^{-1}, along with absorption of coordinated alkyl phosphine in the region 2967−2863

Table 2. Crystallographic Data for **Tc4**, **Re7**·$^1/_2H_2O$, and **Re9**

	Tc4	Re7·$^1/_2H_2O$	Re9
empirical formula	$C_{28}H_{37}ClNP_2STc$	$C_{20}H_{36}N_2PS_3Re\cdot{}^1/_2H_2O$	$C_{15}H_{31}N_5PS_3Re$
fw	615.04	626.86	566.78
crystal system	triclinic	monoclinic	monoclinic
space group	$P\bar{1}$ (No. 2)	$P2_1/c$ (No. 14)	$P2_1/c$ (No. 14)
a (Å)	9.479(2)	20.912(4)	13.177(3)
b (Å)	15.477(3)	13.921(4)	12.032(2)
c (Å)	22.763(5)	17.927(4)	14.207(3)
α (deg)	107.17(3)	90	90
β (deg)	90.54(3)	100.03(3)	107.91(3)
γ (deg)	96.27(3)	90	90
V (Å^3)	3169(1)	5139(2)	2143.3(7)
Z, D_{calcd} (g cm^{-3})	4, 1.289	8, 1.620	4, 1.756
μ(Mo Kα), cm^{-1}	7.21	5.05	6.04
T, °C	21	21	21
scan type	$\omega - 2\theta$	$\omega - 2\theta$	$\omega - 2\theta$
measured reflns	13690	7974	4180
obsd reflns [$I > 2\sigma(I)$]	5616	7701	3656
refined params	613	495	208
R1[a]	0.047	0.044	0.052
wR2[b]	0.106	0.103	0.112
GOF[c]	0.795	1.219	1.364

[a] $R1 = \sum(|F_0|/|F_c|)/\sum(|F_0|)$. [b] $wR2 = \{\sum[w(F_0^2 - F_c^2)^2]/\sum[w(F_0)^2]\}^{1/2}$. [c] $GOF = \{\sum[w(F_0^2 - F_c^2)^2]/(n - p)\}^{1/2}$ (n = reflections; p = parameters).

Table 3. Selected Bond Lengths (Å) and Angles (deg) for **Tc4**, **Re7**·$^1/_2H_2O$, and **Re9**

Tc4		Re7·$^1/_2H_2O$		Re9	
Tc−N	1.610(5)	Re−N(1)	1.64(1)	Re−N(1)	1.66(1)
Tc−Cl	2.406(2)	Re−S(1)	2.336(3)	Re−S(1)	2.333(3)
Tc−S	2.339(2)	Re−S(2)	2.389(3)	Re−S(2)	2.396(3)
Tc−P(1)	2.457(2)	Re−S(3)	2.422(3)	Re−S(3)	2.432(3)
Tc−P(2)	2.457(2)	Re−P(1)	2.376(3)	Re−P(1)	2.383(2)
N−Tc−Cl	112.0(2)	S(1)−Re−P(1)	83.0(1)	S(1)−Re−P(1)	83.6(1)
N−Tc−S	108.7(2)	S(2)−Re−S(3)	73.0(1)	S(2)−Re−S(3)	72.3(1)
N−Tc−P(1)	99.6(2)	N(1)−Re−P(1)	100.6(4)	N(1)−Re−P(1)	100.4(3)
N−Tc−P(2)	96.2(2)	N(1)−Re−S(1)	110.3(4)	N(1)−Re−S(1)	109.8(4)
S−Tc−P(1)	83.5(1)	N(1)−Re−S(2)	107.0(4)	N(1)−Re−S(2)	107.1(3)
Tc−P(1)−C(1)	102.7(2)	N(1)−Re−S(3)	108.5(4)	N(1)−Re−S(3)	107.1(3)
Tc−S−C(2)	109.6(2)	S(1)−Re−S(2)	142.1(1)	S(1)−Re−S(2)	142.0(1)
		S(3)−Re−P(1)	150.8(1)	S(3)−Re−P(1)	152.6(1)

cm^{-1}.The ESI mass spectra of selected representative compounds showed the main peaks corresponding to the protonated $[M + H]^+$ molecules.[16]

The singlet in the ^{31}P NMR spectra of bis-substituted technetium complexes indicated magnetic equivalence of the two phosphine−thiolate P. Such a signal was remarkably downfield shifted (see Table 1) compared with the corresponding signal typical of uncoordinated PSH. As already pointed out in monosubstituted and mixed-substituted complexes, ^{1}H and ^{13}C spectra confirmed the magnetic nonequivalence of the phosphorus substituents and the diastereotopic nature of the bridging methylene groups. For illustrative purposes, the ^{1}H−^{1}H COSY and ^{1}H−^{13}C HMQC maps of [Tc(N)(PS*ibu*)$_2$] (**Tc13**) are reported in Figure S4 (Supporting Information).

As an example of the byproduct generated in substitution reduction reactions in nonprotic media, the NMR characterization of the bis-substituted mixed oxo-phosphinothiolate complex [Tc(N)(PS*ibu*)(OPS*ibu*)] (**Tc13a**) is reported. The complicated patterns shown in ^{1}H and ^{13}C spectra indicated the presence of two nonequivalent phosphinothiolate ligands. This feature was confirmed in the ^{31}P spectrum by the appearance of two signals: a broad singlet at 65.5 ppm, value typical for metal-coordinated PS*ibu*, and a doublet at 46.2 ppm ($^2J_{PP}$ = 135 Hz) corresponding to metal-coordinated OPS*ibu*. The chemical structure of the hypothesized compound is sketched in Scheme 2 with the metal binding bidentate PS*ibu* and OPS*ibu* through the P,S and O,S bites, respectively. Coordination of oxidized phosphinethiolate ligands have previously been observed with various transition metal complexes.[18]

Description of the structures Tc4, Re7·$^1/_2H_2O$, and Re9. Crystals suitable for X-ray studies were obtained by slow diffusion of *n*-hexane into a CH_2Cl_2 solution for **Tc4** and by slow diffusion of MeCN into a $CHCl_3$ solution for **Re7**·$^1/_2H_2O$ and **Re9**. Data collection parameters and crystal data are reported in Table 2. Selected bond lengths and angles are listed in Table 3.

In complexes **Tc4** and **Re7**·$^1/_2H_2O$, as illustrated in Figures 2 and 3, the unique portion of the unit cell comprises two neutral molecules (A and B) and since A and B are virtually superimposable (a part of the *tert*-Bu groups in **Tc4** and the conformation of the five-membered ReS(1)C(1)C(2)P(1) ring in **Re7**·$^1/_2H_2O$), the mean values for bond lengths and angles are reported in Table 3. In the crystal building of **Re7**·

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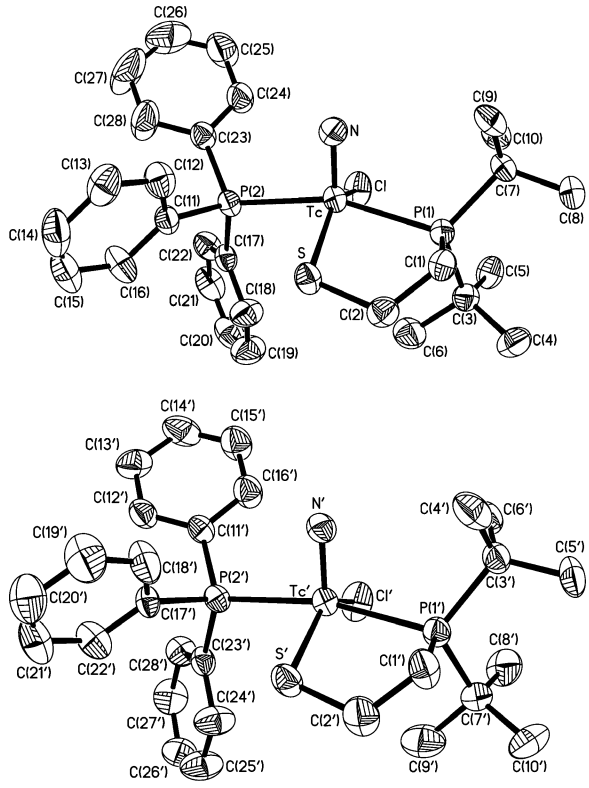

Figure 2. ORTEP view (33.3% probability) of the complex **Tc4**.

$^1/_2H_2O$, a water molecule, without any relevant interaction, goes with each A−B couple.

In **Tc4**, the coordination geometry around the Tc center can be described as intermediate between square pyramidal (*spy*) and trigonal bipyramidal (*tbpy*). In fact, the τ index[19] ($\tau = 0$ for ideal *spy* and $\tau = 1$ for ideal *tbpy*) is 0.33 and 0.48 for A and B, respectively. In the *tbpy* description, the nitrido-group, the chloride, and the thiolato sulfur atoms occupy the equatorial sites (Tc out of 0.02 Å) with the two phosphine phosphorus atoms at the apexes of the bipyramid. The twist-envelope five-membered chelate ring is practically orthogonal to the N−Cl−S basal plane (88.8° and 86.6° in A and B, respectively); the overall environment closely parallels that of the parent complex [Tc(N)Cl(PS*cy*)(PPh$_3$)] (**Tc1**),[12] and the metrical parameters are in good agreement with the literature data.[20]

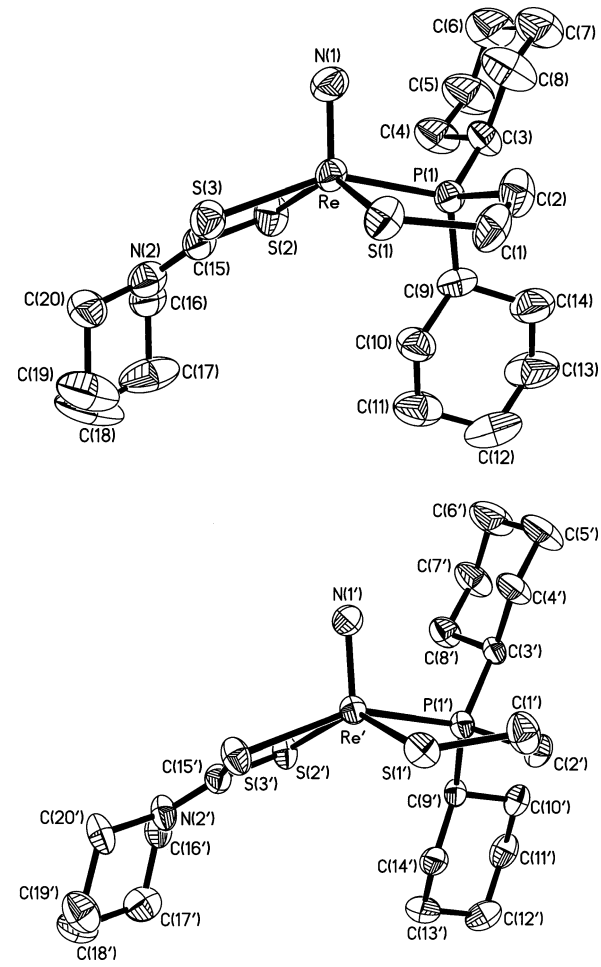

Figure 3. ORTEP view (33.3% probability) of the complex **Re7**·$^1/_2H_2O$. The water molecule is omitted for simplicity.

The coordination geometry of **Re7**·$^1/_2H_2O$ can be better regarded as *spy* ($\tau = 0.14$ and 0.18 for A and B, respectively); the Re atom deviates markedly (by 0.67 Å) from the PS_3 donor set plane toward the nitrido apex, and the basal donors are displaced by ±0.07 Å.

Inspection of the Cambridge Crystallographic Database (CCD; version 5.28 of November 2006 and two updates)[21] reveals that (i) the number of *spy* nitrido-Re(V) mononuclear complexes containing in the basal plane P or S as donor atoms is twenty, (ii) in eight complexes the set is P_2X_2 (X = Cl, Br), (iii) the copresence of P and S donors is restricted to three compounds with donor set PS_2Cl,[22] PS_2N,[23] and P_2S_2.[7]

The Re−S(2) and Re−S(3) bond lengths (2.393 (3) and 2.427(3) Å) match those in the two nitrido−Re(V) complexes containing the monoanionic form of the dithiocarbamate ligand,[24] while the Tc−S(1) distance (2.335(3) Å) represents the shortest one, although in accordance with the values found in the two complexes of reference 22.

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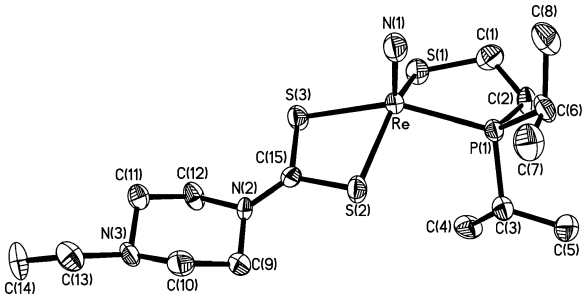

Figure 4. ORTEP view (33.3% probability) of the complex **Re9**.

The Re−P(1) (2.379 (3) Å) and Re−N(1) (1.65 (1) Å) distance are within the range of values observed in the twenty comparable complexes.

The structural difference between A and B resides in the five-membered ring conformation (Figure 3). In both molecules, the twist-envelope C_2 conformation is assumed, but in A the P(1) and C(2) atoms are +0.38 and −0.26 Å out of the Re−S(1)−C(1) plane, respectively, whereas in B, S(1) and C(1)′ are +0.17 and −0.45 Å out of the Re′−P(1)′−C(2)′ plane. As a consequence, the greatest torsion angles are 39.2° about the P(1)−C(2) bond and 41.1° about S(1)′−C(1)′ in A and B, respectively.

The **Re9** complex closely confirms the metrical data exhibited by **Re7**·$^1/_2H_2O$ in its form B (Figure 4). In particular, the twist-enveloped ReS(1)C(1)C(2)P(1) ring shows S(1) and C(1) atoms out of the Re−P(1)−C(2) ring by +0.33 and −0.36 Å, respectively, with the greatest torsion angle (44.1°) about S(1)−C(1) bond.

Discussion

Phosphinothiols (PSH) represent a class of efficient chelate ligands whose reactivity toward several metal ions is well documented, especially for bisaryl-alkyl-phosphinothiols.[25] The combination of π-acceptor P with π-donor S atoms confers peculiar coordination properties to the P,S-chelate allowing the stabilization of metals in different oxidation states. Illustrative examples are the chemistries exhibited by group 7 metals Tc and Re. Starting from $[TcO_4]^-$ precursor, the reducing properties of both P and S donors usually permit the formation of neutral tris-substituted Tc(III) complexes adopting either *tbpy* or octahedral environments and preventing the isolation of mono-oxo containing Tc(V) compounds.[26] The five-coordinate *tbpy* geometry, in which two π-acceptor phosphorus atoms are located at the apexes of the bipyramid and three π-donor sulfurs at the trigonal base, is the preferred arrangement exhibited by M(III) complexes.[27] In these derivatives, two phosphinothiolates act as bidentate ligands, while the third one acts as monodentate only via the sulfur donor. Expansion of the coordination sphere to a six-coordinate octahedron occurs only in the case of tris-aryl-PSH ligands, in which extensive π-delocalization through the benzene ring of the P,S-bite grants chelation of the third ligand.[11]

Introduction of the terminal nitrido group into the metal coordination sphere (giving the $[Tc(N)]^{+2}$ moiety) allows for the synthesis of neutral, five-coordinate bis-substituted $[Tc^V(N)(PS)_2]$ complexes, whose geometry is described as being intermediate between *spy* and *tbpy*.[7] The choice for the arrangement is primarily determined by the length of the alkyl chain of the P,S-ligand. The ethylene bridging chain favors *spy* geometry and the propylene chain favors *tbpy* geometry.

In all reported Tc- and Re-phosphinothiolate complexes, the substituents at P were invariably aromatic groups, either phenyl or substituted phenyl.[17,25]

It is interesting to note that variation of the carbon chain joining the P and S donor drives the coordination geometry around the metal center, even if the five-coordinate geometry is generally favored.[7] In all these five- or six-coordinated complexes, the metal coordination sphere is completely saturated by the phosphinothiolate ligand, while the corresponding monosubstituted compounds were never achieved.

Biodistribution studies of a series of bis-substituted $[^{99m}Tc^V(N)(PS)_2]$ complexes displayed interesting biological properties.[9d] In particular, a tracer of this series, incorporating the 2-dimethylphosphino-propanethiolate ligand, showed the ability to penetrate the intact BBB making these neutral and lipophilic compounds attractive to devise a new class of potential brain perfusion imaging agents. Hence, other phosphinothiols containing linear or branched alkyl substituents (see Figure 1) have been designed for preparing novel, lipophilic bis-substituted nitrido Tc(V) species. However, the diminished π-back properties of alkyl-PS ligands compared with aryl-PS ones and the peculiar steric constraints of the phosphine substituents allowed the isolation of rare mono-substituted compounds, $[M(N)(PS)Cl(PPh_3)]$, in which only one alkylphosphinothiolate was coordinated to the $[M(N)]^{2+}$ group and the coordination sphere was completed by monodentate Cl and PPh_3. The X-ray molecular structure of the representative monosubstituted **Tc4** complex shows that the two different P donors are *trans* coordinated in the solid state. This feature was confirmed in solution by the occurrence of two doublets (with a $^2J_{PP}$ coupling constant of 170 Hz characteristic of a *trans*-P arrangement) in the ^{31}P NMR spectra of **Re1** and **Re2**. The *trans*-P arrangement was crucial for the stabilization of monosubstituted derivatives because it allowed delocalization of the high electronic density of the $[M(N)(PS)]^+$ moiety onto π-accepting PPh_3.

Although monosubstituted complexes were accessible for both metals, their further reactivity with phosphinothiols was remarkably different. In fact, the use of an excess of PSH gave rise to bis-substituted $[Tc(N)(PS)_2]$ complexes, whereas the corresponding bis-substituted $[Re(N)(PS)_2]$ compounds did not form at all under similar or more drastic reaction conditions. Moreover, the different reactivity between the second and third row congeners was evidenced when

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particularly encumbering substituents at P were used. For example, PS*tbu*H straightforwardly afforded monosubstituted [Tc(N)(PS*tbu*)Cl(PPh$_3$)], while the corresponding rhenium analog did not form. In any case, the choice of phosphine substituents played a determining role in the control of the formation of the monosubstituted compound, as illustrated by the behavior of the less sterically hindered PS*me*H ligand, which produced only bis-substituted [Tc(N)(PS*me*)$_2$] without formation of the monosubstituted [Tc(N)(PS*me*)Cl(PPh$_3$)].

Monosubstituted [M(N)(PS)Cl(PPh$_3$)] complexes reacted with dithiocarbamate ligands that selectively replaced monodentate Cl and PPh$_3$ groups giving neutral mixed-substituted [M(N)(PS)(L^n)].

As established by the X-ray molecular structures of **Re7**·$^1/_2$H$_2$O and **Re9** (outlined in Figures 3 and 4), these complexes are shown to adopt a *spy* geometry characterized by the presence of the unprecedented PS$_3$ coordination set on the basal plane and of the terminal nitrido group at the apex of the pyramid. The monoanionic dithiocarbamate ligand bonds the metal through the two sulfur donors producing a neutral species and making possible extensive π-delocalization through the four membered S−C−S−Re ring, as confirmed by the equivalence of the involved M−S bond distance (Table 3). The accurate combination of phosphinothiolate/dithiocarbamate donor/acceptor groups is responsible for the high stability and kinetic inertness of the resulting mixed-substituted complexes.[12] It is worth noting that upon going from monosubstituted to mixed-substituted compounds the [M(N)(PS)]$^+$ moieties remain intact. This behavior indicates that [M(N)(PS)]$^+$ can be considered as a substitution-inert building block useful for the preparation of new classes of mixed-ligand ^{99m}Tc/^{188}Re compounds.

Carrier-free [^{99m}Tc(N)(PS)$_2$] and [^{99m}Tc(N)(PS)(L^n)] species, whose chemical nature has been proven to be identical to those of long-lived [Tc(N)(PS)$_2$] and [M(N)(PS)(L^n)] by chromatographic techniques coupled with radiometric and UV−vis detections, have already been prepared in high radiochemical yield.[13] Interesting biological profiles for some of these compounds have been revealed by *in vivo* studies, indicating their ability to cross in and out of the intact BBB. Hence they are currently under investigation as prototypes to design new potential brain imaging agents.

The full chemical characterization of these bis-substituted and mixed-substituted Tc(N)-compounds, combined with previously reported data give the basis for an initial structure−activity relationship study.[7,9a,12,13] Thus, while the variation of the carbon chain linking P and S donor in bis-substituted [Tc(N)(PS)$_2$] seems to have an effect in driving the coordination geometry from *spy* to *tby*, the brain uptake of two analogue [Tc(N)(PS)$_2$] complexes (where PS is alternatively a 2-dimethylphosphino propanethiolate or a 2-dimethylphosphino ethanethiolate ligand) are almost the same suggesting that probably the geometry is not crucial for the brain uptake. As the cone angle and the sterical hindrance of the substituents on the P atom increase, the percentage of cerebral uptake generally decreases. In mixed-substituted Tc(N) compounds, the replacement of linear dithiocarbamate (L^1) with the corresponding alicyclic ligand (L^2) affects primarily lipophilicity and molecular volume, as well as diminishing the conformational changes. These changes are also responsible for the increase in the percent of injected dose per gram (%ID/g) in the brain.

These results indicated that for these agents the initial brain uptake was mainly driven by the physical properties of the complex (i.e., lipophilicity, dimension, shape) and that the absence on their chemical structures of functional groups (which through enzymatic or chemical conversion or receptor interaction are involved in the cerebral trapping mechanism) is responsible for their rapid tissue washout.

These findings would suggest that future studies should be focused on more compact molecules and on changes of the easily modifiable dithiocarbamate coligand with the appropriate group designed as a trapping mechanism in order to increase the brain retention for longer time intervals.

Conclusion

In this paper, we have continued to explore the coordination chemistry of the group 7 metals Tc and Re with phosphinothiol (PSH) ligands. Alkyl-PSH ligands reacted as mononegative chelates toward labile nitride−M(V) precursors to afford rare examples of monosubstituted compounds of the type [M(N)(PS)Cl(PPh$_3$)]. The accessibility of monosubstituted [M(N)(PS)Cl(PPh$_3$)] species was a function of the metal used and of the substituents at the phosphinothiolate P atom. In these complexes, the [M(N)(PS)]$^+$ moieties were substitution-inert, whereas monodentate chloride and PPh$_3$ were substitution-labile. Hence, [M(N)(PS)Cl(PPh$_3$)] species were employed as starting materials for the preparation of additional neutral, symmetrical bis-substituted [Tc(N)(PS)$_2$] and dissymmetrical mixed-substituted [M(N)(PS)(L^n)] complexes (L^n = monoanionic dithiocarbamate). All isolated compounds were completely characterized in solution and solid states. Crystal structures of mixed-substituted **Re7** and **Re9** complexes revealed a square-pyramidal geometry with the unprecedented PS$_3$ coordination set on the basal plane.

This study confirms that the monosubstituted [M(N)(PS)Cl(PPh$_3$)] compounds play an important role in the development of a new class of dissymmetrical nitrido compounds containing two different bidentate ligands bound to the [Tc≡N]$^{2+}$ core.

The flexibility of this system, owing to the possibility to change the substituents at the P atoms, the bidentate ligand, or both, can be exploited to design a wide range of M≡N mixed compounds useful in diagnosis or therapy.

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Supporting Information Available: NMR data of representative monosubstituted, mixed-substituted and bis-substituted compounds are reported in Figures S1, S2, S3 and S4. This material is available free of charge via the Internet at http://pubs.acs.org.

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