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Synthesis and Characterization of Novel Oxotechnetium (^{99}Tc and ^{99m}Tc) and Oxorhenium Complexes from the 2,2′-Bipyridine (NN)/Thiol (S) Mixed-Ligand System

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The synthesis and characterization of oxotechnetium and oxorhenium mixed-ligand complexes of the general formula $MO[NN][S]_3$ (M = ^{99}Tc and Re), where NN represents the bidentate ligand 2,2′-bipyridine and S represents a monodentate thiophenol, is reported. The complexes were prepared by ligand exchange reactions using ^{99}Tc-gluconate and $ReOCl_3(PPh_3)_2$ as precursors for the oxotechnetium and oxorhenium complexes, respectively. Compound **1** (M = ^{99}Tc, S = 4-methylthiophenol) crystallizes in the monoclinic space group $P2_1/a$, a = 23.12(1) Å, b = 14.349(6) Å, c = 8.801(4) Å, β = 94.81(2)°, V = 2918(2) Å^3, Z = 4. Compound **3** (M = Re, S = 4-methylthiophenol) crystallizes in the monoclinic space group $P2_1/a$, a = 23.018(9) Å, b = 14.421(5) Å, c = 8.775(3) Å, β = 94.78(1)°, V = 2903(2) Å^3, Z = 4. Compound **4** (M = Re, S = 4-methoxythiophenol) crystallizes in the orthorhombic space group *Pbca*, a = 16.32(1) Å, b = 24.55(2) Å, c = 16.94(1) Å, V = 6788(9) Å^3, Z = 8. In all cases, the coordination geometry around the metal is distorted octahedral with the equatorial plane being defined by the three sulfur atoms of the thiophenols and one nitrogen atom of 2,2′-bipyridine, while the apical positions are occupied by the second nitrogen atom of 2,2′-bipyridine and the oxygen of the M═O core. The complexes are stable, neutral, and lipophilic. Complete ^{1}H and ^{13}C NMR assignments are reported for all complexes. The analogous oxotechnetium complexes have been also synthesized at tracer level (^{99m}Tc) by mixing the 2,2′-bipyridine and the corresponding thiol with $Na^{99m}TcO_4$ generator eluate using $NaBH_4$ as reducing agent. Their structure was established by chromatographic comparison with authentic oxotechnetium and oxorhenium complexes using high performance liquid chromatography techniques.

Introduction

The coordination chemistry of technetium has been significantly investigated in the past two decades because one of its isotopes, the metastable ^{99m}Tc, is extensively used in formulating diagnostic radiopharmaceuticals due to its ideal nuclear properties (pure γ-emitter, $t_{1/2}$ = 6 h, E_{max} = 140 keV).[1] Many ^{99m}Tc-radiopharmaceuticals have become available for clinical use, including ^{99m}Tc-HMPAO and ^{99m}Tc-ECD for cerebral blood flow imaging, ^{99m}Tc-MAG_3 for imaging renal function, and ^{99m}Tc-MIBI, ^{99m}Tc-tetrofosmin, and ^{99m}Tc-furifosmin for myocardial perfusion imaging, and many others are under clinical trials.[2,3]

In carrying out synthetic and characterization work, ^{99}Tc, which is a long-lived β-emitter, is often replaced by its third row congener, rhenium (a mixture of ^{185}Re and ^{187}Re), which is cheaper, and easier to obtain and handle. Technetium and

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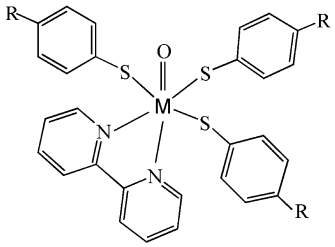
rhenium display similarity in their properties which arises from their position in the periodic table combined with the lanthanide contraction which causes the two elements to have almost identical radii.[4] Furthermore, the β-emitting radionuclides ^{186}Re ($t_{1/2}$ = 3.8 d, E_{max} = 1.07 MeV) and ^{188}Re ($t_{1/2}$ = 0.7 d, E_{max} = 2.12 MeV) are of great interest to nuclear medicine as they possess physical and nuclear properties favorable for use in systemic radiotherapy.[5] Further studies on the chemistry of technetium and rhenium will eventually lead to the design of suitable backbones for the optimum labeling of specific peptides and biomolecules. These studies, therefore, play an important role in the development of novel diagnostic and therapeutic radiopharmaceuticals.

Our laboratory has been involved in the design and synthesis of potential radiopharmaceuticals[6] utilizing the $TcO(V)^{3+}$ and $ReO(V)^{3+}$ cores that give stable, pentacoordinated or hexacoordinated complexes with a variety of ligands carrying the S and N donor atoms. In these studies, the "3 + 1", "2 + 1 + 1", "3 + 1 + 1", or "3 + 2" ligand combinations have been applied in the preparation of a variety of neutral complexes of the MO[SNS][S],[6a,b,d] MO[SNN][S],[6c,e] MO[SN][S][S],[6e,f] and MO[SNN][S][S][6g] types, respectively, where M = Tc and/or Re. The mixed-ligand approach allows the tuning of the physicochemical properties and biodistribution of the complexes synthesized. On the basis of this approach, complexes with affinity for the serotonin receptor[7] as well as the dopamine transporter system in the brain[8] have been successfully synthesized by the incorporation of an appropriate, target-specific group in one of the ligands.

Scheme 1



1 M = ^{99}Tc, R = CH_3
2 M = ^{99}Tc, R = OCH_3
3 M = Re, R = CH_3
4 M = Re, R = OCH_3
5 M = ^{99m}Tc, R = CH_3
6 M = ^{99m}Tc, R = OCH_3

In this paper, we report the synthesis of novel six-coordinated oxotechnetium and oxorhenium complexes **1**−**6** of the $[NN][S]_3$ type (Scheme 1), where NN represents the bidentate 2,2′-bipyridine molecule, while S represents monodentate thiophenols which are commonly used as coligands for the $TcO(V)^{3+}$ and $ReO(V)^{3+}$ cores.[6] 2,2′-Bipyridine (bpy) is a stable aromatic ligand commonly used in transition metal chemistry, and a number of bipyridine complexes with the oxorhenium core have been reported for various applications.[9] The rigid aromatic framework of 2,2′-bipyridine can serve as a model for the study of the coordination of analogues of the amyloid binding dyes, Congo red and thioflavin T. Both of these dyes show specificity for β-amyloid depositions,[10] and therefore, oxotechnetium complexes of these dyes may prove to be important steps in the development of in vivo radiodiagnostics for Alzheimer's disease. Complexes of Tc(I) with Congo red analogues and isonitrile coligands have been reported, and they display affinity for amyloid fibrils; however, the fact that they carry a positive charge limits their applicability as noninvasive imaging agents of brain amyloid.[11]

Experimental Section

Synthesis. Caution!!! Technetium-99 is a weak β-emitter (292 keV) with a half-life of 2.12×10^5 years. All manipulations of solutions and solids containing this radionuclide were carried out in a laboratory approved for the handling of low-energy particle-emitting radionuclides. Normal safety procedures were followed at all times to prevent contamination. Technetium-99m is a γ-emitter (140 keV) with a half-life of 6 h. Handling of solutions containing this radionuclide always proceeded behind lead shielding.

Standard literature procedures were used to obtain the precursor molecules $ReOCl_3(PPh_3)_2$ [12] and ^{99}Tc-gluconate.[13] All ligands and

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organic solvents were purchased from commercial sources. $[NH_4][^{99}TcO_4]$ was purchased from the Oak Ridge National Laboratory and was purified prior to its use by overnight treatment with hydrogen peroxide and ammonium hydroxide in methanol. Evaporation of the solvent afforded ammonium pertechnetate as a white powder. $Na^{99m}TcO_4$ was obtained in physiological saline as a commercial $^{99}Mo/^{99m}Tc$ generator eluate (Cis International).

IR spectra were recorded in KBr pellets in the range 4000−500 cm^{-1} on a Perkin-Elmer 1600 FT-IR spectrophotometer. Elemental analyses were performed on a Perkin-Elmer 2400/II automated analyzer. High-performance liquid chromatography (HPLC) analysis was performed on a Waters 600E chromatography system coupled to both a Waters 991 photodiode array detector (UV trace for ^{99}Tc, Re and ligands) and a GABI γ-detector from Raytest (γ trace for ^{99m}Tc). Separations were achieved on a Techsil C18 (10 μm, 250 mm × 4 mm) column eluted with a binary gradient system at a 1.0 mL/min flow rate. Mobile phase A was methanol with 0.1% TFA and mobile phase B was water with 0.1% TFA. The elution profile was 50% A for 0−10 min followed by a linear gradient to 80% A for 10−27 min. The column was washed with 95% A. Prior to each injection, the column was equilibrated by applying the initial conditions for 10 min.

NMR data for complexes **1**−**4** are reported in the NMR section.

^{99}TcO[bpy][*p*-$CH_3C_6H_4S$]$_3$ (1). A solution of tin(II) chloride (45 mg, 0.24 mmol) in HCl (1 M, 1.0 mL) was added to an aqueous solution of $[NH_4][^{99}TcO_4]$ (36.2 mg, 0.2 mmol) containing $^{99m}TcO_4^-$ (0.1 mL, 0.5 mCi) and sodium gluconate (200 mg) to obtain $^{99/99m}$Tc-gluconate. The pH of the solution was adjusted to 7.5 with NaOH (1 M). This solution was added with stirring to a mixture of 2,2′-bipyridine (31.2 mg, 0.2 mmol) and *p*-methylthiophenol (74.4 mg 0.6 mmol). The solution was stirred for 1 h and then extracted three times with CH_2Cl_2 (3 × 20 mL). The organic phase was separated, dried over $MgSO_4$, and filtered. The volume of the solution was reduced, and then, 3−5 mL of MeOH was added. Slow evaporation of the solvents at room temperature afforded brown-red crystals of the product. Structural characterization was carried out after ^{99m}Tc decay. Yield 55%. HPLC retention time: 17.23 min. UV−vis: 241, 274, 481 nm. FT-IR (KBr, cm^{-1}): 917 (Tc═O stretch), 804, 766. Anal. Calcd (%) for $C_{31}H_{29}N_2OS_3Tc$ (640.68): C, 58.12; H, 4.56; N, 4.37; S, 15.02. Found: C, 58.00; H, 4.50; N, 4.50; S, 15.15.

^{99}TcO[bpy][*p*-$CH_3OC_6H_4S$]$_3$ (2). Complex **2** was synthesized by following the same procedure as that described for **1** and replacing *p*-methylthiophenol with *p*-methoxythiophenol (84.0 mg, 0.6 mmol). Yield 50%. HPLC retention time: 15.35 min. UV−vis: 238, 283, 478 nm. FT-IR (KBr, cm^{-1}): 913 (Tc═O), 826, 762. Anal. Calcd (%) for $C_{31}H_{29}N_2O_4S_3Tc$ (688.66): C, 54.06; H, 4.24; N, 4.07; S, 13.97. Found: C, 54.20; H, 4.30; N, 3.90; S 13.80.

ReO[bpy][*p*-$CH_3C_6H_4S$]$_3$ (3). The precursor $ReOCl_3(PPh_3)_2$ (166 mg, 0.2 mmol) was added to a solution of CH_3COONa (164 mg, 2 mmol) in MeOH (12−15 mL). To this suspension were added 2,2′-bipyridine (31.2 mg, 0.2 mmol) and *p*-methylthiophenol (74.4 mg, 0.6 mmol) under stirring. The mixture was refluxed until the yellow-green suspension turned to a dark brown solution. After cooling to room temperature, the reaction mixture was diluted with CH_2Cl_2 and then washed with water. The organic layer was separated from the mixture and dried over $MgSO_4$. The volume of the solution was reduced, and then, 3−5 mL of MeOH was added. Slow evaporation of the solvents at room temperature afforded the product as brown crystals. Crystals of **3** suitable for X-ray crystallography were obtained by recrystallization from CH_2Cl_2/MeOH. Yield 60%. HPLC retention time: 16.53 min. UV−vis: 247, 301, 397 nm. FT-IR (KBr, cm^{-1}): 942 (Re═O) 808, 763. Anal. Calcd for $C_{31}H_{29}N_2OS_3Re$ (727.94): C, 51.15; H, 4.02; N, 3.85; S, 13.21. Found: C, 51.25; H, 4.00; N, 3.98; S, 13.28.

Table 1. Summary of Crystal, Intensity Collection and Refinement Data for Complexes **1**, **3**, and **4**

	1	**3**	**4**·H_2O·MeOH
empirical formula	$C_{31}H_{29}N_2OS_3Tc$	$C_{31}H_{29}N_2ORES_3$	$C_{32}H_{35}N_2O_6ReS_3$
fw	640.68	727.94	826.00
T	298	298	298
wavelength	Mo Kα, 0.710730	Mo Kα, 0.710730	Mo Kα, 0.710730
space group	$P2_1/a$	$P2_1/a$	*Pbca*
a (Å)	23.12(1)	23.018(9)	16.32(1)
b (Å)	14.394(6)	14.421(5)	24.55(2)
c (Å)	8.801(4)	8.775(3)	16.94(1)
β (deg)	94.81(2)	94.78(1)	
V (Å^3)	2918(2)	2903(2)	6788(9)
Z	4	4	8
D_{calcd}/D_{meas} (Mg m^{-3})	1.456/1.44	1.666/1.65	1.617/1.60
abs coeff μ (mm^{-1})	0.735	4.429	3.809
F(000)	1312	1440	3296
GOF on F^2	1.041	1.063	1.051
R indices	R1 = 0.0376[a] wR2 = 0.0921[a]	R1 = 0.0387[b] wR2 = 0.1003[b]	*R*1 = 0.0545[c] wR2 = 0.1308[c]

[a] For 3654 reflections with $I > 2\sigma(I)$. [b] For 3621 reflections with $I > 2\sigma(I)$. [c] For 3662 reflections with $I > 2\sigma(I)$.

ReO[bpy][*p*-$CH_3OC_6H_4S$]$_3$ (4). Complex **4** was synthesized by following the same procedure as that described for **3** and replacing *p*-methylthiophenol with *p*-methoxythiophenol (84.0 mg, 0.6 mmol). Yield 55%. HPLC retention time: 14.88 min. UV−vis: 250, 298, 400 nm. FT-IR (KBr, cm^{-1}): 938 (Re═O) 826, 763. Anal. Calcd (%) for $C_{31}H_{29}N_2O_4S_3Re{\cdot}H_2O{\cdot}CH_3OH$ (826.00): C, 46.53; H, 4.27; N, 3.39; S, 11.65. Found: C, 46.28; H, 4.15; N, 3.28; S, 11.49.

^{99m}TcO[bpy][*p*-$CH_3C_6H_4S$]$_3$ (5) and ^{99m}TcO[bpy][*p*-$CH_3OC_6H_4S$]$_3$ (6). ^{99m}Tc-pertechnetate ($Na^{99m}TcO_4$) solution (10 mCi, 1.5 mL) was added in a centrifuge tube containing 2,2′-bipyridine (3.1 mg, 0.02 mmol) and *p*-methylthiophenol (7.4 mg, 0.06 mmol) for **5** or *p*-methoxythiophenol (8.4 mg, 0.06 mmol) for **6**. $NaBH_4$ (10 mg) was added, and the mixture was agitated in a vortex mixer and then heated (70 °C) for 10 min. The complexes were extracted with CH_2Cl_2 (3 × 1.5 mL). The labeling yields were 70−80% as calculated by organic solvent extraction of the aqueous reaction mixture. The organic extracts were analyzed by HPLC. HPLC retention times: 18.04 and 16.07 min for **5** and **6**, respectively. The identity of the ^{99m}Tc complexes was established by comparative HPLC studies using as references the well-characterized analogous oxotechnetium **1**, **2** and oxorhenium **3**, **4** complexes.

X-ray Crystal Structure Determination of Complexes 1, 3, and 4. Crystals of **1**, **3**, and **4** suitable for X-ray analysis were mounted in air on a Crystal Logic dual goniometer diffractometer using graphite monochromated Mo Kα radiation. Unit cell dimensions were determined by using the angular settings of 25 automatically centered reflections in the range $11° < 2\theta < 23°$, and they appear in Table 1. Intensity data were recorded using a $\theta-2\theta$ scan. Three standard reflections monitored every 97 reflections showed less than 3% variation and no decay. Lorentz, polarization, and ψ-scan absorption corrections (for **3** and **4** only) were applied using Crystal Logic software. The structures were solved by direct methods using SHELXS-86[14] and refined by full-matrix least-squares techniques on F^2 using SHELXL-93.[15]

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Further crystallographic details for **1**: $2\theta_{max} = 49°$, scan speed 2.2°/min, scan range 2.2 + $\alpha_1\alpha_2$ separation, reflections collected/unique/used 5209/4863 [R_{int} = 0.0155]/4863, 459 parameters refined, $[\Delta\rho]_{max}/[\Delta\rho]_{min}$ = 0.561/−0.383 e/Å^3, $[\Delta/\sigma]_{max}$ = 0.076, R1/wR2 (for all data) = 0.0573/0.1039. All hydrogen atoms were located by difference maps and were refined isotropically; all non-H atoms were refined anisotropically.

Further crystallographic details for **3**: $2\theta_{max} = 47°$, scan speed 2.6°/min, scan range 2.2 + $\alpha_1\alpha_2$ separation, reflections collected/unique/used 4608/4291 [R_{int} = 0.0348]/4291, 429 parameters refined, $[\Delta\rho]_{max}/[\Delta\rho]_{min}$ = 1.128/−1.203 e/Å^3, $[\Delta/\sigma]_{max}$ = 0.042, R1/wR2 (for all data) = 0.0490/0.1091. All hydrogen atoms were located by difference maps and were refined isotropically (except those of the methyl groups, C17, C24, and C31, which were introduced at calculated positions as riding on bonded atoms); all non-H atoms were refined anisotropically.

Further crystallographic details for **4**: $2\theta_{max} = 49°$, scan speed 1.6°/min, scan range 1.9 + $\alpha_1\alpha_2$ separation, reflections collected/unique/used 6171/5602 [R_{int}=0.1225]/5601, 474 parameters refined, $[\Delta\rho]_{max}/[\Delta\rho]_{min}$ = 1.909/−1.051 e/Å^3, $[\Delta/\sigma]_{max}$ = 0.016, R1/wR2 (for all data) = 0.0910/0.1628. All hydrogen atoms were located by difference maps and were refined isotropically (except those of C1, C2, C17, C24, C27, and C31 which were included at calculated positions as riding on bonded atoms; no H-atoms were included for the water and methanol solvent molecules); all non-H atoms were refined anisotropically.

Results and Discussion

Synthesis of Complexes 1−4. The oxotechnetium complexes **1** and **2** were prepared by ligand exchange reactions using ^{99}Tc-gluconate as precursor in a ratio of ^{99}Tc-gluconate/bidentate/monodentate ligand 1:1:3. The oxorhenium complexes **3** and **4** were prepared in a similar manner using $ReOCl_3(PPh_3)_2$ as precursor. All complexes were extracted in CH_2Cl_2 and isolated as crystalline products from CH_2Cl_2/MeOH. The complexes were characterized by elemental analyses, IR, UV−vis, and NMR spectroscopies, and X-ray crystallography. In each case, the NMR data indicated the presence of a single species and were in agreement with the structure of a complex of the general type MO[bpy][S]$_3$, and specifically, the *mer* isomer.

The complexes are soluble in $CHCl_3$ and CH_2Cl_2, less soluble in MeOH and EtOH, and insoluble in ether. They are stable in the solid state and in organic solutions for a period of several weeks, as shown by HPLC and NMR, and their stability is not affected by the presence of moisture or air.

The Tc═O stretch for complexes **1** and **2** occurs at 917 and 913 cm^{-1} while the Re═O stretch for complexes **3** and **4** occurs at 942 and 938 cm^{-1}, respectively, and these values are well within the range of the M═O stretch reported in the literature for oxotechnetium and oxorhenium complexes with aminothiolate ligands.[16] The difference between the Re═O and the Tc═O stretch frequencies in the analogous complexes **3** and **1**, as well as in **4** and **2**, is approximately 25 cm^{-1}, a difference that is consistently observed between analogous oxorhenium and oxotechnetium complexes.[16a]

It should be noted that the Re═O stretch in **3** and **4** appears considerably lower than the reported Re═O stretch in oxorhenium complexes of bipyridine with a Re−N bond *trans* to the oxo ligand, as is the case in **3** and **4**. Specifically, the Re═O stretch in the bipyridine complexes with alkyl,[9a,e] chlorine[f], or chlorine and alkyl coligands combined[9b] ranges between 990 and 970 cm^{-1}. Apparently, the presence of the three aromatic thiol coligands causes a weakening of the Re═O bond in the bipyridine complexes **3** and **4** relative to the other reported complexes. As observed with the oxorhenium complexes **3** and **4**, the Tc═O stretch for complexes **1** and **2** occurs more than 50 cm^{-1} lower than in related bipyridine complexes with halide coligands reported in the literature.[17]

The electronic absorption spectra of the complexes were determined during HPLC analysis by employing the photodiode array detector. The UV−vis spectra of the oxotechnetium complexes are characterized by an intense band at 481 and 478 nm for **1** and **2**, respectively, while the UV−vis spectra of the oxorhenium complexes are characterized by an intense band at 397 and 400 nm for **3** and **4**, respectively.

Synthesis of ^{99m}Tc Complexes. The ^{99m}Tc complexes **5** and **6** were prepared at tracer level by direct reduction of $^{99m}TcO_4^-$ in aqueous solution using $NaBH_4$ as reducing agent, in the presence of the ligands, 2,2′-bipyridine and *p*-methylthiophenol for **5** or *p*-methoxythiophenol for **6**. The complexes were extracted with dichloromethane, and HPLC analysis of the extracts showed one major radioactive peak with retention time similar to those of the analogous ^{99}Tc and Re complexes. This indicates that the complexes prepared at tracer level (^{99m}Tc) and the complexes prepared at macroscopic level (^{99}Tc and Re) have the same chemical structure. Typical HPLC profiles of complexes **1**, **3**, and **5** are given in Figure 1. The radioactivity recovery of the HPLC column after the injection of the complexes **5** and **6** was monitored and found to be quantitative.

X-ray Crystallography. ORTEP diagrams of **1**, **3**, and **4** are given in Figures 2−4, respectively, and selected bond distances and angles are listed in Table 2. The coordination geometry around the metal is distorted octahedral composed of the two nitrogen atoms of the bipyridine, the three sulfur atoms of the aromatic thiols, and the doubly bonded oxygen atom. In all three complexes, the metal lies above the equatorial plane, defined by the three sulfur atoms of the aromatic thiols and the atom N1 of the bipyridine, toward the oxo group (0.32 Å for **1**, 0.30 Å for **3**, 0.34 Å for **4**).

(16) (a) Pelecanou, M.; Pirmettis, I. C.; Papadopoulos, M. S.; Raptopoulou, C. P.; Terzis, A.; Chiotellis, E.; Stassinopoulou, C. I. *Inorg. Chim. Acta* **1999**, *287*, 142−151. (b) O'Neil, J. P.; Wilson, S. R.; Katzenellenbogen, J. A. *Inorg. Chem.* **1994**, *33*, 3, 319−323. (c) Francesconi, L. C.; Graczyk, G.; Wehrli, S.; Shaikh, S. N.; McClinton, D.; Liu, S.; Zubieta, J.; Kung, H. F. *Inorg. Chem.* **1993**, *32* 3114−3124. (d) Rao, T. N.; Brixner, D. I.; Srinivasan, A.; Kasina, S.; Vanderheyden, J.-L.; Wester, D. W.; Fritzberg, A. R. *Appl. Radiat. Isot.* **1992**, *A42*, 525−530. (e) Tisato, F.; Mazzi, U.; Bandoli, G.; Cros, G.; Darbieu, M.-H.; Coulais, Y.; Guiraud, R. *J. Chem. Soc., Dalton Trans.* **1993**, 1301−1307. (f) Rao, T. N.; Adhikesavalu, D.; Camerman, A.; Fritzberg, A. R. *J. Am. Chem. Soc.* **1990**, *112* 5798−5804. (g) Johnson, D. L.; Fritzberg, A. R.; Hawkins, B. L.; Kasina, S.; Eshima, D. *Inorg. Chem.* **1984**, *23*, 4204−4207. (h) Davison, A.; Orvig, C.; Trop, H. S.; Sohn, M.; DePamphilis, B. V.; Jones, A. G. *Inorg. Chem.*, **1980**, *19*, 1988−1992.

(17) Davison, A.; Jones, A. G.; Abrams, M. J. *Inorg. Chem.* **1981**, *20*, 4300−4302.

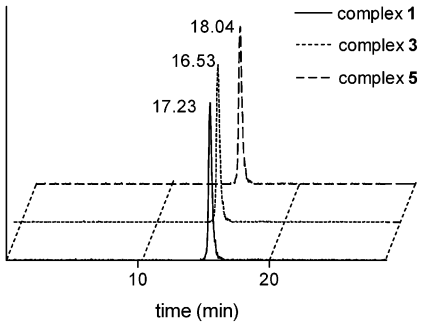

Figure 1. Comparative reverse-phase HPLC chromatograms of complexes **1** and **3** (photometric detection) and **5** (radiometric detection).

Table 2. Selected Bond Lengths (Å) and Angles (deg) for Complexes **1**, **3**, and **4**

	1		**3**	**4**
		Distances		
Tc−O(1)	1.670(3)	Re−O(1)	1.702(5)	1.691(8)
Tc−N(1)	2.229(3)	Re−N(1)	2.197(6)	2.191(9)
Tc−N(2)	2.259(3)	Re−N(2)	2.234(6)	2.255(9)
Tc−S(1)	2.394(2)	Re−S(1)	2.345(2)	2.366(3)
Tc−S(2)	2.327(1)	Re−S(2)	2.320(2)	2.334(3)
Tc−S(3)	2.353(1)	Re−S(3)	2.384(2)	2.395(3)
		Angles		
O(1)−Tc−N(1)	83.8(1)	O(1)−Re−N(1)	84.6(2)	86.5(4)
O(1)−Tc−N(2)	154.5(1)	O(1)−Re−N(2)	155.4(2)	158.2(4)
N(2)−Tc−N(1)	70.8(1)	N(2)−Re−N(1)	70.9(2)	71.8(3)
O(1)−Tc−S(2)	105.5(1)	O(1)−Re−S(2)	104.4(2)	105.4(3)
N(1)−Tc−S(2)	168.6(1)	N(1)−Re−S(2)	169.1(2)	167.5(3)
N(2)−Tc−S(2)	99.9(1)	N(2)−Re−S(2)	100.1(2)	96.3(3)
O(1)−Tc−S(1)	102.5(1)	O(1)−Re−S(1)	102.5(2)	102.6(3)
N(1)−Tc−S(1)	94.3(1)	N(1)−Re−S(1)	96.4(2)	93.5(2)
N(2)−Tc−S(1)	81.2(1)	N(2)−Re−S(1)	80.0(2)	80.0(2)
S(2)−Tc−S(1)	77.4(1)	S(2)−Re−S(1)	87.8(1)	87.8(1)
O(1)−Tc−S(3)	103.1(1)	O(1)−Re−S(3)	102.0(2)	100.9(3)
N(1)−Tc−S(3)	97.1(1)	N(1)−Re−S(3)	94.5(2)	93.7(2)
N(2)−Tc−S(3)	79.5(1)	N(2)−Re−S(3)	81.4(2)	80.5(2)
S(2)−Tc−S(3)	87.4(1)	S(2)−Re−S(3)	77.8(1)	80.4(1)
S(1)−Tc−S(3)	152.9(1)	S(1)−Re−S(3)	154.0(1)	155.8(1)

The M═O_{oxo} axis is inclined at 77.0°, 77.9°, and 80.5° in **1**, **3**, and **4**, respectively, with respect to the equatorial plane which is almost perpendicular to the N−C−C−N chelating plane of the bipyridine (88.4°, 88.9°, and 89.6° in **1**, **3**, and **4**, respectively). The five-membered ring in the coordination sphere, defined by the N−C−C−N chelating atoms of the bipyridine and the metal ion, is planar, and the N1−C5−C6−N2 dihedral angle is very small (3.7°, 3.6°, and 3.1° for **1**, **3**, and **4** respectively). The angles around the metal within the tetragonal plane of the octahedron range from 77.4(1)° to 97.1(1)° in **1**, from 77.8(1)° to 96.4(2)° in **3**, and from 80.4(1)° to 93.7(2)° in **4**, whereas those involving the apical atoms range from 70.8(1)° to 105.5(1)° in **1**, from 70.9(2)° to 104.4(2)° in **3**, and from 71.8(3)° to 105.4(3)° in **4**. As expected, the bite angle of the bidentate ligand (N1−M−N2) is the smallest one in the coordination sphere. The M═O and M−S bond distances are in the usually observed ranges.[6] The M−N2 bond, *trans* to the doubly bonded oxygen, is slightly lengthened with respect to the M−N1 bond distance, as has been observed in analogous complexes.[9b,d]

NMR Studies. ^{1}H (500.13 MHz) and ^{13}C (125.77 MHz) NMR spectra were recorded in $CDCl_3$ (Aldrich) at 25 °C on a Bruker 500 MHz Avance DRX spectrometer with TMS as an internal standard. For the 2D experiments, the standard pulse sequences were employed. ^{1}H and ^{13}C chemical shifts for complexes **1**−**4** are reported in Tables 3 and 4. The atom numbering adopted is the one of the crystallographic structures shown in Figures 2−4.

Table 3. ^{1}H NMR Chemical Shifts (δ_H, ppm) for Complexes **1**−**4**

	1	**2**	**3**	**4**
H-1	9.15	9.20	9.02	9.08
H-2	7.34	7.34	7.31	7.32
H-3	7.62	7.64	7.43	7.49
H-4	7.01	7.11	7.00	7.13
H-7	7.18	7.21	7.21	7.26
H-8	7.63	7.62	7.65	7.65
H-9	7.18	7.16	7.22	7.22
H-10	8.79	8.80	9.04	9.04
H-12/H-16 and H-26/H-30	6.20	6.21	6.13 (broad)	6.15 (broad)
H-13/H-15 and H-27/H-29	6.24	5.99	6.25	6.01
H-17 and H-31	2.01	3.54	2.04	3.54
H-19/H-23	7.75	7.76	7.75	7.77
H-20/H-22	7.28	6.99	7.29	7.01
H-24	2.40	3.84	2.42	3.83

Table 4. ^{13}C NMR Chemical Shifts (δ_C, ppm) for Complexes **1**−**4**

	1	**2**	**3**	**4**
C-1	148.54	148.52	148.96	148.94
C-2	124.52	124.38	124.37	124.25
C-3	138.25	138.31	138.22	138.51
C-4	120.81	120.73	120.35	120.38
C-5	151.04	150.56	151.59	151.28
C-6	148.83	148.53	149.94	148.78
C-7	120.81	120.80	121.93	120.81
C-8	136.81	136.83	136.90	136.92
C-9	124.23	124.22	124.95	124.95
C-10	151.95	151.92	151.73	151.71
C-11, C-25	140.08	133.84	141.63	136.08
C-12/C-16 and C-26/C-30	134.43	135.47	133.91	134.90
C-13/C-15 and C-27/C-29	127.66	112.99	127.83	112.88
C-14/C-28	135.12	157.89	134.91	157.73
C-17/C-31	20.84	55.24	20.78	55.22
C-18	141.93	135.81	144.71	139.46
C-19, C-23	133.95	135.22	133.84	135.06
C-20, C-22	128.73	113.52	128.80	113.58
C-21	136.85	158.84	135.89	158.56
C-24	21.33	55.24	21.24	55.22

In the ^{1}H NMR spectra of all complexes, the bipyridine moiety gave eight signals of equal intensity, indicating that the two rings of bipyridine are inequivalent, and the complex must be the mer isomer, with one bipyridine nitrogen attached *trans* to the oxygen of the oxometal core, a fact that was later confirmed by X-ray crystallography. Due to the plane of symmetry that the complexes possess in this arrangement (incorporating the M═O core and the planar bipyridine ring), the two side thiophenol rings (attached on S1 and S3, Figures 2−4) are in similar magnetic environments and appear together while the middle one (attached on S2) is differentiated. In all spectra, the two most downfield resonances were assigned to the bipyridine protons H-1 and H-10 due to their proximity to the coordinated nitrogens. Distinction between the two was based on the presence in one of them of an nOe correlation peak with the middle thiophenol ring (Figure 5). This proton was assigned to H-10 because examination of the three-dimensional model of the complexes shows that the middle thiophenol ring can only interact with the N2−C6−C7−C8−C9−C10 ring of bipyridine.

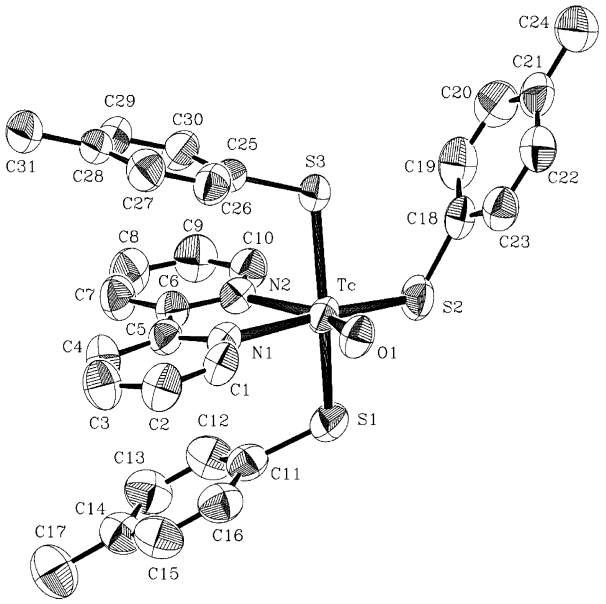

Figure 2. ORTEP diagram of complex **1**.

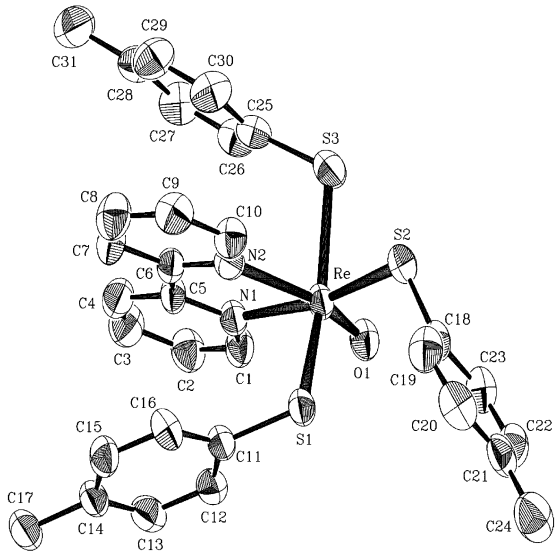

Figure 3. ORTEP diagram of complex **3**.

The aromatic protons of the two side thiophenol rings are shifted upfield apparently due to $\pi-\pi$ stacking interactions between the thiophenol and bipyridine molecules. Intramolecular ring stacking between the aromatic rings of coordinated diamines (as 2,2-bipyridine or phenanthroline)[18] and other aromatic ligands has been previously observed in a number of mixed-ligand transition metal complexes. Recently, a stacking interaction was reported between the phenyl rings of a diphosphine ligand attached to nitrido Tc(V) and Re(V) cores.[19]The fractional population of the stacked species, P_{ST}, is given by the ratio $\Delta\delta/\Delta\delta_{calculated}$ where

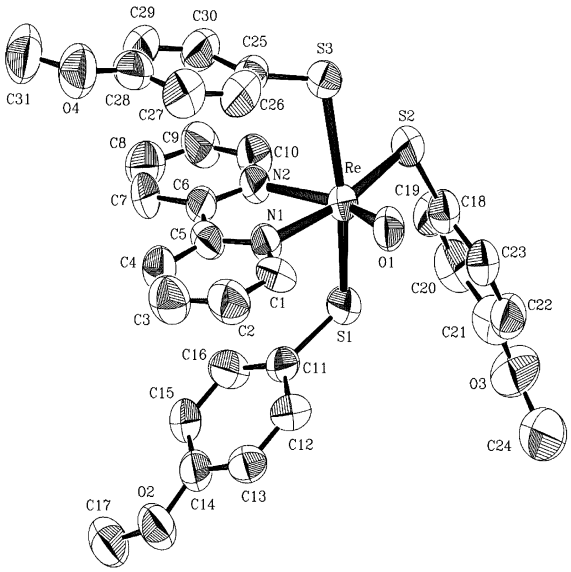

Figure 4. ORTEP diagram of complex **4**.

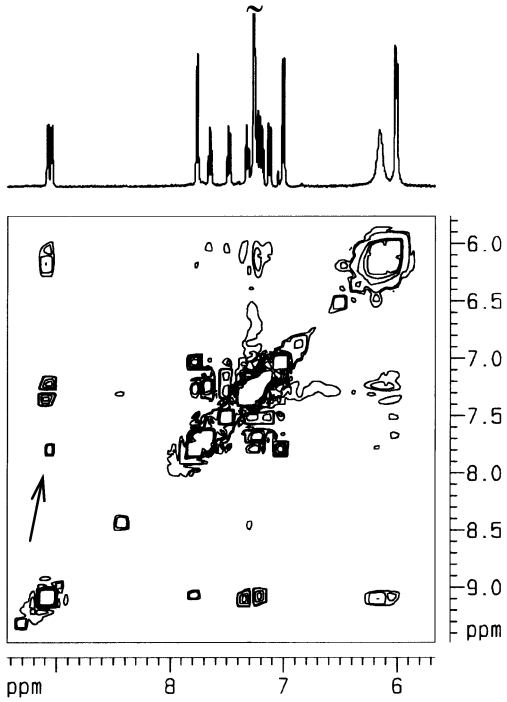

Figure 5. Phase-sensitive NOESY spectrum (aromatic region) of complex **4**. The arrow marks the correlation peak between H-19/H-23 of the middle thiophenol ring and H-10 of the bipyridine moiety.

$\Delta\delta$ is the observed shift and $\Delta\delta_{calculated}$ is the shift expected for complete stacking.[18d] Compared to the chemical shifts of thiophenol ligands in other oxorhenium complexes[16a] where no aromatic stacking is possible, the upfield shift for the *ortho* protons is $\Delta\delta \approx 1.4$ ppm while that for the *meta* protons is $\Delta\delta \approx 0.6$ ppm. The $\Delta\delta_{calculated}$ for the *ortho* protons of **4** was estimated according Johnson and Bovey[20] to be $\approx$1.4 ppm (by assuming that the pyridine ring approximates

(18) (a) Chaudhuri, P.; Sigel, H. *J. Am. Chem. Soc.* **1977**, *99*, 3142−3150. (b) Mitchell, P. R.; Sigel, H. *J. Am. Chem. Soc.* **1978**, *100*, 1564−1570. (c) Malini-Balakrishnan, R.; Scheller, K. H.; Häring, U. K.; Tribolet, R.; Sigel, H. *Inorg. Chem.* **1985**, *24*, 2067−2076. (d) Odani, A.; Deguchi, S.; Yamauchi, O. *Inorg. Chem.* **1986**, *25*, 62−69. (e) Masuda, H.; Sugimori, T.; Odani, A.; Yamauchi, O. *Inorg. Chim. Acta* **1991**, *180*, 73−79.

(19) Bolzati, C.; Boschi, A.; Uccelli, L.; Tisato, F.; Refosco, F.; Cagnolini, A.; Duatti, A.; Prakash, S.; Bandoli, G.; Vittadini, A. *J. Am. Chem. Soc.* **2002**, *124*, 11468−11479.

(20) Johnson, C. E., Jr.; Bovey, F. A. *J. Chem. Phys.* **1958**, *29*, 1012−1014.

the benzene ring and by estimating the distance between the two rings to be ≈3.4 Å based on the bond distances and angles provided by the crystallographical data). That gives $P_{ST} \approx 1$, meaning that on the average stacking predominates in solution. Raising the temperature up to 60 °C did not cause any change in the chemical shifts indicating that stacking in this system is relatively strong. Analogous results are provided by all complexes.

Due to stacking, an upfield shift of 0.4 ppm is recorded for the *p*-CH_3 and *p*-CH_3O substituents of the thiophenol rings of complexes **1**−**4**.

In conclusion, the simultaneous action of 2,2′-bipyridine and an aromatic thiol on the oxotechnetium(V) and oxorhenium(V) precursors has generated complexes of the $MO[NN][S]_3$ type that expand the already existing chelating systems for these cores. The complexes were fully characterized, and their chemistry was successfully transferred at the ^{99m}Tc tracer level. The complexes are stable, neutral, and lipophilic and can therefore serve as a model for the development of radiodiagnostics for Alzheimer's disease by modifying the bipyridine moiety to mimic the basic structural features of the β-amyloid specific dyes.

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Supporting Information Available: Crystallographic data for the structures of complexes **1**, **3**, and **4**. This material is available free of charge via the Internet at http://pubs.acs.org.

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