Synthesis and Characterization of Oxotechnetium(V) Mixed-Ligand Complexes Containing a Tridentate N-Substituted Bis(2-mercaptoethyl)amine and a Monodentate Thiol

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A series of 22 mixed-ligand complexes of the general formula $TcOL_1L_2$, where L_1H_2 are N-substituted bis(2-mercaptoethyl)amine ligands, [SN(R)S], and L_2H are monodentate thiols as coligand, is reported. The complexes were prepared by the ligand exchange method using Tc−gluconate as precursor and equimolar quantities of the two ligands. In all cases the *syn* stereoisomer was formed in high yield and isolated as a crystalline product. In four cases HPLC analysis demonstrated the presence of the *anti* stereoisomer in the reaction mixture. Although the yield was less than 1%, one *anti* isomer, **4a**, was successfully isolated as brown crystals. The isolated complexes were characterized by spectroscopic methods and elemental analysis. The formation of the two diastereomers, *syn* and *anti*, was expected due to the configuration of the nitrogen substituent (R) with respect to the central TcO core. The X-ray crystallography showed that the coordination geometry of the *syn* isomers **9**, **11**, and **18** is trigonal bipyramidal while for the *anti* isomer **4a** it is distorted square pyramidal. This is the first documentation of *syn*/*anti* isomerism in N-substituted TcO[SN(R)S][S] mixed-ligand complexes.

Introduction

During the past decade the inorganic chemistry of technetium has undergone extensive development primarily because of the importance of the isotope ^{99m}Tc in the field of diagnostic nuclear medicine. Technetium-99m is the radioisotope of choice for imaging, due to its ideal γ-photon energy of 140KeV, lack of particular radiation dose, half life of 6 h, and convenient availability. Recently, emphasis has been given to the design and preparation of neutral, lipophilic technetium complexes for brain imaging.[1]

The ^{99m}Tc-HMPAO[2] and ^{99m}Tc-ECD[3] complexes which are structurally based on propylene diamine dioxime (PnAO), an N_4 backbone, and the diamino dithiol (DADT), N_2S_2, ligand system respectively, cross the intact brain blood barrier and remain in the brain long enough to allow single photon emission tomography (SPECT) studies. Both of them contain the monooxotechnetium core, with the technetium center five-coordinated in a square pyramidal geometry.[4,5] The oxo ligand is at the apical position of the pyramid while the basal plane is defined by either N_4 or N_2S_2 chelate for the HMPAO and ECD complexes respectively.

An alternative concept for designing neutral oxotechnetium complexes is based on the simultaneous action of a tridentate dianionic ligand (SOS) or (SSS) and a monodentate thiol as coligand on a suitable TcO^{3+} precursor (mixed ligand approach, 3 + 1 donor combination).[6] The tridentate ligand upon coordination to the TcO^{3+} core leaves open one coordination site, cis to the oxo group, to be occupied by the monodentate coligand. In a previous work,[7] we have synthesized and characterized the $TcOL_1L_2$ complex, where the L_1H_2 is the tridentate ligand *N*,*N*-bis(2-mercaptoethyl)-*N*′,*N*′-diethylethylenediamine, [SN(R)S], and L_2H is the monodentate thiol,

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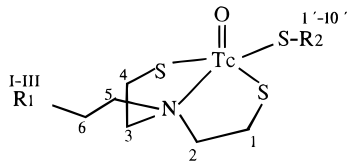

Complex	R1	R2
1	H-	2′ 3′ 1′ 4′ 7′ 6′ 5′ OCH_3
2	CH_3O-	OCH_3
3	$(CH_3)_2N$-	OCH_3
4	$(CH_3CH_2)_2N$-	OCH_3
4a		
5	$(CH_3CH_2)_2NCH_2$-	OCH_3
6	$(CH_3CH_2)_2N$-	OCH_3
7	$(CH_3CH_2)_2N$-	CH_3O
8	$(CH_3CH_2)_2N$-	
9	$(CH_3CH_2)_2N$-	Br
10	$(CH_3CH_2)_2N$-	I
11	$(CH_3CH_2)_2N$-	7′ CH_3

Complex	R1	R2
12	$(CH_3CH_2)_2N$-	7′ 8′ CH_2CH_3
13	$(CH_3CH_2)_2N$-	7′ 8′ $CH(CH_3)_2$
14	$(CH_3CH_2)_2N$-	7′ 8′ 9′ 10′ $CH_2CH_2CH_2CH_3$
15	$(CH_3CH_2)_2N$-	7′ $C(CH_3)_3$
16	$(CH_3CH_2)_2N$-	7′ CH_3 CH_3 8′
17	$(CH_3CH_2)_2N$-	8′ 1 2′ 7′ 6′ 5′ 4′ 3′
18	$(CH_3CH_2)_2N$-	7′ $-CH_2$
19	$(CH_3CH_2)_2N$-	7′ $-CH_2$ 8′ OCH_3
20	$(CH_3CH_2)_2N$-	7′ $-CH_2$ 8′ $C(CH_3)_3$
21	CH_3O-	7′ $-CH_2$
22	$(CH_3CH_2)_2N$-	8′ 7′ 2′ 3′ $-CH_2CH_2N$ 4′ 6′ 5′

Figure 1. $^{99}TcO(L_1)(L_2)$ mixed-ligand complexes and the numbering used for the ^1H NMR studies.

4-methoxythiophenol. On the basis of this concept, we have synthesized a series of $^{99m}TcO(L_1)(L_2)$ mixed ligand complexes. Biodistribution studies in mice have shown that these complexes demonstrated high uptake and significant retention in brain.[8]

In the present study, we report the synthesis and characterization of the $^{99}TcOL_1L_2$ complexes (Figure 1) to better understand the chemistry of these potential brain imaging agents. The mixed ligand complexes were prepared by the ligand exchange method using Tc(O)−gluconate as precursor. All the complexes were analyzed by IR, ^1H NMR, and UV−vis spectroscopy and elemental analysis. The formation of two diastereomeric complexes, *syn* and *anti*, was expected since on complexation the N-substituent can assume *syn* or *anti* configuration with respect to the TcO^{3+} core.[9] The crystal structure of the complexes **9**, **11**, **18**, (*syn* configuration), and **4a** (*anti* configuration) were determined by X-ray crystallography.

Results and Discussion

Mixed ligand complexes **1**−**22** (Figure 1) were readily prepared by reacting the tridentate ligands, L_1H_2, and monodentate thiols, L_2H, with the Tc(V)−gluconate precursor in a ratio of L_1H_2:L_2H:Tc = 1:1:1. The lipophilic $TcOL_1L_2$ complexes were extracted into CH_2Cl_2 and isolated as crystalline products. All complexes gave correct elemental analysis and were characterized by IR, UV−vis, and ^1H NMR spectroscopy. The complexes are soluble in CH_3COCH_3, $CHCl_3$, and CH_2Cl_2, slightly soluble in MeOH and EtOH, and insoluble in ether, pentane, and water. They are indefinitely stable in the solid state and in solution, and their stability is not affected by the presence of air or moisture.

Attempts to synthesize these complexes using $Bu_4NTcOCl_4$ as precursor did not result in the desired products, giving instead a black powder. IR spectra of the isolated solids demonstrated the absence of the TcO^{3+} core (890−1020 cm^{-1}).[10]

Ligands based on the diamino dithiol (DADT) backbone containing a monoamine side chain have been reported to form two diastereoisomeric complexes with TcO^{3+} core.[9,11] The rapid nitrogen inversion occurring in the ligand itself is halted on complexation with technetium. As a result the side arm attached to the nitrogen atom is locked into either a *syn* or *anti* position relative to the technetium oxo core. Although the formation of two isomers during the coordination of the N-substituted tridentate and monodentate ligand with TcO^{3+} core is expected, the *syn* and *anti* isomers were not always observed.[7,12]

In our study, HPLC analysis (μ Bondapak, C18 RP column, methanol/water, 95/5 as mobile phase) of the reaction mixtures of **4**, **8**, **9**, and **20** demonstrates the formation of two complexes,

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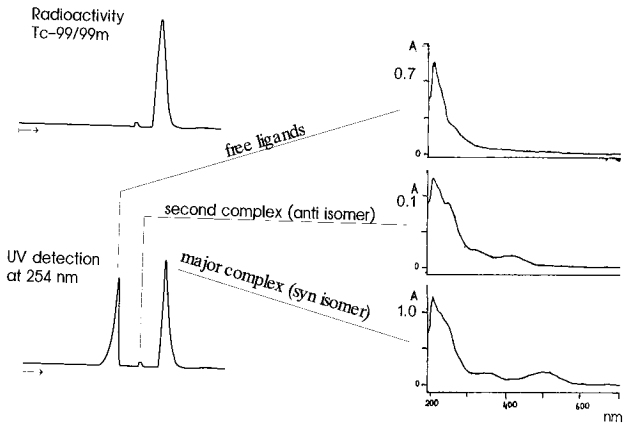

Figure 2. HPLC analysis of the reaction mixture (organic phase) and UV−vis spectum of each peak.

Table 1. Color and Characteristic Spectroscopic Data for Complexes $TcO(L_1)(L_2)$

complex	color	intense bands in UV−vis (nm)[a]	Tc═O str band (cm^{-1})[b]
1	dark red	214, 350, 510	917
2	dark red	215, 275, 355, 520	926
3	dark red	205, 274, 355, 517	919
4	dark red	202, 276, 358, 518	921
4a	orange	202, 422	948
5	dark red	205, 280, 360, 525	924
6	dark red	217, 285, 350, 505	916
7	dark red	202, 284, 337, 502	927
8	dark red	210, 349, 502	918
8a	orange	210, 315, 417	
9	dark red	205, 349, 502	913
9a	orange	204, 245, 330, 416	
10	dark red	205, 349, 502	919
11	dark red	202, 352, 508	910
12	dark red	206, 355, 510	909
13	dark red	208, 352, 511	910
14	dark red	205, 349, 514	910
15	dark red	205, 361, 508	923
16	dark red	206, 350, 510	925
17	dark red	220, 295, 502	917
18	brown	234, 309, 486	922
19	brown	202, 225, 482	920
20	brown	206, 310, 482	924
20a	orange	206, 285, 402	
21	brown	230, 494	920
22	brown	202, 300, 476	916

[a] Spectra were recorded upon HPLC analysis by a Photodiote Array Detector. (Solvent Methanol/Water 95/5). [b] KBr pellets.

in a ratio of 50:1 (Figure 2). In these cases the major complex, which is retained longer on the C18 column, was isolated from the reaction mixture and proved to be the *syn* isomer. The isolation of the minor component was accomplished only in the preparation of **4**. In this case, dark red crystals of **4** were first isolated as the major product (50% yield). The minor component, **4a**, was isolated from the filtrate as brown crystals (1% yield). Complex **4a**, precipitated from a CH_2Cl_2/C_5H_{12} solution on standing at −20 °C and turned out to be the *anti* isomer. In all other cases, only the *syn* isomer was detected and successfully isolated from the reaction mixture. The detection was accomplished by HPLC, using a PDA, that recorded the UV−vis spectra of the eluting complexes (Figure 2).

The infrared spectra of all *syn* $TcOL_1L_2$ complexes show the expected Tc═O stretch for the monooxo species in the region 907−927 cm^{-1} (Table 1). These are at the low energy end of the range thus far observed for TcO-complexes (890−1020 cm^{-1}).[10] The infrared spectra of **4** (major component, *syn* isomer) and **4a** (minor component, *anti* isomer) exhibit intense absorptions for the Tc═O stretch at 921 and 940 cm^{-1}, respectively which indicates that the TcO bond in the *syn* isomer is slightly weaker. All IR spectra showed that both tridentate and monodentate ligands were combined to form the oxotechnetium complex. The absence of bands associated with SH stretching modes is a sign of the deprotonation of this group upon complexation with oxotechnetium.

The electronic absorption spectra of the complexes was determined from HPLC eluent using a photodiode array detector. The UV−vis spectra of all complexes are characterized by an intense band in the 402−525 nm region (Table 1) and additional absorptions at shorter wavelengths. The band in the region 402−525 nm is probably due to a S→Tc charge transfer transition where S is the sulfur donor atom of the monodentate thiol. This band is found at lower energies (500−520 nm) in *syn* complexes with thiophenols or thionapthol (**1**−**17**) than the *syn* complexes with the sulfur atom attached to the aliphatic carbon (476−494 nm, complexes **18**−**22**). In all *syn* thiophenolato complexes a second intense band is also observed at 337−361 nm. The UV−vis spectra of the isolated *anti* isomer (**4a**) is characterized by an intense band at a shorter wavelength (422 nm). These data allow the assignment of the small peaks (<1%) observed by HPLC analyses at earlier retention times, as the *anti* isomers. The ^1H NMR signals of the complexes **1**−**22** are presented in Table 2. In general, the data confirm the presence of both types of ligands in the complex. The integration of the peaks (data not shown) demonstrate that in each case one tridentate and one monodentate ligand were combined to form the oxotechnetium(V) mixed ligand complex. The coligands, L_2H, show the expected signals which can be unambiguously assigned (Table 2). The signals of the tridentate ligand fall in the region 0.92−4.23 ppm. The signals in the region 2.61−4.23 ppm are assigned to the methylene protons of the two chelated NCH_2CH_2S moieties. The four protons of each moiety are diastereotopic each one resulting in a multiplet. The downfield overlapped multiplets (3.36−4.23 ppm) are assigned to the protons which are close (endo) to the TcO core, while the other two multiplets (2.61−3.42 ppm) are assigned to the protons which are remote (exo).[13] The protons attached to the C5 of the N-subtituent (Figure 1) of the isolated major complexes are found in a deshielded environment at 3.87−4.06 ppm indicating that all have the same configuration (*syn*). The same protons for the minor complex **4a** (*anti* isomer) are found upfield at 2.24 ppm (3.98 ppm for the major analog **4**, the *syn* isomer). This is understandable on the basis of diamagnetic anisotropy caused by the circulating electrons of the TcO bond. Thus, consistent with crystallographic analysis (see below), the ^1H NMR results suggest that when the methylene group of the N-substitution bonded to the coordinated nitrogen is in the *syn* configuration with respect to the oxotechnetium core, this group lies within a deshielding zone. On the contrary, the *anti* configuration, **4a**, puts the methylene group out of this zone.

The X-ray crystallography data establishes the *syn* configuration of the N-substituted side chain in the major component of **9**, **11**, and **18** (Figure 3) and the *anti* configuration of the minor component, **4a** (Figure 4). Selected bond distances and angles are given in Table 3. In complexes **9**, **11**, and **18**, the crystallographic data demonstrated that the coordination geometry can be described as distorted trigonal bipyramidal. Analysis of the shape-determining angles using the approach of Addison

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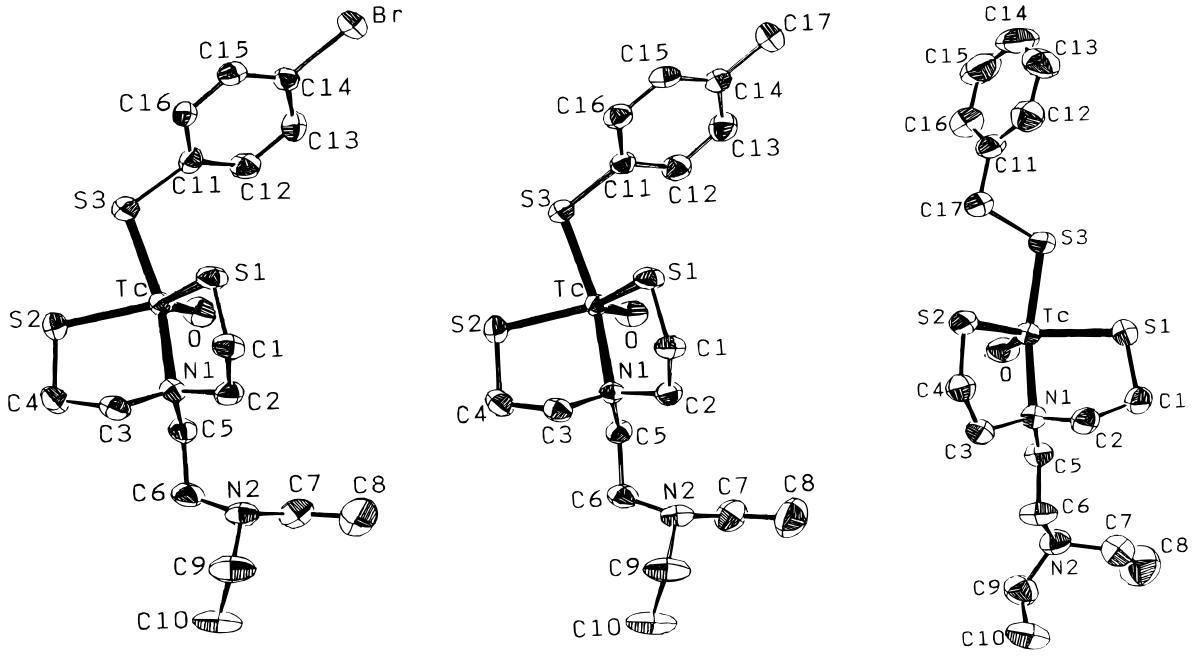


9 **11** **18**

Figure 3. ORTEP diagrams of complexes **9** (left), **11** (center), and **18** (right), with 50% thermal ellipsoid probability showing the atomic labeling.

Table 2. ^{1}H NMR Signals (δ, ppm) for TcO(L_1)(L_2) Complexes

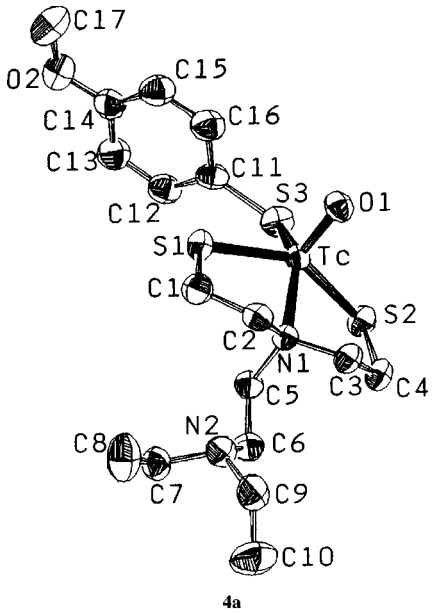
compd	H1 (H4) exo	H1 (H4) endo	H2 (H3) exo	H2 (H3) endo	H5	H6	H-I	H-II	H2′	H3′	H4′	H5′	H6′	H7′	H8′
1	2.89	3.43	2.61	3.48	3.94	1.33			7.47	6.82		6.82	7.47	3.76	
2	2.86	3.55	2.72	3.50	4.06	3.77	3.33		7.47	6.85		6.85	7.47	3.77	
3	2.90	3.50	2.72	3.53	3.95	2.80	2.25		7.47	6.81		6.81	7.47	3.76	
4	2.88	3.51	2.73	3.53	3.97	2.82	2.52	1.00	7.48	6.83		6.83	7.48	3.76	
4a	3.40	3.40	4.23	3.92	2.24	2.49	2.36	0.92	7.43	6.87		6.87	7.43	3.77	
5[a]	2.89	3.36	2.61	3.50	3.87	1.89	2.47	0.96	7.51	6.82		6.82	7.51	3.76	
6	2.92	3.53	2.77	3.56	3.94	2.82	2.51	1.00	7.19		7.19	6.75	7.19	3.76	
7	2.89	3.54	2.73	3.57	3.94	2.81	2.50	0.99		6.89	7.22	6.89	7.45	3.82	
8	2.90	3.53	2.76	3.56	3.94	2.82	2.54	1.00	7.60	7.29	7.18	7.29	7.60		
9	2.93	3.54	2.75	3.58	3.93	2.82	2.55	1.00	7.42	7.40		7.40	7.42		
10	2.93	3.51	2.78	3.54	3.92	2.82	2.51	1.00	7.59	7.32		7.32	7.59		
11	2.91	3.52	2.75	3.56	3.95	2.82	2.51	1.00	7.45	7.12		7.12	7.45	2.32	
12	2.91	3.52	2.74	3.55	3.94	2.82	2.50	1.00	7.47	7.14		7.14	7.47	2.60	1.19
13	2.91	3.52	2.74	3.56	3.94	2.82	2.51	1.00	7.47	7.17		7.17	7.47	1.58	1.19
14[b]	2.91	3.52	2.74	3.56	3.94	2.82	2.53	1.00	7.46	7.12		7.12	7.46	2.53	1.55
15	2.91	3.53	2.75	3.56	3.94	2.82	2.51	1.00	7.48	7.32		7.32	7.48	1.27	
16	2.90	3.51	2.73	3.55	3.94	2.82	2.51	1.00	7.35	7.07		7.07	7.27	2.22	2.20
17	2.91	3.48	2.73	3.53	3.92	2.81	2.51	1.00	8.32	7.45	7.76	7.76	7.45	7.45	7.76
18	3.05	3.57	2.65	3.60	3.89	2.80	2.50	1.00	7.34	7.28	7.15	7.28	7.34	4.87	
19	3.05	3.57	2.63	3.61	3.89	2.82	2.51	1.00	7.26	6.87		6.87	7.26	4.83	3.71
20	3.05	3.58	2.64	3.62	3.90	2.82	2.51	1.00	7.29	7.27		7.27	7.29	4.84	1.23
21	3.00	3.60	2.64	3.56	4.00	3.78	3.33		7.34	7.22	7.15	7.22	7.34	4.88	
22	3.00	3.55	2.70	3.60	3.90	2.81	2.52	1.00	2.46	1.54	1.37	1.54	2.46	2.71	3.86

[a] 2.47 (H-III). [b] 1.31 (H-9′) and 0.86 (H−10′).

et al.,[14] yields a trigonaly index, τ, of 0.62 for all three complexes ($\tau = 0$ for square pyramidal geometry and $\tau = 1$ for trigonal bipyramidal geometry). We have until now solved 10 structures of mixed-ligand complexes of the type MO[SN(R)S][S] (M = Re, Tc). Two of these have the *anti* configuration and are square pyramidal ($\tau = 0.05$) while the eight have the *syn* configuration and are distored trigonal bipyramidal ($\tau = 0.63 \pm 3$). All thiol groups undergo deprotonation during complexation so that the complexes are neutral. The technetium lies 0.062−0.077 Å above the basal plane of the trigonal bipyramid formed by S1, S2, and the oxo group with the N1 and S3 atoms occupying the two apical positions. The N1−Tc−S3 angles are 157.3(1), 157.7(1), and 158.4(1)° for complexes **9**, **11**, and **18** respectively.

An ORTEP diagram of complex **4a** is shown in Figure 4, and selected bond distances and angles are given in Table 3. In this complex, the metal atom is also coordinated to five atoms (S1, S2, S3, N1, and oxo group) but in square pyramidal geometry ($\tau = 0.05$). The atoms, N1, S1, S2, and S3 form the basal plane with the oxo ligand occupying the apex of the pyramid. The distance of Tc from the basal plane is 0.74 Å. The bond angles between the diametrically opposite coordinated atoms in the basal plane S1−Tc−S2 and S3−Tc−N1 are 143.1(1) and 140.2(1) Å, respectively.

The metal−oxygen bond distances 1.653(3)−1.669(2) Å are well within the range of several well-characterized monooxo Tc complexes.[10] The metal−sulfur bond distances are in the range 2.265(2)-2.315(1) Å, also consistent with those for other



4a

Figure 4. ORTEP diagram of complex **4a** (*anti* isomer), with 50% thermal ellipsoid probability showing the atomic labeling.

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

	4a	**9**	**11**	**18**
Tc−O1	1.656(4)	1.658(5)	1.669(2)	1.653(3)
Tc−S1	2.295(1)	2.265(2)	2.269(1)	2.289(1)
Tc−S2	2.308(2)	2.279(2)	2.280(1)	2.273(1)
Tc−S3	2.292(2)	2.311(2)	2.315(1)	2.285(1)
Tc−N1	2.165(5)	2.205(5)	2.212(2)	2.223(3)
O1−Tc−S1	108.0(2)	120.6(1)	120.9(1)	121.2(1)
O1−Tc−S2	108.4(2)	118.5(2)	118.3(1)	117.9(1)
O1−Tc−S3	108.0(2)	105.1(2)	105.4(1)	104.9(1)
O1−Tc−N1	111.7(2)	97.6(2)	96.9(1)	96.3(1)
S1−Tc−S2	143.1(1)	120.6(1)	120.0(4)	120.5(1)
S1−Tc−S3	91.0(1)	86.3(1)	86.0(4)	82.0(1)
S2−Tc−S3	83.5(1)	84.0(1)	84.0(4)	90.0(1)
S1−Tc−N1	80.4(1)	83.6(1)	83.5(1)	83.2(1)
S2−Tc−N1	80.9(1)	83.8(2)	83.9(1)	84.1(1)
S3−Tc−N1	140.2(1)	157.3(1)	157.7(1)	158.4(1)

Tc−thiolate complexes.[10] The Tc−N1 bond distances are in the range 2.165(5)−2.223(3) Å. All of these parameters are in general agreement with the structural parameters for a large number of complexes containing the same donor atoms.[10] The tridentate ligand (L_1) displays conformational flexibility. The torsion angles S1−C1−C2−N1 and S2−C4−C3−N1 are equal to 38.8(1)/41.4(1), 47(1)/52.2(1), 48.4(3)/53.3(3), and 44.7(6)/54.9(6)° for complexes **4a**, **9**, **11**, and **18** respectively. The two five membered rings formed by the atoms Tc, S1, C1, C2, and N1 and Tc, S2, C4, C3, and N1 exist in the envelope form in all four complexes. But while in **4a**, N1 is the "flap" atom and is 0.89 Å above the mean plane of the "pocket" atoms Tc, S1, C1, and C2 and Tc, S2, C4, and C3, in complexes **9**, **11**, and **18** the "flap" atoms are C2 and C3 and their distances from the mean planes of their respective "pocket" atoms vary between 0.55 and 0.64 Å. For the *anti* isomer (**4a**), C5 and O1 lie −2.369(1) and +1.516(1) Å, respectively, below and above the mean plane of the atoms S1, S2, and N1. The same distances for the *syn* isomers **9**, **11**, and **18** are 2.619(1)/0.918(1), 2.625-(1)/0.914(1), and 2.608(1)/0.937(1) Å, respectively.

In conclusion, upon simultaneous action of a tridentate N-substituted bis(2-mercaptoethyl)amine and a monodentate thiol on the Tc(O)−gluconate precursor, the *syn* isomer of the pentacoordinated oxotechnetium complex is preferably formed. In the preparation of some compounds, the formation of small amounts (<1%) of the *anti* isomer was also observed. The isomerism is due to the orientation of N-substitution with respect to the Tc═O core. Crystallographic analysis showed that the *syn* isomers (**9**, **11**, **18**) have a trigonal bipyramidal geometry whereas the square pyramidal geometry is found for the *anti* isomer (**4a**). IR and ^{1}H NMR spectral data show characteristic differences which allow the assignment of the two isomers as *syn* and *anti*. The neutral mixed-ligand oxotechnetium complexes which were studied in this work are of special interest as potential new brain Tc-99m radiopharmaceuticals. Biodistribution studies in rodents have shown a significant brain uptake and retention.[8]

Experimental Section

Caution! Technetium-99 is a weak β-emitter (0.292 MeV) with a half life of 2.12×10^5 years. All manipulations of solutions and solids were carried out in a laboratory approved for the handling of low level radioisotopes. Normal safety procedures were followed at all times to prevent contamination.

IR spectra were recorded as KBr pellets in the range 4000−500 cm^{-1} on a Perkin-Elmer 1600FT-IR spectrophotometer. The ^{1}H NMR spectra were recorded in deuterochloroform with a 250AF FT-NMR (Bruker) spectrometer operated at 250 MHz. The chemical shifts are given in ppm, downfield from internal tetramethyl silane. Elemental analyses were performed on a Perkin-Elmer 2400/II automated analyzer. High-performance liquid chromatography (HPLC) analyses were performed on a Waters chromatograph equipped with the 600E solvent delivery system, and a μ-Bondapak C-18 RP or a Porasil column using either methanol/water, (95/5), or dichloromethane/methanol (85/15) as the mobile phase at a flow rate of 1.0 mL/min. Detection of ^{99}Tc complexes was accomplished with a photodiode array detector, Waters 991 PDA, that recorded the UV−vis spectrum of the eluting complexes and a Beckman 171 radioisotope detector.

All laboratory chemicals were reagent grade. Solvents used in high performance liquid chromatography were specified as being of HPLC purity. ^{99}Tc was purchased as ammonium pertechnetate from the Oak Ridge National Laboratory. The impure black solid was purified prior to its use by treatment overnight with hydrogen peroxide and ammonium hydroxide in methanol. Evaporation of the solvent gave ammonium pertechnetate as a white powder. The precursors Tc(V)-gluconate and $(Bu)_4NTcOCl_4$ were synthesized by literature methods.[15] Ethylene sulfide, thiophenol, 2-methoxythiophenol, 3-methoxythiophenol, 4-methoxythiophenol, 4-toluenethiol, benzyl mercaptan, diethanolamine, (2-methoxyethyl)amine, *N*,*N*-dimethylethylenediamine, *N*,*N*-diethylethylenediamine, *N*,*N*-diethylpropylenediamine (Fluka Chemika), bromobenzene, iodobenzene, ethylbenzene, isopropylbenzene, butylbenzene, *tert*-butylbenzene, 1-naphthalenesulfonyl chloride, 4-methoxybenzyl chloride, 4-*tert*-butylbenzyl chloride, and 3,4-dimethylthiophenol, (Aldrich Chemical Co), where necessary were purified by distillation or by recrystallization. 4-Bromobenzenesulfonyl choride, 4-iodobenzenesulfonyl choride, 4-ethylbenzenesulfonyl choride, 4-isopropylbenzenesulfonyl choride, 4-butylbenzenesulfonyl choride, and 4-*tert*-butylbenzenesulfonyl choride were synthesized by a modification of a published procedure.[16]

4-Bromothiophenol, 4-iodothiophenol, 4-ethylthiophenol, 4-isopropylthiophenol, 4-butylthiophenol, 4-*tert*-butylthiophenol, 3,4-dimethylthiophenol and α-thionaphthol were prepared by a method similar to that employed by *Organic Syntheses*[17] for making thiophenol from the corresponding sulfonyl chlorides, zinc dust, and sulfuric acid. The boiling points (or melting points for 4-bromothiophenol and 4-iodothiophenol) agreed with the published values.[18]

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Table 4. Summary of Crystal, Intensity Collection, and Refinement Data

	4a	**9**	**11**	**18**
formula	$C_{17}H_{29}N_2O_2S_3Tc$	$C_{16}H_{26}N_2OS_3BrTc$	$C_{17}H_{29}N_2OS_3Tc$	$C_{17}H_{29}N_2OS_3Tc$
fw	487.63	537.48	472.61	471.63
a (Å)	8.3553(7)	13.203(2)	13.1286(9)	10.465(1)
b (Å)	27.943(2)	7.475(1)	7.5227(5)	17.719(2)
c (Å)	9.3806(8)	21.312(3)	21.222(2)	11.516(1)
β (deg)	99.962(2)	102.969(4)	103.026(2)	102.427(2)
V (Å^3)	2157.12	2049.60	2042.03	2085.24
Z	4	4	4	4
D_{calcd}/D_{measd} (Mg m^{-3})	1.501/1.49	1.739/1.72	1.534/1.52	1.502/1.48
space group	$P2_1/n$	$P2_1/c$	$P2_1/c$	$P2_1/n$
temp, K	296	296	296	296
radiation, λ	Mo Kα 0.7107	Mo Kα 0.7107	Mo Kα 0.7107	Mo Kα 0.7107
abs coeff (μ), cm^{-1}	3.40	22.80	3.50	3.50
max. abs. cor factor		1.26		1.14
no. of data collcd/unique	4160/3787	4015/3597	4036/3542	4447/4085
no. of data used	2677 [$F_o \geq 4.0\sigma(F_o)$]	2545 [$F_0 \geq 4.0\ \sigma(F_0)$]	2985 [$F_0 \geq 6.0\sigma(F_0)$]	2920 [$F_0 \geq 5.0\sigma(F_0)$]
$R = \sum\|\|F_0\| - \|F_c\|\|/\sum\|F_0\|$	0.0355	0.0378	0.0187	0.0322
$R_w = (\sum w(\|F_0\| - \|F_c\|)2/\sum w\|F_0\|^2)^{1/2}$	0.0419[a]	0.0420[a]	0.0212[a]	0.0351[a]

[a] Unit weights were used.

4-Methoxybenzyl mercaptan,[19] 4-*tert*-butylbenzyl mercaptan,[20] 1-(2-mercaptoethyl)piperidine,[21] 2,2′-dimercaptotriethylamine,[22] *N*,*N*-bis-(2-mercaptoethyl)-*N*′,*N*′-dimethylethylenediamine,[23] and *N*,*N*-bis(2-mercaptoethyl)-*N*′,*N*′-diethylethylenediamine[23] were prepared according to the literature.

***N*,*N*-Bis(2-mercaptoethyl)(2-methoxyethyl)amine.** A solution of (2-methoxyethyl)amine (7.5 g, 0.1 mol) in 40 mL of dry toluene was mixed with a solution of ethylene sulfide (12 g, 0.2 mol) in 40 mL of dry toluene at 40−50 °C. The resultant solution was immediately placed in an autoclave, which was flushed with nitrogen, sealed, and then heated at 110 °C in an oil bath. After 20-h reaction time the solution was cooled and filtered to remove a small amount of polyethylene sulfide. The solvent was removed and the residual liquid fractionally distilled under reduced presure to give *N*,*N*-bis(2-mercaptoethyl)(2-methoxyethyl)amine, 6.3 g (32%) as a colorless liquid boiling at 85-88 °C (0.15 mm). IR: no ν(N−H) band, 2545 cm^{-1} ν(S−H), 1112 cm^{-1} ν(C−O−C). Monosubstituted N-(2-mercaptoethyl)(2-methoxyethyl)amine was also recovered from this reaction in 38% yield as a colorless liquid boiling at 63−65 °C (1.5 mm) (lit.[24] 84 °C (17 mm)). A ν(N−H) band at 3317 cm^{-1}, a ν(S−H) band at 2548 cm^{-1}, and a ν(C−O−C) band at 1116 cm^{-1} are seen in the infrared spectrum.

***N*,*N*-Bis(2-mercaptoethyl)-*N*′,*N*′-diethylpropylenediamine.** The reaction was run in the same manner as used for the above compound. Workup as above and distillation gave *N*,*N*-bis-(2-mercaptoethyl)-*N*′,*N*′-diethylpropylenediamine in 11% yield as a colorless liquid boiling at 115−118 °C (0.1 mm). IR: no ν(N−H) band, 2546 cm^{-1} ν(S-H). Monosubstituted N-(2-mercaptoethyl)-*N*′,*N*′-diethylpropylenediamine was also recovered from this reaction in 30% yield as a colorless liquid boiling at 80−85 °C (0.1 mm) (lit.[24] 80 °C (0.02 mm)). A ν(N−H) band at 3278 cm^{-1} and a ν(S−H) band at 2523 cm^{-1} are seen in the infrared spectrum.

Preparation of the $TcOL_1L_2$ Complexes. A typical procedure is given for complex **1**. ^{99}Tc−gluconate was prepared as previously described,[7] by the addition of stannous chloride (45 mg, 0.24 mmol) in HCl (1 N, 1.0 mL) to a solution of NH_4TcO_4 (36.2 mg, 0.2 mmol) and sodium gluconate (200 mg) in water, containing $^{99m}TcO_4^-$ (0.1 mL, 0.5 mCi). The pH of the solution was adjusted to 7.5 with NaOH (1 N). This solution was added, with stirring, to a mixture of *N*,*N*-bis(2-mercaptoethyl)ethylamine (33 mg, 0.2 mmol) and 4-methoxythiophenol (28 mg, 0.2 mmol). The solution was stirred for 20 min and then extracted two times with dichloromethane (20 mL). The organic phase was separated, dried over $MgSO_4$, and filtered. Analysis of the solution by HPLC (C18, RP column using methanol/water, 95:5, as mobile phase) demonstrated the formation of one complex. The volume of the solution was reduced to 5 mL, and then 5 mL of ethanol was added. Slow evaporation of the solvents at room temperature afforded the product as dark red crystals.

In the preparation of **9**, **10**, and **11** a small amount of dichloromethane was added prior to the addition of Tc(O)−gluconate in order to dissolve the monothiol. In the preparations of **4**, **8**, **9**, and **20**, HPLC analyses demonstrated the presence of a second complex (yield < 1%) at an earlier retention time.

In all but one case the *syn* isomer was the isolated complex. The yields were 35-70%, depending on the ligands. During the preparation of complex **4** (where L_1H_2 = *N*,*N*-bis(mercaptoethyl)-*N*′,*N*′-diethylethylenediamine and L_2H = 4-methoxythiophenol) two complexes were successfully isolated. Complex **4** was first precipitated as the major product (*syn* isomer, 50% yield) of the reaction while the minor complex **4a** (*anti* isomer) was isolated from the filtrate in a very low yield (1%). Complex **4a** precipitated from a CH_2Cl_2/*n*-C_5H_{10} solution on standing at −20 °C for several days. All isolated complexes were characterized by IR, UV−vis, and ^{1}H NMR (Tables 1 and 2). The complexes gave also correct elemental analysis for C, H, N, and S. The crystal structures of complexes **4a**, **9**, **11**, and **18** were solved by X-ray crystallography.

X-ray Crystal Structural Determination. Diffraction measurements were made on a $P2_1$ Nicolet diffractometer upgraded by Crystal Logic using Zr-filtered Mo radiation. Unit cell dimensions were determined and refined by using the angular settings of 25 automatically centered reflections in the range 11° < 2θ < 23° and they appear in Table 4. Intensity data were recorded using a $\theta-2\theta$ scan: for **4a** and **9**, 2θ(max) = 50°, scan speed 3.0 deg/min, scan range 2.5 + $\alpha_1\alpha_2$ separation; for **11**, 2θ(max) = 52°, scan speed 4.5 deg/min, scan range 2.5 + $\alpha_1\alpha_2$ separation; for **18**, 2θ(max) = 52°, scan speed 4.5 deg/min, scan range 2.7 + a_1a_2 separation. Three standard reflections monitored every 97 reflections showed less than 3% variation and no decay. Lorentz, polarization, and ψ-scan absorption correction (**9** and **18**) were applied using Crystal Logic software. The structures were solved by direct methods using SHELXS-86[25a] and refined by full-matrix least-squares techniques with SHELX-76.[25b]

For complex **4a:** 4160 collected reflections were averaged with R = 0.0422 to give 3787 independent reflections of which only the 2677 reflections with $F_o > 4\sigma(F_o)$ were used for the refinement of 318 parameters. All hydrogen atoms (except those of the methyl groups which were introduced at calculated positions as riding on bonded atoms) were located by difference maps and their positions were refined

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isotropically. All non-hydrogen atoms were refined anisotropically. The final values for R and R_w for observed data are in Table 4; for all data, they are 0.0762, 0.1174 respectively. The maximum and minimum residual peaks in the final difference map were +0.520 and −0.352 e/Å^3. The largest shift/esd in the final cycle was 0.001.

For complex **9:** Symmetry equivalent data were averaged with R = 0.0324 to give 3597 independent reflections from a total 4015 collected. For the refinement of 310 parameters 2545 reflections with $F_o > 4\sigma(F_o)$ were used. All hydrogen atoms (except those of methyl group (C10) which were introduced at calculated positions as riding on bonded atom) were located by difference maps and their positions were refined isotropically. All non-hydrogen atoms were refined anisotropically. The final values for R and R_w for observed data are in Table 4; for all data they are 0.0712 and 0.0717, respectively. The maximum and minimum residual peaks in the final difference map were +0.624 and −0.433 e/Å^3. The largest shift/esd in the final cycle was 0.088.

For complex **11:** 4036 reflections were collected which were averaged to give 3542 unique ones (R = 0.0237); 2985 reflections with $F_o > 6\sigma(F_o)$ were used for the refinement of 322 parameters. All hydrogen atoms (expect those of the methyl group (C17), which were introduced at calculated positions as riding on the bonded atom) were located by difference maps and their positions were refined isotropically. All non-hydrogen atoms were refined anisotropically. The final values for R, and R_w for observed data are in Table 4; for all data, they are 0.0277 and 0.0313, respectively. The maximum and minimum residual peaks in final difference map were +0.300 and −0.248 e/Å^3. The largest shift/esd in the final cycle was 0.028.

For complex **18:** from a total of 4447 reflections collected, only 4085 were independent (R = 0.0310) while for the refinement of 333 parameters, 2920 reflections with $F_o > 5\sigma(F_o)$ were used. All hydrogen atoms were located by difference maps and their positions refined isotropically. The final values for R and R_w for observed data are in Table 4; for all data, they are 0.0594 and 0.0599, respectively. The maximum and minimum residual peaks in the final difference map were +0.748 and −0.340 e/Å^3. The largest shift/esd in the final cycle was 0.003. Atomic scattering factors and anomaluous dispresion corrections were from ref 25.

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Supporting Information Available: Tables of fractional atomic coordinates and anisotropic thermal parameters for all non-hydrogen atoms, fractional atomic coordinates of H-atoms, and full bond lengths and angles for **4a**, **9**, **11**, and **18** (16 pages). Ordering information is given on any current masthead page.

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