A New Donor Atom System [(SNN)(S)] for the Synthesis of Neutral Oxotechnetium(V) Mixed-Ligand Complexes

M. S. Papadopoulos,[†] M. Pelecanou,[‡] I. C. Pirmettis,[†] D. M. Spyriounis,[†] C. P. Raptopoulou,[§] A. Terzis,[§] C. I. Stassinopoulou,[‡] and E. Chiotellis*,[†]

Institutes of Radioisotopes-Radiodiagnostic Products, Biology, and Materials Science, NCSR "Demokritos", P.O. Box 60228, 15310 Aghia Paraskevi, Athens, Greece

Received October 20, 1995[⊗]

A new approach to the "3 + 1" mixed ligand oxotechnetium complexes of the general formula TcOL1L2, with ligands ($L1H_2$) containing the SNN donor set and various monodentate thiols as coligands (L2H) is reported. The ligands $L1H_2$ (**1**−**3**, general formula $R_1CH_2CH_2NHCH_2C(R_2)_2SH$ where $R_1 = N(CH_3)_2$ and $R_2 = H$ in **1**, R_1 = pyrrolidin-1-yl and $R_2 = H$ in **2**, and R_1 = piperidin-1-yl and $R_2 = CH_3$ in **3**) act as tridentate SNN chelates to the TcO^{3+} core, leaving open one coordination site *cis* to the oxo group. In the presence of a monodentate thiol (L2H) and using ^{99}Tc(V)−gluconate as precursor, the vacancy is filled by the thiol which acts as the coligand. With this approach four neutral oxotechnetium complexes (**4**−**7,** general formula $TcO[R_1CH_2CH_2NCH_2C(R_2)_2S][SR]$ where RSH = *p*-methoxybenzenethiol, or *p*-methylbenzenethiol or benzyl mercaptan) were prepared in high yield by reacting $L1H_2$ and L2H with Tc(V)−gluconate in a ratio 1:1:1. The complexes were characterized by elemental analysis and spectroscopic methods. Complete assignments of ^{1}H and ^{13}C NMR resonances were made for all complexes. X-ray crystallographic studies of **5** (R_1 = pyrrolidin-1-yl, $R_2 = H$, RSH = *p*-methylbenzenethiol) and **7** (R_1 = piperidin-1-yl, $R_2 = CH_3$, RSH = benzyl mercaptan) showed that the complexes crystallize in the monoclinic space group $P2_1/n$ ($a = 10.223(1)$ Å, $b = 9.283(1)$ Å, $c = 18.337(2)$ Å, $\beta = 97.262(2)°$, $V = 1726.3(4)$ Å^3, $Z = 4$; $a = 11.876(2)$ Å, $b = 10.470(2)$ Å, $c = 17.098(3)$ Å, $\beta = 105.990(4)°$, $V = 2043.8(6)$ Å^3, $Z = 4$, for **5** and **7,** respectively). Complexes **5** and **7** have distorted square pyramidal coordination geometry with the oxo ligand in the axial position. The steric requirements of the oxo group cause the Tc atom to be displaced 0.68 Å out of the mean equatorial plane of the NNSS donor atoms in both complexes.

Introduction

The "3 + 1" concept for the preparation of neutral oxotechnetium and oxorhenium mixed-ligand complexes, MOL1L2, has been applied recently[1,2] in the development of novel diagnostic or therapeutic radiopharmaceuticals. The advantage of the mixed-ligand concept in the design of radiopharmaceuticals lies in the variety of possible tridentate/monodentate complexes that can be synthesized either by modifying the tridentate or by changing the monodentate ligand.

In general, the preparation of "3 + 1" mixed ligand complexes requires the simultaneous action of a dianionic tridentate ligand ($L1H_2$) carrying the SSS, SOS, or SN(R)S donor atom set and a monodentate thiol (L2H, coligand) on a suitable oxotechnetium(V) or oxorhenium(V) precursor. The geometry of mixed-ligand complexes with the tridentate ligand, $L1H_2$, having the SSS or the SOS donor atom set is usually distorted square pyramidal.[2c] The basal plane is formed by the (SSS)(S) or the (SOS)(S) donor atoms while the oxo group occupies the apex of the square pyramid. When the tridentate ligand has the SN(R)S donor atom set, two stereoisomers are expected, *syn* and *anti*, depending on the orientation of the R-functionality with respect to the Tc═O or Re═O group.[3] Our findings demonstrate that usually only the *syn* isomer is formed.[1a−c,e] In very few cases, we have detected the formation of the *anti* isomer (<1%), and in two of those we succeeded in its isolation and extensive characterization.[4] The *syn* isomer has trigonal bipyramidal geometry, something that is relatively rare for oxotechnetium(V) and oxorhenium(V) complexes. The basal plane is defined by the two sulfur atoms of the tridentate ligand and the oxygen of the oxo group, whereas the two apical positions are occupied by the nitrogen of the tridentate ligand and the sulfur atom of the coligand thiol. The *anti* isomer forms a square pyramid with the basal plane defined by the donor atoms [SN(R)S][S] and the apex occupied by the oxo group. The two stereoisomers have different physical and chemical characteristics. A series of ^{99m}TcO[SN(R)S][S] complexes have been synthesized and evaluated in experimental animals as potential

[†] Institute of Radioisotopes-Radiodiagnostic Products.
[‡] Institute of Biology.
[§] Institute of Materials Science.
[⊗] Abstract published in *Advance ACS Abstracts,* May 15, 1996.

(1) (a) Mastrostamatis, S. G.; Papadopoulos, M. S.; Pirmettis, I. C.; Paschali, E.; Varvarigou, A. D.; Stassinopoulou, C. I.; Raptopoulou, C. P.; Terzis, A.; Chiotellis, E. *J. Med. Chem.* **1994,** *37*, 3212. (b) Stassinopoulou, C. I.; Pelecanou, M.; Mastrostamatis, S.; Chiotellis, E. *Magn. Reson. Chem.* **1994**, *32*, 532. (c) Spyriounis D.; Pelecanou, M.; Stassinopoulou, C. I.; Raptopoulou, C. P; Terzis, A.; Chiotellis, E. *Inorg. Chem.* **1995**, *34*, 1077. (d) Mastrostamatis, S.; Pirmettis, I.; Papadopoulos, M.; Paschali, E.; Raptopoulou, C.; Terzis, A.; Chiotellis, E. In *Technetium and Rhenium in Chemistry and Nuclear Medicine 4*; Nicolini, M., Bandoli, G., Mazzi, U., Eds.; SGE Padova: Padova, Italy, 1995; p 409. (e) Papadopoulos, M.; Pirmettis, I.; Raptopoulou, C.; Terzis, A.; Chiotellis, E. In *Technetium and Rhenium in Chemistry and Nuclear Medicine 4*; Nicolini, M., Bandoli, G., Mazzi, U., Eds.; SGE Padova: Padova, Italy, 1995; p 223.

(2) (a) Pietzsch, H.-J.; Spies, H.; Hoffmann, S.; Stach, J. Lipophilic technetium complexes-V. *Inorg. Chim. Acta* **1989**, *161*, 15. (b) Pietzch, H.-J.; Spies, H.; Hoffmann, S.; Scheller, D. *Appl. Radiat. Isot.* **1990**, *41*, 185. (c) Spies, H.; Johannsen, B.; Pietzsch, H.; Noll, B.; Noll, St.; Scheunemann, M.; Fietz, T.; Berger, R.; Brust, P.; Leibnitz, P. *XI International Symposium on Radiopharmaceutical Chemistry*; Vancouver, Canada, 1995; p 319. (d) Spies, H.; Fietz, T.; Glaser, M.; Pietzsch, H.; Johannsen, B. In *Technetium and Rhenium in Chemistry and Nuclear Medicine 4*; Nicolini, M., Bandoli, G., Mazzi, U., Eds.; SGE Padova: Padova, Italy, 1995; p 243.

(3) (a) Epps, L.; Burns, H. D.; Lever, S. Z.; Goldfarb, H. W.; Wagner, H. N. *Appl. Radiat. Isot.* **1987**, *36*, 661. (b) Kung, H. G.; Guo, Y. Z.; Yu, C. C.; Billings, J.; Subramanyam, V.; Calabrese, J. *J. Med. Chem.* **1989**, *32*, 433. (c) Lever, S. Z.; Baidoo, K. E.; Mahmood, A. *Inorg. Chim. Acta* **1990**, *176*, 183 (d) O'Neil, J.; Wilson, S.; Katzenellenbogen, J. *Inorg. Chem.* **1994**, *33*, 319.

(4) (a) Pirmettis, I. C.; Papadopoulos, M. S.; Mastrostamatis, S. G.; Raptopoulou, C. P.; Terzis, A.; Chiotellis, E. *Inorg. Chem.* **1996**, *35*, 1685. Papadopoulos, M. S.; Pirmettis, I. C. Unpublished data.

S0020-1669(95)01364-4 CCC: $12.00

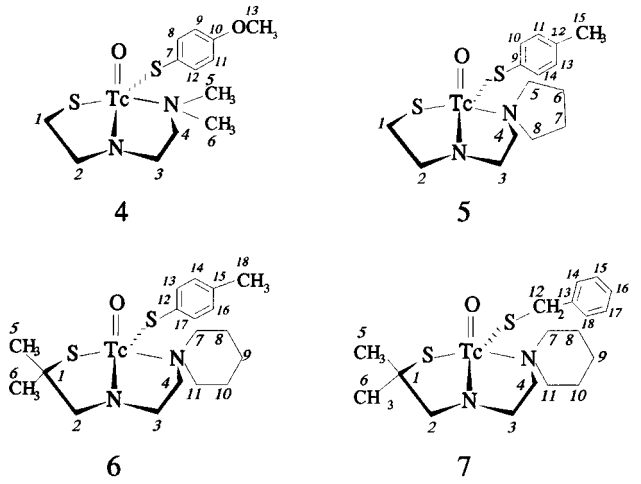
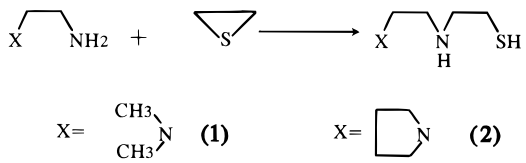


Figure 1. Structures of complexes **4**−**7**. Numbering is according to the crystallographic structures (Figures 2 and 3) in order to facilitate comparisons.

Scheme 1



brain radiopharmaceuticals. They have shown high brain uptake and significant retention.[5]

In this study, we report the synthesis and characterization of four novel mixed ligand oxotechnetium(V) complexes using tridentate ligands having the new donor atom set SNN. In this alternative approach to the "3 + 1" concept, the coordination sphere is filled by both a tridentate ligand and a monodentate thiol resulting in neutral complexes. The complexes **4**−**7** (Figure 1) were characterized by elemental analysis and spectroscopic methods. Complete assignments of ^{1}H and ^{13}C NMR resonances were made for all complexes. The crystal structures of complexes **5** and **7** were determined by X-ray crystallography.

Results and Discussion

Synthesis. The synthesis of the tridentate ligands **1** and **2** (Scheme 1) was done according to the reported procedure by Marabella et al.[6] for mercaptoethylations of amines with ethylene sulfide. The tridentate ligand **3** (Scheme 2) was prepared by a procedure similar to that of D'Amico and Corbin.[7] When the diimine was treated with sodium borohydride in ethanol, the disulfide bond remained intact and only the C═N bonds were reduced, giving the diamine disulfide. Treatment of the disulfide with Na/NH_3 afforded ligand **3** in high yield. Symmetrical substitution of the tertiary amine was chosen in order to avoid the formation of stereoisomers.

The mixed-ligand complexes **4**−**7** were prepared by reacting the tridentate ligands **1**−**3** ($L1H_2$) and monodentate thiols (L2H) with ^{99}Tc-gluconate[8] precursor in a ratio of $L1H_2$:L2H:Tc = 1:1:1. Complexes **4**−**7** are crystalline solids, soluble in CH_2Cl_2 and $CHCl_3$, slightly soluble in EtOH and MeOH, and insoluble in pentane and water. They are neutral, stable in the solid state and in solution ($CHCl_3$, CH_3OH, $C_6H_5CH_3$, H_2O), and lipophilic as indicated by their quantitative extraction from the aqueous to the dichloromethane layer during isolation. The infrared spectra of the complexes exhibit a strong Tc═O stretching vibration at 907, 931, 925, 929 cm^{-1} for **4**, **5**, **6**, and **7** respectively. These values are consistent with other values reported for monooxo−Tc(V) species.[9]

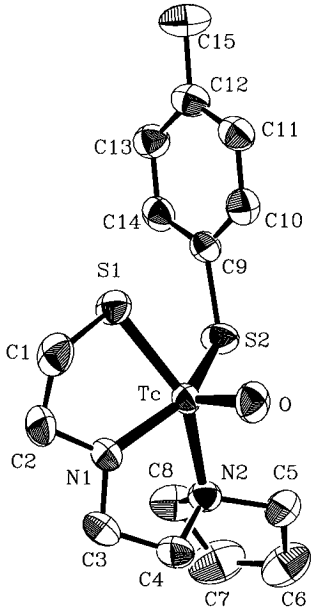
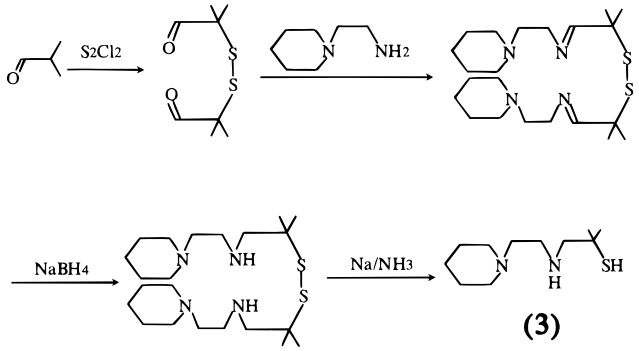


Figure 2. ORTEP diagram of complex **5**, with 50% thermal probability ellipsoids showing atomic labeling scheme.

Scheme 2



X-ray Crystallographic Studies of Complexes 5 and 7. ORTEP diagrams with the atomic labeling scheme of the complexes **5** and **7** are shown in Figures 2 and 3 respectively. Selected bond distances and angles for both complexes are given in Table 1. Crystallographic data are given in Table 2. In both complexes, the coordination sphere of technetium is formed by two sulfur atoms, two nitrogen atoms, and one doubly bonded oxygen atom in a distorted square pyramidal geometry with the trigonality index, τ,[10] taking a value of 0.21 for complex **5** and

(5) (a) Pirmettis, I.; Papadopoulos M.; Paschali, E.; Varvarigou A.; Chiotellis, E. *Eur. J. Nucl. Med.* **1994**, *21*, S7. (b) Pirmettis, I.; Papadopoulos M.; Mastrostamatis, S.; Tsoukalas, Ch.; Chiotellis, E. *J. Nucl. Med.* **1995**, *36*, 145P. (c) Pirmettis, I.; Papadopoulos, M.; Paschali, E.; Varvarigou, A. D.; Chiotellis, E. *J. Nucl. Med.* **1995**, *36*, 145P.

(6) Marabella, C.; Enemark, J.; Miller, A.; Bruce, A.; Pariyadath, N.; Corbin, J.; Stiefel, E. J. O*rg. Chem.* **1983**, *22*, 3456.

(7) (a) D'Amico, J.; Dahl, W. *J. Org. Chem.* **1975**, *40*, 1224. (b) Corbin, J.; Work, D. *J. Org. Chem.* **1976**, *41*, 489.

(8) Johannsen, B.; Spies, *H.* In *Chemie und Radiopharmakologie von technetiumkomplexen;* Akademie der Wissd. DDR, Dresden, East Germany, 1981.

(9) (a) Davison, A.; Jones, A. G.; Orving, C.; Sohn, M. *Inorg. Chem.* **1981**, *20*, 1629. (b) Bandoli, G.; Mazzi, U.; Roncari, E.; Deutch, E. *Coord. Chem. Rev.* **1982**, *44*, 191. (c) Melnik, M.; Van Lier, J. E. *Coord. Chem. Rev.* **1987**, *77*, 275. (d) Rao, T. N.; Adhikesavalu, D.; Camerman, A.; Fritzberg, A. R. *J. Am. Chem. Soc.* **1990**, *112*, 5798. (e) Stassinopoulou, C. I.; Mastrostamatis, S.; Papadopoulos, M.; Vavouraki, H.; Terzis, A.; Hountas, A.; Chiotellis, E.; *Inorg. Chim. Acta* **1991**, *189*, 219. (f) Ohmoro, Y.; Francesconi, L.; Kung, M.-P.; Kung, H. F. *J. Med. Chem.*, **1992**, *35*, 157. (g) Tisato, F.; Refosco, F.; Bandoli, J. *Coord. Chem. Rev.* **1995**, *135/136*, 325.

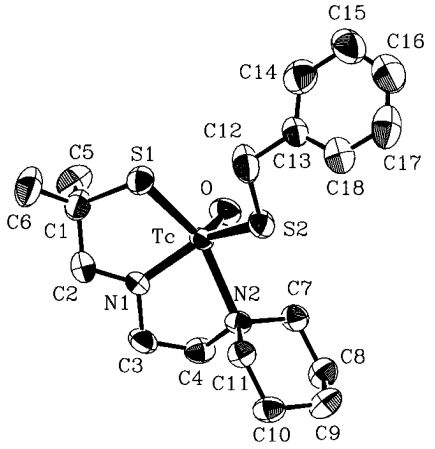


Figure 3. ORTEP diagram of complex **7**, with 50% thermal probability ellipsoids showing atomic labeling scheme.

Table 1. Selected Bond Distances (Å) and Angles (Deg)

	complex **5**	complex **7**
Tc−O	1.677(3)	1.667(3)
Tc−S1	2.285(1)	2.272(2)
Tc−S2	2.335(1)	2.309(2)
Tc−N1	1.930(3)	1.919(4)
Tc−N2	2.202(3)	2.219(4)
O−Tc−S1	110.0(1)	109.3(1)
O−Tc−N2	100.6(1)	99.4(2)
O−Tc−N1	112.8(2)	113.0(2)
O−Tc−S2	110.5(1)	111.0(2)
S1−Tc−N2	148.7(1)	150.2(1)
S1−Tc−S2	88.94(4)	90.52(5)
S2−Tc−N2	86.33(9)	86.4(1)
N2−Tc−N1	79.3(1)	79.2(2)
N1−Tc−S1	82.9(1)	82.3(1)
N1−Tc−S2	136.2(1)	135.3(1)

Table 2. Summary of Crystal, Intensity Collection, and Refinement Data

	5	**7**
formula	$C_{15}H_{23}N_2OS_2Tc$	$C_{18}H_{29}N_2OS_2Tc$
fw	408.47	451.55
a (Å)	10.223(1)	11.876(2)
b (Å)	9.283(1)	10.470(2)
c (Å)	18.337(2)	17.098(3)
β (deg)	97.262(2)	105.990(4)
V (Å^3)	1726.3(4)	2043.8(6)
Z	4	4
D_{calcd}/D_{measd} (Mg m^{-3})	1.572/1.55	1.468/1.44
space group	$P2_1/n$	$P2_1/n$
temp (K)	298	298
abs coeff, μ (mm^{-1})	1.004	0.916
wavelength (λ (Å))	Mo Kα (0.710 73)	Mo Kα (0.710 73)
range of *h*, *k*, *l*	−12 to +12, −11 to 0, 0−21	−13 to +13, −12 to 0, 0−19
goodness-of-fit on F^2	1.142	1.085
R indices[a]	R1 = 0.0333[b] wR2 = 0.080	R1 = 0.0382[c] wR2 = 0.085

[a] R1 based on *F*'s, wR2 based on F^2. [b] 2481 references with $I > 2\sigma(I)$. [c] 2393 references $I > 2\sigma(I)$.

0.25 for complex **7** ($\tau = 0$ for a perfect square pyramid, $\tau = 1$ for a perfect trigonal bipyramid). In both complexes **5** and **7**, technetium lies 0.68 Å out of the basal plane of the square pyramid (defined by the atoms S1, S2, N1, N2) toward the doubly bonded oxygen atom. The five-membered rings formed by the atoms Tc, S1, C1, C2, N1 and Tc, N1, C3, C4, N2 exist in the envelope form where C1 and C4, in both complexes, lie out of the plane defined by the remaining four atoms (in **5** displacements of C1 and C4 are 0.664 and 0.667 Å, respectively; in **7** these values are 0.665 and 0.649 Å, respectively). The torsion angles S1−C1−C2−N1 and N1−C3−C4−N2 take similar values in both complexes (43.5(1)/−45.4(6)° for **5** and 42.7(7)/−44.4(7)° for **7**). The pyrrolidine ring in **5** exists in the envelope form where the "flap" atom, N2, lies 0.550 Å out of the plane defined by C5, C6, C7, and C8. The piperidine ring in **7** exists in the most stable chair conformation where atoms C8 and C11 are −0.658 and +0.634 Å respectively, out of the plane of the remaining four atoms (N2, C7, C9, C10). The Tc═O bond lengths (1.677(3) and 1.667(3) Å for **5** and **7**, respectively) are in the long end of the range expected for monooxotechnetium(V) complexes (1.610(4)−1.672(8) Å).[11] This weakening of the Tc═O bond is not surprising if the short Tc−N1 bond length is taken into account. The typical Tc−N single bond for square pyramidal oxotechnetium(V) complexes is 2.1 Å[12] while a value of 1.61 Å is acceptable for the Tc≡N triple bond in nitridotechnetium(V) complexes.[13] The values of Tc−N1 bond lengths observed in **5** and **7** are 1.930(3) and 1.919(4) Å, indicating a double bond character. These values are consistent with those found in other oxotechnetium(V) complexes containing Tc−N amide bonds.[11] The three bond angles around the deprotonated N1 atom are close to 120° ranging from 114.13 to 124.52° and from 114.46 to 124.81° for **5** and **7**, respectively, as expected for the sp^2 hybridization of these atoms, and Tc, N1, and the carbon atoms adjacent to the nitrogen are nearly coplanar. The Tc−N2 bond distances (2.202(3), 2.219(4) Å for **5** and **7**) are in the range observed for typical Tc−N(amine) single bonds[11,12] (2.088(3)−2.259(4) Å) while the angles about N2 are close to 109° as expected for the sp^3 hybridization of this atom. The metal−sulfur bond distances are in the range 2.272(1)−2.335(1) Å, also consistent with those for other Tc−thiolate complexes.[9a−e]

Table 3. ^{13}C Chemical Shifts δ_H (ppm) for Complexes **4**−**7**

4		**5**		**6**		**7**	
1	41.54	1	41.43	1	56.42	1	56.26
2	68.94	2	69.14	2	81.55	2	81.24
3	61.85	3	62.78	3	61.98	3	61.60
4	67.62	4	63.04	4	56.91	4	57.01
5	56.23	5	65.86	5	27.41	5	27.78
6	47.47	6	23.68	6	30.13	6	30.02
7	132.61	7	22.02	7	63.66	7	63.46
8, 12	135.52	8	54.48	8	21.62	8	21.52
9, 11	113.44	9	138.14	9	23.12	9	22.89
10	158.50	10, 14	134.32	10	19.65	10	19.62
13	55.19	11, 13	128.67	11	50.29	11	50.50
		12	136.19	12	138.06	12	38.03
		15	21.27	13, 17	134.27	13	143.22
				14, 16	128.61	14, 18	129.01
				15	135.83	15, 17	128.34
				18	21.28	16	126.28

NMR Studies of Complexes 4−7. ^{13}C and ^{1}H chemical shifts for complexes **4**−**7** are presented in Tables 3 and 4. For assignment purposes, protons on the SN_2 ligand backbone are distinguished as *endo* (facing toward the oxygen of the Tc═O core) and *exo* (remote from the oxygen of the Tc═O core). In addition, in complexes **5**−**7** the protons of the chelated pyrrolidine or piperidine rings are further distinguished according to their orientation toward the coligand: those facing toward

(10) Addison, A. W.; Rao, T. N.; Reedijk, J.; Rijn, J.; Verschoor, G. C. *J. Chem. Soc., Dalton Trans.* **1984**, 1349.

(11) Jurisson, S.; Schlemper, E. O.; Troutner, D. E.; Canning, L. R.; Nowotnik, D. P.; Neirinckx, R. D. *Inorg. Chem.* **1986**, 25, 543 and references therein.

(12) (a) Cotton, F. A.; Davison, A.; Day, V. W.; Gage, L. G.; Trop, H. S. *Inorg. Chem.* **1979**, *18*, 3024. (b) Kastner, M. E.; Lindsay, M. J.; Clarke, M. *Inorg. Chem.* **1982,** *21*, 2037. (c) Zuckman, S. A.; Freeman, G. M.; Troutner, D. E.; Volkert, W. A.; Holmes, R. A.; Van Derveer, D. G.; Barefield, E. K. *Inorg. Chem.* **1981**, *20*, 2386.

(13) Marchi, A.; Rossi, R.; Magon, L.; Duatti, A.; Casellato, U.; Graziani, R.; Vidal, M.; Riche, F. *J. Chem. Soc., Dalton Trans.* **1990**, 1935 and references therein.

Table 4. ^{1}H Chemical Shifts δ_H (ppm) for Complexes **4**−**7**

4		**5**[a]		**6**[a]		**7**[a]	
1 *endo*	3.65[b]	1 *endo*	3.64[b]	2 *endo*	3.82 (J = 11.7 Hz)	2 *endo*	3.86 (J = 11.7 Hz)
1 *exo*	3.22[b]	1 *exo*	3.22	2 *exo*	3.68 (J = 11.7 Hz)	2 *exo*	3.70[b]
2 *endo*	4.12[b]	2 *endo*	4.11	3 *endo*	3.77[b]	3 *endo*	3.73[b]
2 *exo*	3.75[b]	2 *exo*	3.75[b]	3 *exo*	3.49	3 *exo*	3.45
3 *endo*	3.86[b]	3 *endo*	3.85	4 *endo*	4.07	4 *endo*	4.01
3 *exo*	3.54[b]	3 *exo*	3.52	4 *exo*	3.73	4 *exo*	3.65[b]
4 *endo*	4.07[b]	4 *endo*	3.68[b]	5	1.66	5	1.86
4 *exo*	3.19[b]	4 *exo*	3.37	6	1.38	6	1.50
5	3.56	5	3.74[b]	7	3.87[b]	7	3.71[b]
6	2.18	5′	4.60	7′	4.64	7′	4.53
8	7.56	6	2.18[b]	8	2.10	8	2.04
9	6.87	6′	2.21[b]	8′	1.72[b]	8′	1.62[b]
11	6.87	7	2.08[b]	9	1.90[b]	9	1.85[b]
12	7.56	7′	2.11[b]	9′	1.68[b]	9′	1.64[b]
13	3.83	8	2.47	10	1.85[b]	10	1.80[b]
		8′	3.02	10′	1.47[b]	10′	1.39[b]
		10	7.52	11	1.82[b]	11	1.75[b]
		11	7.12	11′	3.25	11′	3.24
		13	7.12	13	7.52	12	4.77
		14	7.52	14	7.09	12′	4.63
		15	2.37	16	7.09	14	7.44
				17	7.52	15	7.30
				18	2.36	16	7.19
						17	7.30
						18	7.44

[a] Protons of the chelated piperidine and pyrrolidine rings noted with a single prime are those facing toward the coligand. Proton 12′ of the benzyl moiety of complex **7** is the one facing toward the piperidine ring. [b] Chemical shifts of overlapping multiplets were defined from the correlation peaks of the 2D experiments.

the coligand are indicated with a prime. Due to the asymmetry of the molecules all protons and carbons of the SN_2 backbone as well as of the chelated pyrrolidine (complex **5**) and piperidine rings (complexes **6** and **7**) have distinct resonances.

At room temperature one average conformation is observed. Low temperature ^{1}H spectra obtained for complex **7** in the range +25 to −70 °C in toluene-d_8 showed that as the temperature is lowered the resonances of the SN_2 ligand backbone lose their fine structure and broaden as a result of decreasing fluxional mobility. Spectra at −70 °C still appear broad, indicating that the slow exchange limit has not yet been reached. Thus, the singlet signals of the methyl protons on C-5 and C-6, which are expected to show easily observable line shape changes if "freezing" of the SN_2 ligand backbone in two conformations would occur, continue to be distinct at −70 °C, merely starting to broaden. High temperature ^{1}H spectra of complex 7 obtained in the range 25−85 °C in toluene-d_8 show no significant change with increasing temperature; only a sharpening of the hydrogens on carbons C-3 and C-4 and on the piperidine ring indicates increased mobility.

1D ^{1}H spectra are complex, consisting of overlapping multiplets. The benzylic protons on C-12 of complex **7** are magnetically nonequivalent, being diastereotopic,[14] and appear as an AB quartet. Chemical shift assignments of the SN_2 ligand backbone were based on ^{1}H−^{1}H correlation (COSY), ^{13}C−^{1}H correlation (HETCOR), and 2D nOe (NOESY) data. The basic reasoning in analyzing the spectral data is exemplified below.

Analysis of the COSY spectra identified in all cases the isolated spin systems (S−C-1−C-2−N and N−C-3−C-4−N) of the SN_2 ligand backbone and of the chelated rings. In complexes **4** and **5**, which lack methyl substituents at C-1, the S−C-1−C-2−N spin system was distinguished from the N−C-3−C-4−N system by first assigning the carbon next to sulfur (C-1) and then identifying in the HETCOR spectra the protons to which C-1 is coupled.

Ássignment of the methyl protons on the coordinated nitrogen of complex **4** (protons on C-5 and C-6 appearing as singlets at δ_H 3.56 and 2.18) was based on well-supported literature data on oxotechnetium[1bc3c,15] and oxorhenium[3d] complexes indicating that protons spatially close to the oxygen of the oxo−metal core are deshielded relative to those remote from the oxygen: the singlet at δ_H 3.56 was therefore assigned to the *endo* methyl group (H-5) while the singlet at δ_H 2.18 was assigned to the *exo* methyl group (H-6). It should be noted that the observed chemical shift difference of 1.4 ppm between the *endo* and *exo* methyl groups on the coordinated nitrogen is comparable to the one of 1.5 ppm found in oxotechnetium complexes of the *N*-methyl-substituted diaminedithiol ligand system.[3c] Assignment of the *endo* and *exo* methyl groups in complex **4** led through the presence of nOe interactions to the assignment of the geminal protons on C-3 and C-4. The same trend in chemical shift differentiation was observed; i.e., *endo* protons appeared at higher frequency as compared to the *exo* protons. This differentiation was considered valid for the assignment of *endo* and *exo* protons of the S−C-1−C-2−N side of the molecule. Similar arguments were employed in the assignment of the SN_2 backbone protons in the rest of the complexes.

NOESY peaks were crucial in distinguishing between diastereotopic protons on the chelated pyrrolidine (complex **5**) and piperidine rings (complexes **6** and **7**) as well as those of the N−C-3−C-4−N spin system. Thus, in complex **7** (Figure 4) assignment of the most downfield piperidine multiplet at δ_H 4.53 to the proton on C-7 facing the coligand (H-7′) was based on the presence of a nOe correlation between the peak at δ_H 4.53 and one of the benzylic protons of the thiobenzyl coligand (H-12′). This unambiguous assignment was considered valid for complexes **5** and **6** (which carry a thiophenyl instead of thiobenzyl coligand) and served as reference for the assignment of resonances of the geminal diastereotopic ring protons in all complexes: neighboring protons facing the coligand were expected to have nOe's with the downfield multiplet while their geminals were likely to have nOe correlation peaks with the

(14) Jennings, W. B. *Chem. Rev.* **1975**, *75*, 307.

(15) (a) Francesconi, L. C.; Graczyk, G.; Wehrli, S.; Shaikh, S. N.; McClinton, D.; Liu, S.; Zubieta, J.; Kung, H. F. *Inorg. Chem.* **1993**, *32*, 3114. (b) John, C. S.; Francesconi, L. C.; Kung, H. F.; Wehrli, S.; Graczyk, G.; Carroll, P. *Polyhedron* **1992**, *11*, 1145.

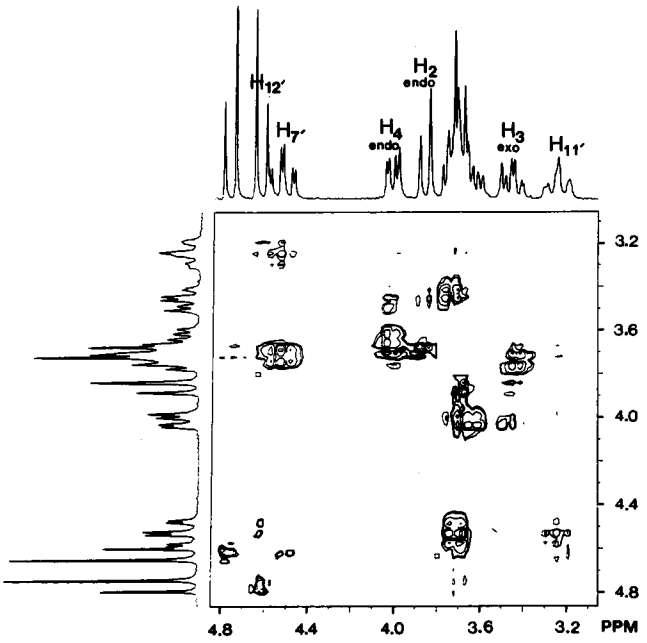


Figure 4. Phase-sensitive NOESY spectrum of complex **7** (range δ_H 4.84−3.06). Only positive levels are plotted.

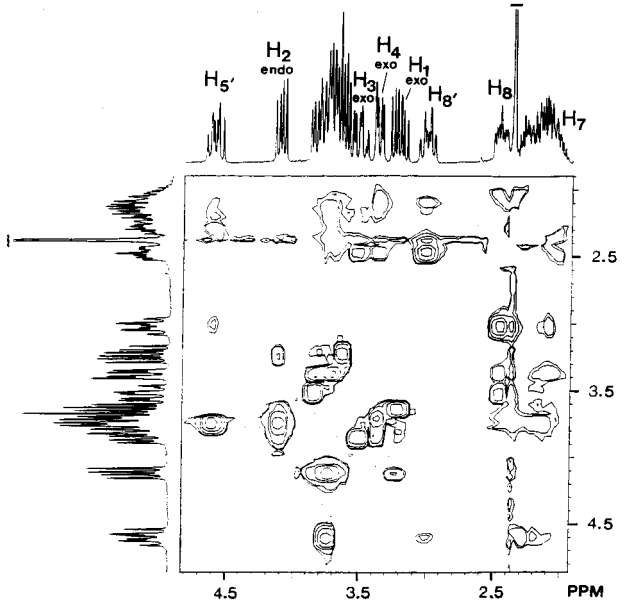


Figure 5. Phase-sensitive NOESY spectrum of complex **5** (range δ_H 4.82−1.94). Only positive levels are plotted.

N−C-3−C-4−N protons. Thus, in complex **7**, of the two multiplets belonging to protons on C-11, the one presenting a nOe correlation peak with proton H-7′ was assigned to H-11′ (Figure 4). NOe interactions between the chelated pyrrolidine or piperidine ring and the SN_2 backbone led to the assignment of each proton of the N−C-3−C-4−N spin system. For example, in complex **5** (Figure 5), of the multiplets belonging to the four protons on C-3 and C-4, the one presenting a correlation with proton H-7 of the chelated pyrrolidine ring belongs to the H-4 *exo* proton, which is spatially closer. Similarly, the H-3 *exo* proton is distinguished from the H-3 *endo* proton on the basis of a correlation peak with proton H-8.

The chemical shift difference between *endo* and *exo* geminal protons of the SN_2 backbone ranges from 0.13 to 0.88 ppm (Table 4). Differentiation in chemical shifts is present between *endo* and *exo* carbons as well. The difference in chemical shift between N-methyl carbons C-5 and C-6 in complex **4** is 8.76 ppm; corresponding carbons, C-5/C-8 in complex **5** and C-7/C-11 in complexes **6** and **7** show chemical shift differences of 11.4, 13.4, and 13.0 ppm respectively (Table 3).

Chemical shift difference is also observed between the diastereotopic geminal protons of the piperidine and pyrrolidine rings. This difference gets smaller the further the protons are from the coordinated nitrogen atom. Concentrating on the geminal protons adjacent to the coordinated nitrogen (H-5/H-5′ and H-8/H-8′ in complex **5**, H-7/H-7′ and H-11/H-11′ in complexes **6** and **7**) one observes that protons facing the coligand appear downfield compared to their geminals facing toward the N−C-3−C-4−N backbone. For example, in complex **6** the difference between the chemical shift of H-11′ and H-11 is 1.43 ppm. It seems unlikely that the presence of the phenyl ring of the coligand contributes to the observed anisotropy since the presence of the CH_2 of the benzyl coligand in complex **7**, which changes the relative distance between the aromatic and the piperidine rings does not cause changes in the chemical shifts. It appears possible that the electrostatic field created by the lone pairs of the sulfur of the coligand might be responsible for the observed chemical shift differences.

To sum up, a novel class of neutral, stable, and lipophilic oxotechnetium (V) complexes, $TcO[SNN(R)_2][S]$, was synthesized based on the (3 + 1) mixed-ligand concept. Synthesis of the $SNN(R)_2$ ligands is simple and quantitative. The proper selection of the R leads, after complexation, to the formation of only one stereoisomer. X-ray studies of two of those (**5** and **7**) showed distorted square pyramidal geometry, which is the usually observed geometry for oxotechnetium complexes. Due to the asymmetry of the complexes and the anisotropic environment around the Tc═O core, all protons and carbons have dinstict NMR resonances which were assigned through detailed studies. Data obtained so far provide a solid foundation for the synthesis of potential radiopharmaceuticals. Work on ^{99m}Tc level and its radiopharmaceutical chemistry is in progress.

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.

Materials and Methods. IR spectra were recorded as KBr pellets in the range 4000−500 cm^{-1} on a Perkin-Elmer 1600 FT-IR spectrophotometer and were referenced to polystyrene. The NMR spectra were recorded in deuterochloroform on a Bruker AC 250E spectrometer. Elemental analyses were performed on a Perkin-Elmer 2400/II automated analyzer. All laboratory chemicals were reagent grade.

^{99}Tc was purchased as ammonium pertechnetate from the Oak Ridge National Laboratory. The impure black solid was purified prior to its use by overnight treatment with hydrogen peroxide and ammonium hydroxide in methanol. Evaporation of the solvent gave ammonium pertechnetate as a white powder. The precursor Tc(V)−gluconate was generated *in situ* by a known method described in the synthetic procedure.[8]

The thiols used as coligands were obtained from Fluka. Tridentate ligands **1** and **2** (Scheme 1) were synthesized according to a published procedure[6] by reaction of the *N*,*N*-dimethylethylenediamine or 1-(2-aminoethyl)pyrrolidine with ethylene sulfide in an autoclave at 110 °C. After completion of the reaction, the compounds were purified by vacuum distillation. The tridentate ligand **3** (Scheme 2) was prepared according to reported methods with minor modifications.[7] Reaction of dithioisobutyraldehyde with 1-(2-aminoethyl)piperidine in refluxing ethanol (3 h) gave the corresponding Schiff base in 85% yield. Reduction of the diimine with sodium borohydride in refluxing ethanol (20 h) gave the appropriate amine (90% yield). The final ligand **3** was produced by the Na/NH_3 reduction of the disulfide and it was isolated as the dihydrochloride salt (75% yield). Ligands **1**, **2**, and **3** were characterized by IR, ^1H NMR, and elemental analysis. The analytical data were consistent with the assigned structures.

Synthesis of Complexes 4−7. The typical synthetic procedure is given for complex **4**: A solution of stannous chloride (45 mg, 0.24 mmol) in HCl (1 N, 1.0 mL) was added to an aqueous solution of NH_4TcO_4 (36.2 mg, 0.2 mmol) containing $^{99m}TcO_4^-$ (0.1 mL, 0.5 mCi) and sodium gluconate (200 mg) to obtain the ^{99}Tc−gluconate. 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*-dimethyl-*N*′-(2-mercaptoethyl)ethylenediamine (27 mg, 0.2 mmol) and 4-methoxythiophenol (28 mg, 0.2 mmol). The solution was stirred for 20 min and then extracted twice 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 the mobile phase) showed the presence of one complex. The volume of the solution was reduced to 5 mL, and then 5 mL of ethanol 96% was added. Slow evaporation of the solvents at room temperature afforded the product as dark red crystals.

[*p*-Methoxybenzenethiolato][*N*-(2-mercaptoethyl)(2-dimethylamino)ethylamine]oxotechnetium(V) (4). Yield: 52 mg (65%). Anal. Calcd for $C_{13}H_{21}N_2O_2S_2Tc$: C, 38.99; H, 5.29; N, 7.00; S, 16.01. Found: C, 39.10; H, 5.18; N, 6.59; S, 16.27. FTIR (cm^{-1}, KBr pellet): 907 (Tc═O).

[*p*-Methylbenzenethiolato][*N*-(2-mercaptoethyl)(2-pyrrolidin-1-yl)ethylamine]oxotechnetium(V) (5). Yield: 60 mg (70%). Anal. Calcd for $C_{15}H_{23}N_2OS_2Tc$: C, 43.89; H, 5.65; N, 6.82; S, 15.62. Found: C, 43.45; H, 5.48; N, 6.99; S, 15.88. FTIR (cm^{-1}, KBr pellet): 931 (Tc═O).

[*p*-Methylbenzenethiolato][*N*-(2,2-dimethyl-2-mercaptoethyl)(2-piperidin-1-yl)ethylamine]oxotechnetium(V) (6). Yield: 54 mg (60%). Anal. Calcd for $C_{18}H_{29}N_2OS_2Tc$: C, 47.77; H, 6.46; N, 6.19; S, 14.17. Found: C, 47.57; H, 6.83; N, 6.45; S, 14.13. FTIR (cm^{-1}, KBr pellet): 925 (Tc═O).

[Toluenethiolato][*N*-(2,2-dimethyl-2-mercaptoethyl)(2-piperidin-1-yl)ethylamine]oxotechnetium(V) (7). Yield: 59 mg (65%). Anal. Calcd for $C_{18}H_{29}N_2O_2S_2Tc$: C, 47.77; H, 6.46; N, 6.19; S, 14.17. Found: C, 47.51; H, 6.70; N, 6.38; S, 14.44. FTIR (cm^{-1}, KBr pellet): 929 (Tc═O).

X-ray Crystal Structure Determination of Complexes 5 and 7. Diffraction measurements were made on a Crystal Logic Dual Goniometer diffractometer using graphite-monochromated Mo radiation. Unit cell dimensions were determined and refined by using the angular settings of 25 automatically centered reflections in the range $11° < 2\theta < 23°$ and they appear in Table 2. Intensity data were recorded using a $\theta-2\theta$ scan to $2\theta(\max) = 50°$ (complex **5**), $2\theta(\max) = 48.5°$ (complex **7**) with scan speed 1.5 deg/min and scan range 2.5 plus $\alpha_1\alpha_2$ separation. Three standard reflections monitored every 97 reflections showed less than 3% variation and no decay. Lorenz and polarization correction were applied using Crystal Logic software.

Slow evaporation of a solution of complex **5** in ethanol/water yielded red-brown prismatic crystals. A crystal with approximate dimensions $0.18 \times 0.25 \times 0.50$ mm was mounted in air. Red-brown crystals of complex **7** were derived by slow evaporation of a methanol/water solution. A crystal with approximate dimensions $0.08 \times 0.15 \times 0.40$ mm was mounted in air.

The structures were solved by direct methods using SHELXS-86 and refined by full-matrix least squares techniques on F^2 with SHELXL-93.[16]

For Complex 5: Data collected/unique/used 3136/3035 (R = 0.0157)/3031; refined params 256; $[\Delta/\sigma]\max = 0.001$; $[\Delta\rho]\max/[\Delta\rho]\min = 0.474/-0.404$ e/Å^3; for all data, R1/wR2/GOF = 0.0473/0.1050/1.338. All hydrogen atoms (except those of C6, C7 and C15 which were introduced at calculated positions as riding on bonded atoms) were located by difference maps, and their positions were refined isotropically. All non-hydrogen atoms were refined anisotropically.

For Complex 7: Data collected/unique/used 3421/3301 (R = 0.0334)/3301; refined params 333; $[\Delta/\sigma]\max = 0.011$; $[\Delta\rho]\max/[\Delta\rho]\min = 0.934/-0.306$ e/Å^3; for all data, R1/wR2/GOF = 0.0680/0.0991/1.085. All hydrogen atoms were located by difference maps, and their positions were refined isotropically. All non-hydrogen atoms were refined anisotropically.

NMR 2D Methodology. The ^1H (250.13 MHz) and ^{13}C (62.90 MHz) NMR spectra were recorded on a Bruker AC 250E spectrometer equipped with an Aspect 3000 computer (using the DISNMR program, version 1991) and a 5 mm $^{13}C/^1H$ dual probe head ^1H 90° pulse width = 10.2 μs, ^{13}C 90° pulse width = 10.4 μs). Samples were dissolved in $CDCl_3$ at a concentration of ca. 1−2%. Except for the variable temperature studies, spectra were obtained at 25 °C. Chemical shifts (δ, ppm) are relative to internal TMS.

2D $^1H-^1H$ shift correlated spectra (COSY) were acquired with a spectral window of 2180 Hz, 1024 data points, 256 t_1 increments, and a 1 s relaxation delay between pulse cycles. The data were processed by applying a sine−bell (nonshifted) multiplication in both dimensions and by zero-filling to 512 data points in the F_1 domain. After inspection, the final matrix (digital resolution 4.3 Hz/point) was symmetrized.

Phase-sensitive NOESY spectra were acquired with the same parameters as for the COSY experiment and a mixing time of 0.5 s. The data were processed by applying a sine-bell squared ($\pi/2$ shifted) multiplication in both dimensions and by zero-filling to 1024 data points in the F_1 dimension. After inspection the final matrix was symmetrized.

2D $^{13}C-^1H$ shift correlated spectra (HETCOR) were obtained with spectral windows of 2180 Hz in the F_1 dimension and 8930 Hz in the F_2 dimension, 2048 data points, 128 t_1 increments, and a relaxation delay of 1 s. The experiment was optimized for $J(^{13}C, ^1H) = 130$ Hz. The data were processed by applying a sine−bell ($\pi/2$ shifted) multiplication in both dimensions and by zero-filling to 256 data points in the F_1 dimension. Digital resolution was 17.0 Hz/point in the F_1 dimension and 8.7 Hz/point in the F_2 dimension.

Acknowledgment. A.T. is grateful to Mrs. Athina Athanassiou for financial support.

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 (12 pages). Ordering information is given on any current masthead page.

IC9513649

(16) (a) Sheldrick, G. *M. SHELXS-86, Structure Solving Program*, University of Göttingen: Göttingen, Germany, 1986. (b) Sheldrick, G. M. *SHELXL93, Crystal Stucture Refinement;* University of Göttingen: Göttingen, Germany, 1993 (c) *International Tables for X-ray Crystallography*; Kynoch Press: Birmingham, England, 1974; Vol. IV.