Synthesis and Characterization of Novel Trigonal Bipyramidal Technetium(III) Mixed-Ligand Complexes with SES/S/P Coordination (E = O, N(CH_3), S)

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Five-coordinate oxotechnetium(V) mixed-ligand complexes [TcO(SES)(S-*p*-C_6H_4-OMe)], where SES is a tridentate dithiolato fragment of the type $^-S(CH_2)_2E(CH_2)_2S^-$ (E = O, **1**; E = S, **2**; E = NMe, **3**) are converted via reduction−substitution reactions in the presence of PMe_2Ph into the corresponding five-coordinate Tc(III) complexes [Tc(SES)(S-*p*-C_6H_4-OMe)(PMe_2Ph)] (E = O, **4**; E = S, **5**; E = NMe, **6**). Rearrangement of the original square pyramidal "3 + 1" oxo species to the trigonal bipyramidal "3 + 1 + 1" Tc(III) complexes occurs by placing the three thiolate donors on the basal plane, the phosphine phosphorus, and the heteroatom of the tridentate ligand at the apexes of the bipyramid. These Tc(III) complexes are diamagnetic species, thereby allowing multinuclear NMR characterization in solution, which confirm their structures to be identical to those observed in the solid state via X-ray determinations.

Introduction

In the nineties the so-called "3 + 1" approach has represented one of the most investigated systems in technetium and rhenium chemistries as a new potential tool for radiopharmaceutical design.[1−4] The coordination sphere of these five-coordinated neutral oxo−Tc(V) mixed-ligand compounds is filled by a combination of a dianionic tridentate ligand carrying the SSS, SOS, SN(R)S, or SNN(R) donor atom set (R = various alkyl, alkyl-substituted and aryl-substituted pendant groups) with a monodentate thiol.[5] In these quite flexible systems the incorporation of a biologically active fragment, the major challenge in the radiopharmaceutical field at this time,[6] has been usually achieved through derivatization at the monothiol ligand. Hence, several examples of receptor-binding tracers for the central nervous system have been proposed, including bio-fragments[7] such as tropane,[8] fragments of ketanserin,[9−11] or ergoline.[12] However, recent evidence has established that oxo−Tc(V) 3 + 1 systems undergo further substitution reactions in vivo in thiolate-rich (cysteine and/or glutathione) tissues[13] such as the liver and the brain.[14,15] Such substitution has been determined to occur at expenses of the monothiolate group. In fact, incubation of representative [MO(SN(R)S)(SR)] complexes (M = Tc, Re) with excess GSH has revealed complete conversion of the starting lipophilic derivatives to a mixture of hydrophilic GS-related species with release of the monothiolate fragment. While the intrinsic instability of these system could be utilized to increase the accumulation of the tracer in certain districts, the in vivo instability constitutes a serious drawback when the application aims at the imaging of high-specificity low-capacity receptors systems with ^{99m}Tc-labeled biomolecules.[16,17]

For this reason, oxo−Re(V) 3 + 2 prototype compounds, in which the monodentate thiol has been replaced by the bidentate phosphinophenolato, have been proposed as substitution-inert

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d^2 species.[18] Simple expansion of the coordination sphere from five to six allows the generation of a class of complexes which are resistant to GSH or cysteine attack in vitro.

In this study we approach the problem of the instability of oxo−M(V) 3 + 1 derivatives by using a different strategy. Thus, taking advantage of the well-known ability of tertiary phosphines to work both as reducing and coordinating agent toward Tc,[19,20] we have treated oxo−Tc(V) precursors [TcO(SES)(S-*p*-C_6H_4-OMe)], where SES is a tridentate dithiolato fragment of the type $^-S(CH_2)_2E(CH_2)_2S^-$ (E = O, **1**; E = S, **2**; E = NMe, **3**) with an excess of PMe_2Ph to generate the class of corresponding reduced five-coordinate Tc(III) complexes [Tc(SES)(S-*p*-C_6H_4-OMe)(PMe_2Ph)] (E = O, **4**; E = S, **5**; E = NMe, **6**). In these compounds the electron density at the metal center has been increased (d^4 configuration) maintaining the original five-coordinate environment with changes only in the related geometry (from square pyramidal to trigonal bipyramidal). Other trigonal bipyramidal Tc(III) complexes have been prepared previously.[21−23] They are characterized by the presence of strong π-donor atoms at the trigonal base and π-acceptor in the trans-axial positions, which is exactly the coordination sphere exhibited by our proposed system. Tc(III) complexes have been characterized by means of common physicochemical techniques, including X-ray analysis, multinuclear NMR spectroscopy, and cyclic voltammetry studies.

Experimental Section

Materials. All solvents and commercially available substances were of reagent grade and used without further purification. The tridentate $HSCH_2CH_2N(CH_3)CH_2CH_2SH$ ligand was prepared according to standard procedures starting from *N*-methyl-2,2′-iminodiethanol (MERCK−Schuchart).[24] ^{99}Tc as NH_4TcO_4 was obtained from AMERSHAM as 0.3 M aqueous solution. $^{99m}TcO_4^-$ was eluated from a commercial ^{99}Mo/^{99m}Tc generator (Mallinckrodt).

Instrumentation. Elemental analyses were performed on a LECO Elemental Analyzer CHNS-932. Melting points were obtained on a BOËTIUS-Mikroheiztisch and are uncorrected. IR spectra were measured as KBr pellets on a Perkin-Elmer FTIR-spectrometer SPECTRUM 2000. UV/vis spectra were measured on a SPECORD S10 spectrometer from Carl Zeiss Jena. Proton, ^{13}C and ^{31}P NMR spectra were collected on a Bruker 300 instrument, using $SiMe_4$ as internal reference (^{1}H, ^{13}C) and 85% aqueous H_3PO_4 as external reference (^{31}P). Samples were dissolved in deuterated chloroform at a concentration of ca. 1−2%. Chemical shifts are given as δ in ppm. Cyclic voltammetry of complexes **4**−**6** was carried out in CH_2Cl_2 solutions (3.5×10^{-3} mol dm^{-3}), with [*n*-Bu_4N][ClO_4] (0.1 mol dm^{-3}) as supporting electrolyte, at a stationary platinum-disk electrode (area ca. 1.28 mm^2), which was cleaned after each run, with scan rate 0.2 V s^{-1} at $T = 293$ K. Potentials were measured relative to an Ag-wire pseudo-electrode using the Fc/Fc^+ couple as internal reference. Controlled potential coulometries of CH_2Cl_2 solution of **6** were performed using an Amel model 721 integrator, in a H-shaped cell containing, in arm 1, a platinum-gauze working electrode and an Ag/Ag^+ reference isolated inside a salt bridge by a medium glass frit, and in arm 2, an auxiliary platinum-foil electrode. TLC and HPLC analyses were used to determine the radiochemical purity and stability of the preparations. TLC analyses were performed using silica gel strips (Silufol or Kieselgel 60) developed with *n*-butanol/methanol/water/concentrated ammonia (60/20/20/1) (method I) or methanol/0.1 N HCl (3/1) (method II) as solvents. For HPLC studies a Perkin-Elmer device consisting of a Turbo LC System with a quarternary pump (Series 200 LC Pump), a Programmable Absorbance Detector Model 785A, and a homemade γ-detector (Bohrloch NaI(Tl) crystal) was used. HPLC analyses were carried out with a Hypersil ODS column (250 × 4 mm) using an premixed eluent of 80% methanol and 20% 0.01 M phosphate buffer of pH 7.4 and a flow rate of 1.0 mL/min. The eluate from the column was monitored by UV absorbance at 254 nm for ^{99}Tc reference complexes or γ detection for the ^{99m}Tc complexes.

Synthesis of oxo−Tc(V) Complexes: TcO($SCH_2CH_2OCH_2CH_2S$)(*p*-SC_6H_4OMe), 1; TcO($SCH_2CH_2SCH_2CH_2S$)(*p*-SC_6H_4OMe), 2; TcO($SCH_2CH_2N(CH_3)CH_2CH_2S$)(*p*-$SC_6H_4OMe$), 3. These precursors were prepared by common ligand-exchange reactions of oxo−Tc(V) gluconate with mixtures of the appropriate tridentate ligand and 4-methoxybenzenethiol as described elsewhere.[5]

Synthesis of Tc(III) Complexes 4−6. All Tc(III) compounds were prepared using a common procedure. One hundred micromoles of the appropriate oxotechnetium(V) complex and 400 μmol of dimethylphenylphosphine were dissolved in 3 mL of acetone. After addition of 0.5 mL of acetic acid the mixture was stirred at room temperature under argon for 60 min. The solution turned from yellowish-brown to violet. The reaction mixture was reduced in volume to 1 mL, and methanol was added until the solution became turbid. The mixture was then allowed to stand overnight in the refrigerator. Recrystallization of the raw precipitate from chloroform/methanol at −20 °C gave dark-violet (**4** and **5**) and dark-blue crystals (**6**) suitable for X-ray diffraction analysis.

Tc($SCH_2CH_2OCH_2CH_2S$)(p-SC_6H_4OMe)(PMe_2Ph), 4. Yield: 73%, mp 155−156 °C. Anal. Calcd (found) for $C_{19}H_{26}O_2PS_3Tc$ (512): C, 44.5 (44.5); H, 5.1 (5.2); S, 18.7 (18.5). IR (KBr): ν_{C-H} = 2830−3050 cm^{-1}, $\nu_{C=C(aromat)}$ = 1568, 1587, 1635 cm^{-1}, ν_{P-C} = 1434 cm^{-1}, δ_{C-O-C} = 1237 cm^{-1}. UV/vis ($CHCl_3$): λ_{max} (log ϵ) = 327 nm (3.93), 520sh, 563 (2.72). ^{1}H NMR (300 MHz, Me_4Si, $CDCl_3$): 1.91 (d, $^2J_{HP}$ = 9 Hz, P(CH_3)$_2$Ph, 6H), 2.82 and 3.01 (m, Tc−S−CH_2−, 4H), 3.26 and 3.43 (m, −CH_2−O, 2H), 3.80 (s, −OCH_3, 3H), 6.75 and 7.21 (d, $^3J_{HH}$ = 8 Hz, SC_6H_4−, 4H), 7.39 and 7.81 (m, P(CH_3)$_2$*Ph*, 5H). ^{13}C NMR (300 MHz, Me_4Si, $CDCl_3$): 22.81 (d, $^2J_{CP}$ = 31 Hz, P(CH_3)$_2$-Ph), 35.58 (Tc−S−CH_2−), 55.24 (−OCH_3), 72.64 (−CH_2−O), 113.27, 138.13, 138.19 and 158.39 (*p*-SC_6H_4−), 128.13, 128.89, 130.23 and 142.55 (P(CH_3)$_2$*Ph*). ^{31}P NMR (300 MHz, 85% H_3PO_4, $CDCl_3$): 42.7 (bs, $\tau_{1/2}$ = 970 Hz).

Tc($SCH_2CH_2SCH_2CH_2S$)(p-SC_6H_4OMe)(PMe_2Ph), 5. Yield: 75%, mp 153−154 °C. Anal. Calcd (found) for $C_{19}H_{26}OPS_4Tc$ (528): C, 43.2 (42.8); H, 5.0 (5.3); S, 24.3 (24.0). IR (KBr): ν_{C-H} = 2833−3050 cm^{-1}, $\nu_{C=C(aromat)}$ = 1566, 1587, 1637 cm^{-1}, ν_{P-C} = 1436 cm^{-1}, δ_{C-O-C} = 1241 cm^{-1}. UV/Vis ($CHCl_3$): λ_{max}(log ϵ) = 336 nm (3.97), 495sh, 563 (2.72). ^{1}H NMR (300 MHz, Me_4Si, $CDCl_3$): 2.07 (d, $^2J_{HP}$ = 9 Hz, P(CH_3)$_2$Ph, 6H), 2.18 and 2.58 (m, −CH_2−S, 4H), 2.82 and 2.98 (m, Tc−S−CH_2−, 4H), 3.79 (s, −OCH_3, 3H), 6.71 and 7.07 (d, $^3J_{HH}$ = 8 Hz, SC_6H_4−, 4H), 7.42 and 7.90 (m, P(CH_3)$_2$*Ph*, 5H). ^{13}C NMR (300 MHz, Me_4Si, $CDCl_3$): 20.60 (d, $^2J_{CP}$ = 28 Hz, P(CH_3)$_2$-Ph), 34.52 (Tc−S-CH_2−), 38.14 (d, $^3J_{CP}$ = 11 Hz, (−CH_2−S), 55.19 (−OCH_3), 113.07, 133.16, 140.81 and 158.20 (*p*-SC_6H_4−), 128.08, 129.04, 130.46 and 141.10 (P(CH_3)$_2$*Ph*). ^{31}P NMR (300 MHz, 85% H_3PO_4, $CDCl_3$): 20.3 (bs, $\tau_{1/2}$ = 510 Hz).

Tc($SCH_2CH_2N(CH_3)CH_2CH_2S$)(p-$SC_6H_4OMe$)($PMe_2Ph$), 6. Yield: 68%, mp 175−176 °C. Anal. Calcd (found) for $C_{20}H_{29}NOPS_3Tc$ (525): C, 45.7 (45.3); H, 5.6 (5.7); N, 2.7 (2.5); S, 18.3 (17.9). IR (KBr): ν_{C-H} = 2830−3057 cm^{-1}, $\nu_{C=C(aromat)}$ = 1567, 1587, 1637 cm^{-1}, ν_{P-C} = 1433 cm^{-1}, δ_{C-O-C} = 1239 cm^{-1}. UV/Vis ($CHCl_3$): λ_{max}(log ϵ) = 334 nm (3.99), 525sh, 590 (2.63). ^{1}H NMR (300 MHz, Me_4Si, $CDCl_3$ at 223 K): 1.47 (d, $^2J_{HP}$ = 8 Hz, P(CH_3)$_2$Ph, 6H), 2.70 (m, N−CH_2−, 4H), 2.89 (s, N−CH_3, 3H), 3.08 and 3.41 (m, Tc−S−CH_2−, 4H), 3.72 (s, −OCH_3, 3H), 6.31 and 6.76 (d, $^3J_{HH}$ = 8 Hz, SC_6H_4−, 4H), 7.24 and 7.39 (m, P(CH_3)$_2$*Ph*, 5H). ^{13}C NMR (300 MHz, Me_4Si, $CDCl_3$ at 223 K): 22.80 (d, $^2J_{CP}$ = 30 Hz, P(CH_3)$_2$Ph), 40.13 (Tc−S−CH_2−), 47.81 (N−CH_3), 55.17 (−OCH_3), 61.72 (N−CH_2−), 113.39,

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Scheme 1

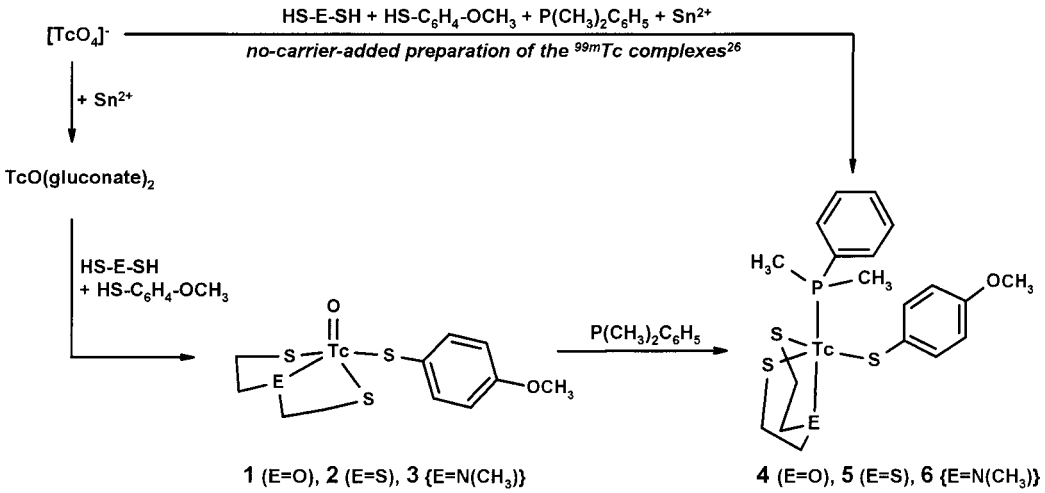

Table 1. HPLC Data of ^{99}Tc Complexes **4**−**6** and Corresponding ^{99m}Tc Species[a]

complex		R_t (min) Hypersil ODS	R_t (min) PRP-3
[^{99}Tc(SOS)(S-*p*-C_6H_4−OMe)(PMe_2Ph)]	**4**	9.3	13.3
[^{99m}Tc(SOS)(S-*p*-C_6H_4−OMe)(PMe_2Ph)]	^{99m}**4**	9.3	13.3
[^{99}Tc(SSS)(S-*p*-C_6H_4−OMe)(PMe_2Ph)]	**5**	9.9	13.6
[^{99m}Tc(SSS)(S-*p*-C_6H_4−OMe)(PMe_2Ph)]	^{99m}**5**	9.8	13.5
[^{99}Tc(SNMeS)(S-*p*-C_6H_4−OMe)(PMe_2Ph)]	**6**	13.6	14.5
[^{99m}Tc(SNMeS)(S-*p*-C_6H_4−OMe)(PMe_2Ph)]	^{99m}**6**	13.5	14.3

[a] Hypersil ODS: MeOH/0.01 M PBS pH 7.4, (80/20). PRP-3: CH_3CN/0.01 M PBS pH 7.4, linear gradient 0−70 % CH_3CN in 5 min.

133.57, 142.02 and 158.36 (*p*-SC_6H_4−), 127.68, 127.80, 130.13 and 142.58 ($P(CH_3)_2$*Ph*). ^{31}P NMR (300 MHz, 85% H_3PO_4, $CDCl_3$): 31.4 (bs, $\tau_{1/2}$ = 670 Hz) and 34.68 (s, O=*P*Me_2Ph).

Synthesis of ^{99m}Tc Complexes [^{99m}Tc]4, [^{99m}Tc]5, and [^{99m}Tc]6. A solution of 20 μl $SnCl_2$ (1.0−1.5 mg of $SnCl_2$/5.0 mL of 0.1 N HCl) was added to a mixture of 0.5 mL of pertechnetate solution (10−500 MBq generator eluate), 0.3 mL of propylene glycol, 0.2 mL of acetonitrile, 0.3−0.4 mg of methoxythiophenol dissolved in ethanol, 0.05 mg of the appropriate SES ligand dissolved in ethanol, and 0.02 mL of 0.1 M NaOH. The resulting solution was neutralized with trifluoroacetic acid to pH 5.0−6.0, and after that, 0.2 mg of dimethylphenylphosphine, dissolved in acetonitrile, was added. The vial was closed, and the reaction solution was heated at 50−60 °C for 15 min. The labeling yield for all complexes was between 90 and 95% as established by HPLC analysis (Table 1). The identity of the species obtained was confirmed by comparison with the HPLC profiles of ^{99}Tc analogues.

X-ray Crystallographic Study. The X-ray data were collected at room temperature (293 K) on a SMART-CCD diffractometer (SIEMENS), using graphite-monochromatized Mo Kα radiation (λ = 0.71073 Å). A summary of the crystallographic data is given in Table 2. The positions of the non-hydrogen atoms were determined by the heavy atom technique. After anisotropic refinement of the positions of these, the hydrogen positions were calculated according to ideal geometries. Empirical absorption corrections were made using psi scans. Most of the calculations were carried out in the SHELXTL system with some local modifications.

Relevant bond lengths and angles are contained in Table 3. Atomic positional and thermal parameters, full lists of bond lengths and angles, and F_o/F_c values have been deposited as Supporting Information.[25]

Results and Discussion

The 3 + 1 oxo−Tc(V) mixed-ligand complexes of the general formula [TcO(S−CH_2CH_2−E−CH_2CH_2−S)(S−C_6H_4−OCH_3)] {E = O, **1**; E = S, **2**, E = N(CH_3) **3**} were prepared by consolidated ligand-exchange reactions of the labile technetium gluconate precursor with mixtures of the appropriate tridentate ligand and 4-methoxybenzenethiol as described elsewhere[5] (Scheme 1). These oxo−Tc(V) derivatives undergo facile reduction and substitution to the corresponding neutral 3 + 1 + 1 Tc(III) complexes [Tc(S−CH_2CH_2−E−CH_2CH_2−S)(S−C_6H_4−OCH_3)(PMe_2Ph)] {E = O, **4**; E = S, **5**, E = N(CH_3) **6**} (Scheme 1) in acetone solutions via oxygen abstraction operated by tertiary phosphines, according to equation I.

Elemental analyses, as reported in the Experimental Section, are in agreement with the proposed formulation. IR spectra of Tc(III) complexes **4**−**6** exhibit strong absorptions characteristic of the Tc−P stretching vibrations. No additional bands indicating the presence of the Tc=O core in the region 900−1000 cm^{-1} are observed. The UV/vis spectra of **4**−**6** (recorded in chloroform) are characterized by intense bands at 327−336 nm and less intense absorptions in the visible region (563−590 nm).

Preparation of ^{99m}Tc Complexes at No-Carrier-Added Level. To prepare the corresponding ^{99m}Tc(III) complexes directly from pertechnetate a one-pot reaction, shown in Scheme 1, was developed.[26] High yields (90−95%) can be reached using optimized reaction parameters such as ligand amounts, reducing agent and pH value. A reaction time of 1 h is necessary to complete the reaction at room temperature. The formation of the desired complex is accelerated by heating the reaction solution at 60 °C for 15 min. Higher temperatures diminish the yield of the product. Without stannous chloride as second reducing agent only low yields of the desired product are obtained.

To establish the structure of the ^{99m}Tc complexes prepared at tracer level, comparison by HPLC with the corresponding ^{99}Tc complexes prepared in macroscopic amounts was pursued applying parallel radiometric and photometric detection. Thus, after co-injection of the appropriate ^{99}Tc and ^{99m}Tc couples practically identical retention times were observed, and the recovery through the column was nearly quantitative (Table 1).

(25) Crystallographic data (excluding structure factors) for the structures reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC-146934 (complex **5**), 146935 (**6**), and 146936 (**4**). Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax +44−1223/336−033; e-mail deposit@ccdc.cam.ac.uk).

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Table 2. Crystal Data and Structure Refinement for Complexes **4**−**6**

complex	**4**	**5**	**6**
formula	$C_{19}H_{26}O_2PS_3Tc$	$C_{20}H_{29}NOPS_3Tc$	$C_{19}H_{26}OPS_4Tc$
fw	511.55	524.59	527.61
cryst syst	triclinic	monoclinic	triclinic
space group	*P*-1	*P*2(1)/*c*	*P*-1
a (Å)	7.6294(4)	13.3054(5)	8.3869(4)
b (Å)	12.2524(6)	9.4678(4)	11.1578(6)
c (Å)	12.8379(7)	18.7909(7)	12.3806(6)
α (deg)	73.0120(10)	90.00	95.4960(10)
β (deg)	81.8690(10)	100.7080(10)	99.3760(10)
γ (deg)	79.7550(10)	90.00	92.2350(10)
V (Å^3)	1124.29(10)	2325.9(2)	1136.08(10)
Z	2	4	2
temp (K)	293(2)	293(2)	293(2)
d (g/cm^3)	1.511	1.498	1.542
abs. coeff. (mm^{-1})	1.001	0.968	1.078
F(000)	524	1080	540
μ (Å) radiation	0.71073	0.71073	0.71073
cryst size (mm^3)	0.72 × 0.54 × 0.07	0.54 × 0.54 × 0.07	0.54 × 0.27 × 0.06
2*θ*-range	1.67−23.27	1.56−23.27	1.68−23.27
hkl	$-8\le h\le 8$	$-14\le h\le 12$	$-9\le h\le 7$
	$-13\le k\le 13$	$-10\le k\le 10$	$-12\le k\le 8$
	$-12\le l\le 14$	$-20\le l\le 18$	$-13\le l\le 13$
no. of coll reflns	4878	9673	5101
no. of indep reflns	3202	3344	3236
GOF	1.139	1.064	0.748
R [$I > 2\sigma(I)$]	R1 = 0.0297	R1 = 0.0238	R1 = 0.0280
	WR2 = 0.0874	wR2 = 0.0594	wR2 = 0.0855
R (all data)	R1 = 0.0302	R1 = 0.0257	R1 = 0.0300
	WR2 = 0.0879	wR2 = 0.0665	wR2 = 0.0885
largest diff peak	0.430	0.452	0.604
largest diff hole	−0.528	−0.487	−0.473

Table 3. Selected Bond Lengths (Å) and Angles (deg) of Complexes **4**−**6**

4		**5**		**6**	
Tc(1)−S(1)	2.2258(9)	Tc(1)−S(1)	2.2197(6)	Tc(1)−S(1)	2.2195(9)
Tc(1)−S(2)	2.2213(9)	Tc(1)−S(2)	2.2327(6)	Tc(1)−S(2)	2.3985(9)
Tc(1)−S(3)	2.2391(9)	Tc(1)−S(3)	2.2550(6)	Tc(1)−S(3)	2.2356(10)
Tc(1)−O(1)	2.236(2)	Tc(1)−N(1)	2.273(2)	Tc(1)−S(4)	2.2540(10)
Tc(1)−P(1)	2.2820(10)	Tc(1)−P(1)	2.3185(6)	Tc(1)−P(1)	2.3587(9)
S(2)−Tc(1)−S(1)	119.97(4)	S(1)−Tc(1)−S(2)	116.77(3)	S(1)−Tc(1)−S(3)	116.23(4)
S(2)−Tc(1)−O(1)	83.36(7)	S(1)−Tc(1)−S(3)	120.02(3)	S(1)−Tc(1)−S(4)	119.52(4)
S(1)−Tc(1)−O(1)	83.58(6)	S(2)−Tc(1)−S(3)	121.87(2)	S(3)−Tc(1)−S(4)	124.26(4)
S(2)−Tc(1)−S(3)	120.55(4)	S(1)−Tc(1)−N(1)	84.42(5)	S(1)−Tc(1)−P(1)	89.74(3)
S(1)−Tc(1)−S(3)	119.03(4)	S(2)−Tc(1)−N(1)	84.70(5)	S(3)−Tc(1)−P(1)	91.87(3)
O(1)−Tc(1)−S(3)	96.48(6)	S(3)−Tc(1)−N(1)	89.23(5)	S(4)−Tc(1)−P(1)	88.67(3)
S(2)−Tc(1)−P(1)	94.59(4)	S(1)−Tc(1)−P(1)	90.00(2)	S(1)−Tc(1)−S(2)	87.09(3)
S(1)−Tc(1)−P(1)	92.82(4)	S(2)−Tc(1)−P(1)	92.45(2)	S(3)−Tc(1)−S(2)	86.25(3)
O(1)−Tc(1)−P(1)	174.21(6)	S(3)−Tc(1)−P(1)	98.82(2)	S(4)−Tc(1)−S(2)	96.08(3)
S(3)−Tc(1)−P(1)	89.23(3)	N(1)−Tc(1)−P(1)	171.77(5)	P(1)−Tc(1)−S(2)	175.15(3)

Five-coordinate Tc(III) complexes **4**−**6**, as prototypic representatives of this novel class of neutral Tc(III) compounds, were studied by X-ray structure analysis. A summary of the crystallographic data is given in Table 2, and selected bond lengths and angles are cumulated in Table 3.

As illustrated in Figures 1−3, the complexes adopt a trigonal bipyramidal geometry with the trigonal plane formed by the three thiolate sulfurs of the tridentate and monodentate ligands. The phosphine phosphorus and the neutral heteroatom of the chelate ligand occupy the apical positions.

The Tc−$S_{thiolato}$ distances are restricted in a narrow range (2.22−2.26 Å) and compare well with those previously reported for trigonal bipyramidal [$Tc(SR)_3(L)_2$]-type complexes (SR = sterically hindered arenethiolates, L = small *π*-accepting molecules).[27,28]

The unique axial metal thioether−sulfur interaction elongates to 2.398(1) Å in **5**. The P−Tc−E axis shows slight deviation from linearity, the major inclination occurring in **6**, in which the nitrogen heteroatom of the tridentate ligand carries a methyl substituent. Other angles of the inner coordination sphere are consistent with the trigonal bipyramidal (tbp) arrangement. The substituted benzenethiolate ring is oriented toward the unsubstituted heteroatom of the tridentate ligand in **4** and **5**, whereas it is oriented toward the tertiary phosphine in **6**.

The Tc(III) complexes show sharp proton and carbon signals characteristic of diamagnetic compounds, in agreement with low-spin d^4 tbp configurations. NMR profiles confirm the solution structures of complexes **3**−**6** to be identical to those observed in the solid state. In particular, the different orientation (vide supra) of the *p*-methoxy benzenethiolato group is retained. In fact, an appreciable upfield shift is observed (see Table 4) for both monothiolate and phosphine protons in complex **6** at

(27) Davison, A.; De Vries, N.; Dewan, J.; Jones, A. *Inorg. Chim. Acta* **1986**, *120*, L15−L16.
(28) de Vries, N.; Dewan; J. C.; Jones, A. G.; Davison, A. *Inorg. Chem.* **1988**, *27*, 1574−1580.

Table 4. Selected Data for Tc(III) Complexes **4**−**6**

					$^1H^c$			
compound	color	Tc−P[a]	Tc−X [a,b]	$^{31}P^c(w_{1/2})$	P−CH_3	P−C_6H_5	S−C_6H_4−	$E_p{}^{a\,d}$ Tc^{III}/Tc^{IV}
4 − SOS	violet	2.282	2.236	42.7 (970)	1.91	7.4−7.8	6.75, 7.21	0.175
5 − SSS	violet	2.358	2.398	20.4 (510)	2.07	7.4−7.9	6.71, 7.07	0.262
6 − SN(Me)S	blue	2.318	2.273	31.4 (670)	1.47	7.2−7.4	6.31, 6.76	0.063

[a] In Å. [b] X is the central atom of the tridentate ligand. [c] In ppm, values recorded at room temperature in chloroform-*d*. [d] In mV, potentials are vs the ferricinium/ferrocene couple.

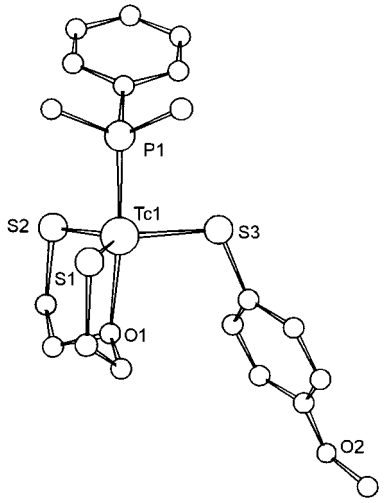

Figure 1. Molecular structure of complex **4**.

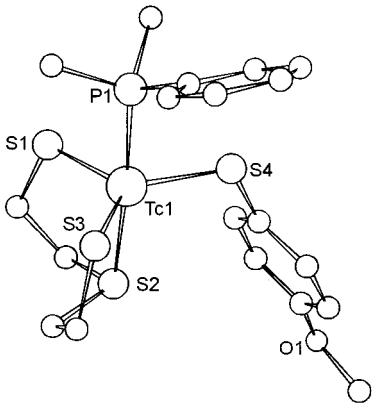

Figure 2. Molecular structure of complex **5**.

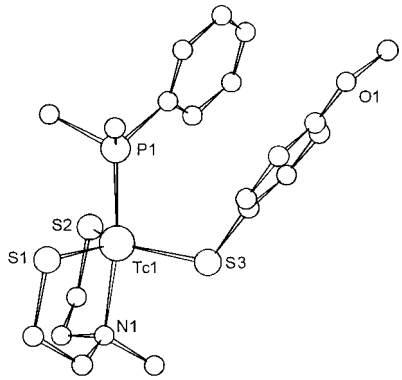

Figure 3. Molecular structure of complex **6**.

low temperature (233 K), likely arising from π-stack interactions, compared to the corresponding signals in complexes **4** and **5**. Room-temperature $^{31}P\{^1H\}$ NMR spectra of these Tc(III) complexes exhibit only broad signals which sharpen somewhat on lowering the temperature. Similar signal broadening was previously observed with diamagnetic technetium complexes and explained with the quadrupolar relaxation induced by the ^{99}Tc nucleus ($I = {}^9/_2$) at the neighbor P atoms.[29] As reported in Table 4, chemical shift and broadening of the ^{31}P signal, as well as the Tc−P bond distances, are affected by the nature of the trans-axial heteroatom of the tridentate ligand. For instance, the electronic balance arranged within the P−Tc−S axis in complex **5** lengthens the Tc−P bond to 2.358 Å. As a consequence, the ^{31}P chemical shift (δ = 20.3 ppm vs δ = −47.2 ppm of uncoordinated PMe_2Ph) and the line broadening ($w_{1/2}$ = 510 Hz) are less affected compared to the variation induced by N and O in the isostructural species **6** and **4**, respectively. Complex **5**, which shows the optimal trans-axial π-accepting combination in the series (thioether/phosphine), is the most stable compound. In fact, close inspection of proton and carbon spectra of chlorinated solutions of complexes **4** and **6** reveal that they rearrange back to the original oxo−Tc(V) precursors with the time in the presence of air or moisture. In

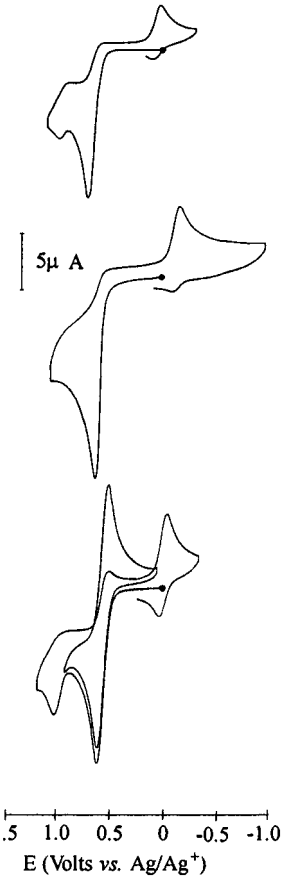

Figure 4. Cyclic voltammograms of complexes **4**−**6** (from the top) in 0.2 mM CH_2Cl_2 solution. Potentials are vs Ag/Ag^+. The scan rate is 200 mV s^{-1}.

(29) Abram, U.; Lorenz, B.; Kaden, L.; Scheller, D. *Polyhedron* **1988**, *7*, 285−289.

addition, steric constrains dictated by the methyl pendant group makes complex **6** the less stable of the series. In fact, while lower temperature freezes the conformation with the substituted benzenethiolate facing the phosphine ligand (vide supra), room-temperature spectra evidence marked broadening of the methyl-amino and arylthiolate signals.

CV data support the observations pointed out above. Thus, complex **6** is easier to oxidize (by 112 mV) than complex **5**, which in turn is easier to oxidize (by 87 mV) than complex **4**. Cyclic voltammetric oxidation potentials (E_p^a) are reported in Table 4 and representative voltammograms in Figure 4. The responses,[30] assigned to the oxidation process $Tc^{III}-Tc^{IV}$, are irreversible regardless of the scan rate for complexes **4** and **5**, whereas complex **6** shows a quasi-reversible wave ($E_{1/2} = 0.006$ V). All complexes display, upon scanning the potential from the positive region, a further quasi-reversible electron transfer as a consequence of a chemical reaction which follows the charge-transfer $Tc^{III}-Tc^{IV}$. Compounds **4** and **5** show a second less intense oxidation wave at 0.487 and 0.413 V, respectively.

(30) Dichloromethane solution of the Tc(III) complexes display one-electron electroactivity at the metal site as indicated by controlled potential electrolysis.

Conclusions

Trigonal-bipyramidal 3 + 1 + 1 compounds [Tc(SES)(S-*p*-C_6H_4-OMe)(PMe_2Ph)], obtained by reduction−substitution reactions operated by PMe_2Ph onto suitable mono-oxo precursors, represent a new class of mixed ligand Tc(III) complexes, that are highly versatile because of the coordination of three different ligands at the metal center. Since each of the ligand is, at least in principle, able to bear functional groups, this type of complexes is well-suited for the design of new radiotracers. However, this class of 3 + 1 + 1 complexes appear to suffer the disadvantages already encountered by the parent 3 + 1 oxo compounds. In fact, challenge reactions performed with excess GSH both at "carrier added" and "no-carrier-added" level evidence extensive decomposition with formation of GS-related hydrophilic species. Aiming at the formation of substitution-inert species, related coordination environments which retain identical tbp geometry and donor set are under scrutiny by replacing monodentate groups with bidentate chelates.

Supporting Information Available: Crystallographic data, in CIF format. This material is available free of charge via the Internet at http://pubs.acs.org.

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