Trithiacyclononane as a Ligand for Potential Technetium and Rhenium Radiopharmaceuticals: Synthesis of $[M(9S3)(SC_2H_4SC_2H_4S)][BF_4]$ (M = ^{99}Tc, Re, ^{188}Re) via C−S Bond Cleavage

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Chemical or electrochemical reduction of the 1,4,7-trithiacyclononane (9S3) complexes $[M^{II}(9S3)_2][BF_4]_2$ (M = Re (**3a**) or Tc (**3b**)) results in instantaneous C−S bond cleavage to yield ethene and the stable M^{III} thiolate complexes $[M^{III}(9S3)L][BF_4]$ (M = Re (**4a**) or Tc (**4b**), L = $SCH_2CH_2SCH_2CH_2S$). Compounds **4** have been characterized by ^{1}H NMR spectroscopy, and the pseudo-octahedral geometry of **4b** has been confirmed by X-ray crystallography. Upon electrochemical reduction **4a** loses ethene, while **4b** can be reversibly reduced to $[Tc^{II}(9S3)L]$, which is then further reduced to Tc(I) with loss of ethene. Successive ethene loss is observed in the mass spectra of compounds **3** and **4**. The radiosynthesis of **4a** with ^{188}Re can be comfortably completed within 10 min starting with $^{188}ReO_4^-$ from a $^{188}W/^{188}Re$ generator, with a radiochemical yield in excess of 90%, and thus represents a practical approach to the preparation of stable ^{188}Re (and ^{99m}Tc) thioether complex derivatives/conjugates for clinical use. Crystal data: **4b**, $C_{10}H_{20}S_6Tc$, orthorhombic *Pbca*, a = 12.233(2) Å, b = 14.341(2) Å, c = 20.726(3) Å, Z = 8.

Introduction

In recent years the chemistry of rhenium has been developing toward new applications in therapeutic nuclear medicine, and new complexes have been developed for the selective delivery of cytotoxic radionuclides ^{186}Re and ^{188}Re to tumors.[1] Interest in this field stems from the excellent physical properties and availability of the radionuclides and from the chemical analogy with technetium, which has long been the most important radioisotope in use in diagnostic nuclear medicine.[2] Most rhenium radiopharmaceuticals contain rhenium in higher oxidation states, in particular the pentavalent oxo and nitrido complexes.[2] Complexes containing rhenium in its lower oxidation states are now receiving more attention, however. This development offers the opportunity to broaden the range of complex types available for "metal-essential" targeting agents, and to exploit low oxidation state complexes in bioconjugate design. Ligands that stabilize the metals in their lower oxidation states typically have soft or "class b" donor groups,[3] which compared to "class a" ligands (which complex higher oxidation states) are relatively nonbasic. In addition, soft donor groups have low affinity for the harder metal ions present in serum. Similarly, the low oxidation state rhenium center has low affinity for the hard nitrogen and oxygen donors abundant in serum. These factors offer increased kinetic inertness of radionuclide complexes in vivo by protecting against acid-catalyzed ligand dissociation. Development of low oxidation state technetium, and particularly rhenium, radiopharmaceuticals has been hampered by the harsh conditions (high temperatures and pressures) and prolonged reactions times used in classical synthetic routes.[4] These conditions are incompatible with the stringent requirements of radiopharmacy, which include the necessity to use MO_4^- as the source of M (M = Re or Tc), and short reaction times under mild conditions. Alberto and co-workers have recently described progressively milder routes to tricarbonylrhenium(I) complexes suitable for bioconjugate synthesis,[5] while Wenzel has developed a remarkable double ligand metathesis reaction in which cyclopentadienyl and carbonyl ligands are transferred to technetium from other metal complexes.[6] This approach has subsequently been elegantly developed and optimized by Katzenellenbogen and co-workers.[7,8]

Investigations of the chemistry of rhenium and technetium with 1,4,7-trithiacyclononane (9S3) have led to a new class of reduced complexes, $[M(9S3)_2]^{2+}$, accessible through mild reactions. The 9S3 ligand is unusual among thioether ligands in that its unique conformational properties endow it with the ability to stabilize many metals in a range of oxidation states.[9] For many related thioether macrocycles, where the free ligands have exodentate sulfurs, it has been suggested that a (usually

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unfavorable) conformational switch to an endodentate form is a prerequisite for complexation. However, the small 9S3 ligand is unique in being endodentate[10] and thus preorganized for facial coordination to appropriate soft metal atoms. Moreover it can be functionalized for bioconjugate synthesis without detriment to this characteristic.[11] The low-spin complexes $[M(9S3)_2]^{2+}$ (M = Tc,[12] Re[13]) can be prepared from MO_4^- and have been structurally characterized by X-ray crystallography. It has been suggested[12,13] that electrochemical reduction of these M(II) complexes affords the corresponding M(I) complexes, $[M(9S3)_2]^+$. In this paper we show that this reduction in fact leads instead to fragmentation of the ligand,[14] but that this chemistry nevertheless provides a convenient mild route to low oxidation state rhenium and technetium complexes suitable for radiopharmaceutical use.

Experimental Section

All manipulations were performed without the exclusion of air, unless otherwise stated. $NH_4[^{99}TcO_4]$ was purchased from Nycomed Amersham, U.K. $NH_4[ReO_4]$ was purchased from Johnson Matthey. $HBF_4 \cdot Et_2O$ (85%), L-ascorbic acid and $SnCl_2$ were all used as received from Aldrich. Technetium-99 is a weak β^- emitter and has a $t_{1/2}$ of 2.14×10^5 years. All work with it was therefore carried out in a radioactive controlled area in accordance with the rules governing the use of radioactive substances. 1,4,7-Trithiacyclononane (9S3) was either purchased from Sigma (Poole, U.K.) or prepared according to the literature method.[15] Diethyl ether, acetone, and glacial acetic acid were commercially available as AR grade and used without further purification. Acetonitrile (HPLC grade) was dried over calcium hydride and distilled under dinitrogen.

Microanalyses (C, H, and N) were carried out by the analytical services in the School of Physical Sciences at the University of Kent. Infrared spectra were recorded on a Matteson ATi Genesis series FTIR spectrometer as KBr pellets or as Nujol mulls between KBr disks or in a CaF_2 solution cell. UV−vis spectra were recorded in quartz cells on a Philips PU8730 UV−vis scanning spectrophotometer. Cyclic voltammetric measurements were performed on an EG&G model 362 scanning potentiostat using Condecon 310 data analysis software using a glassy carbon working electrode (BAS Technicol, Stockport, U.K.), a platinum gauze auxiliary electrode and a Ag/AgCl reference electrode. Dry acetonitrile containing 0.1 mol dm^{-3} $[^nBu_4N][BF_4]$ was used as supporting electrolyte. RP-HPLC studies were performed on a Pharmacia LKB Bromma model 2150/2152 HPLC system equipped with a Pharmacia LKB Bromma model 2151 UV−vis detector and a Reeve Analytical model 9701 (Glasgow, U.K.) gamma radiation detector. All samples were analyzed on a Hamilton PRP-1 (Reno, NV) reverse phase analytical column (150 × 4.1 mm). The samples were eluted with a linear gradient system comprising solvent A (0.1% TFA/H_2O) and solvent B (0.1% TFA/MeCN). The gradient was defined by the following points (min, %B): 0, 0; 1, 0; 10, 100; 12, 0; 14, 0; 16, 0; at a flow rate of 2 mL/min. The UV−vis absorbance of the eluent was monitored at 271 or 460 nm. Concordance experiments were performed to confirm that tracer level complexes were chemically identical to their macroscopic counterparts. Gas chromatography studies were carried out on a Philips PU 4500 chromatograph, using a SE-30 column.

Table 1. X-ray Crystal Data Collection, Solution and Refinement for **4b**

empirical formula	$C_{10}H_{20}S_6TcBF_4$
mw	517.43
color, habit	dark red, needle
cryst size/mm	0.315 × 0.147 × 0.053
cryst syst	orthorhombic
space group	*Pbca*
temp/K	293
a/Å	12.233(2)
b/Å	14.341(2)
c/Å	20.726(3)
α/deg	90
β/deg	90
γ/deg	90
V/Å^3	3636.0(9)
Z	8
$D_{calc.}$/g cm^{-3}	1.890
μ/cm^{-1}	15.08
F(000)	2080
radiation used	Mo Kα
θ range/deg	2.40−30.49
rflns collected	29143
obsd rflns	4230
params	280
goodness of fit	0.988
R1[a] ($F > 4\sigma(F)$)	0.0465
wR2[b] (all data)	0.0935
largest diff peak, hole/e Å^{-3}	1.093, −0.692

[a] $R1 = \sum||F_o| - |F_c||/\sum|F_o|$. [b] $wR2 = [\sum w(F_o^2 - F_c^2)^2]/[\sum w(F_o^2)^2]]^{1/2}$.

GC−MS studies were carried using an AMS model 93 gas chromatograph, with a BP-5 column connected to a Finnigan MAT ion trap detector. Low-resolution fast atom bombardment mass spectra (FAB-MS) were measured by EPSRC National Mass Spectrometry Service (Swansea) using a VG Autospec instrument, with cesium ion bombardment at 25 kV on a sample in 3-nitrobenzyl alcohol (NOBA) matrix. Electrospray mass spectra were recorded on a Finnigan MAT LCQ ion trap mass spectrometer (Wellcome Trust Protein Science Facility, University of Kent). Samples were dissolved in MeCN and injected, via a Rheodyne valve fitted with a 10 μL loop, into a water−methanol mobile phase at a flow rate of 0.02 mL/min. The nebulizer tip was at +3.5 kV and 60 °C, with nitrogen used as both a drying and a nebulizing gas. The cone voltage was set at 15 V to obtain mild fragmentation of the complex. ^{1}H NMR spectra were recorded using a Varian Unity Inova 600 operating at 600.1 MHz, with tetramethylsilane as the reference. Data were collected and processed using the software VNMR[16] on a Sun Ultra Sparc workstation (Solaris 2.4.1). Two-dimensional spectra were plotted using the graphics package Azara.[17]

Crystal Structure Determination of $[Tc(9S3)(SC_2H_4SC_2H_4S)][BF_4]$. Details of the X-ray structure analysis are summarized in Table 1. Data were collected using a MSC/Rigaku Raxis IIc diffractometer, and images were collected as image plate oscillation photographs with an oscillation angle of 5° at 70 mm from the detector. The diffractometer was equipped with a graphite-monochromated Mo Kα X-radiation (λ_{max} = 0.71073 Å), T = 293 K, $\omega-2\theta$ scans. The structure was solved by direct methods (SHELXL97[18]) with a least-squares refinement on F^2 (SHELXL93[19]). The tetrafluoroborate anion shows some evidence of slight orientational disorder showing large anisotropic displacement factors. All non-hydrogen atoms were refined anisotropically, and hydrogen atoms were included in fixed, calculated positions with d(C−H) = 0.95 Å.

Preparation of $[^nBu_4N][ReO_4]$ (1a). A solution of $[NH_4][ReO_4]$ (2.0 g, 7.45 mmol) in water (100 mL) at 60 °C was added dropwise to a

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stirred solution of [^{n}Bu$_4$N]Cl (2.6 g, 9.35 mmol) in water (100 mL) at 60 °C. The mixture was stirred for a further 30 min at room temperature. The white crystalline solid which formed was filtered off and washed with water (4 × 20 mL) followed by diethyl ether (4 × 20 mL) and dried in vacuo to afford white crystals (2.7 g, 75%). Found: C, 39.2; H, 7.4; N, 2.8. $C_{16}H_{36}NO_4Re$ requires C, 39.0; H, 7.3; N, 2.9. UV−vis (MeCN): λ_{max}/nm (ϵ/M^{-1} cm^{-1}) 233 (2529), 204 (4000). HPLC (retention time, area): 0.85 min, 99% (perrhenate anion).

Preparation of [^{n}Bu$_4$N][TcO$_4$] (1b). A filtered solution of [NH$_4$][TcO$_4$] (0.15 g, 0.83 mmol) dissolved in water (5 mL) was added dropwise to a stirring solution of [^{n}Bu$_4$N]Cl (0.30 g, 1.1 mmol) in water (5 mL). The mixture was stirred for a further 10 min. The off-white solid which formed was filtered off and washed with water (4 × 5 mL) followed by diethyl ether (4 × 5 mL). The solid was then dried in vacuo (0.25 g, 68%). IR (Nujol): ν/cm^{-1} 894 (s, Tc═O). UV−vis (MeCN): λ_{max}/nm (ϵ/M^{-1} cm^{-1}) 287 (1995), 253 (4188), 244 (4578).

Preparation of [ReO$_3$(9S3)][BF$_4$] (2a). To a stirred solution of **1a** (0.20 g, 0.40 mmol) in glacial acetic acid (20 mL) was added 9S3 (0.0756 g, 0.40 mmol). After all the 9S3 had dissolved, HBF$_4$·Et$_2$O (1 mL) was added dropwise. A yellow solution formed which immediately precipitated a pale yellow solid. The mixture was stirred for a further 30 min, after which the solid was collected using a sintered funnel and washed with diethyl ether (3 × 10 mL) to afford **2a** as a pale yellow powder (0.178 g, 84%). Found: C, 14.3; H, 2.4. $C_6H_{12}BF_4O_3ReS_3$ requires C, 14.4; H, 2.4. IR (Nujol): ν/cm^{-1} 932 s, 906 s (Re═O) and 1080 s (BF$_4^-$). UV−vis (MeCN): λ_{max}/nm (ϵ/M^{-1} cm^{-1}) 339 (1840), 288 (5033), 264 (5144), 217 (2956), 201 (2021). HPLC (retention time, area): 3.31 min, 100% ([ReO$_3$(9S3)]$^+$). FAB-MS (*m*/*z*): 415 ([ReO$_3$(9S3)]$^+$, 100%). ^{1}H NMR (CD$_3$CN): δ (ppm) 3.812, 3.767 [AA′BB′, *J* (8.2 Hz), *J*′ (4.7 Hz), J_{gem} (−15.1 Hz)].

Preparation of [Re(9S3)$_2$][BF$_4$]$_2$ (3a). To a stirred solution of **1a** (0.20 g, 0.40 mmol) in glacial acetic acid (20 mL) was added 9S3 (0.0756 g, 0.40 mmol). After all the 9S3 had dissolved, HBF$_4$·Et$_2$O (1 mL) was added dropwise, forming **2a**, to which 9S3 (0.0756 g, 0.40 mmol) was added, and the mixture was stirred until all solids had dissolved. To this solution was added SnCl$_2$ (0.28 g, 1.20 mmol), and the mixture was stirred for 1 h. A greenish-brown precipitate formed, which was filtered off and washed with ether (4 × 10 mL) to afford **3a** as a greenish-brown powder (0.24 g, 85%). Found: C, 20.2; H, 3.4. $C_{12}H_{24}B_2F_8ReS_6$ requires C, 20.1; H, 3.3. IR (Nujol): ν/cm^{-1} 1055 s (BF$_4^-$). UV−vis (MeCN): λ_{max}/nm (ϵ/M^{-1} cm^{-1}) 425 (3570), 245 (7708), 206 (11831). HPLC (retention time, area): 3.7 min, 85% ([Re(9S3)$_2$]$^{2+}$). FAB-MS (*m*/*z*): 634 ([Re(9S3)$_2$BF$_4$]$^+$, 20%), 538 ([Re(9S3)(L)(F)]$^+$, 30%), 519 ([Re(9S3)L]$^+$, 55%), 491 ([ReS$_6$(C$_2$H$_4$)$_4$]$^+$, 45%), 463 ([ReS$_6$(C$_2$H$_4$)$_3$]$^+$, 15%), 435 ([ReS$_6$(C$_2$H$_4$)$_2$]$^+$, 10%), 402 ([ReS$_5$(C$_2$H$_4$)$_2$]$^+$, 10%), 375 ([ReS$_5$(C$_2$H$_4$)]$^+$, 10%), 273 ([Re(9S3)$_2$]$^{2+}$, 15%), 259 ([Re(9S3)L]$^{2+}$, 10%).

Preparation of [Tc(9S3)$_2$][BF$_4$]$_2$ (3b). 9S3 (12.6 mg, 0.07 mmol) was added to a stirred solution of **1b** (0.015 g, 0.034 mmol) dissolved in acetonitrile (5 mL). After all the 9S3 had dissolved, fresh HBF$_4$·Et$_2$O (0.140 mL) followed by SnCl$_2$ (0.045 g, 0.2 mmol) was added. Upon refluxing for 30 min a red/orange precipitate formed, which was filtered off and washed with diethyl ether (4 × 5 mL) to afford **3b** (0.0198 g, 92%). IR (Nujol): ν/cm^{-1} 1049s (BF$_4^-$). UV−vis (MeCN): λ_{max}/nm (ϵ/M^{-1} cm^{-1}) 466 (2330), 387 (250), 340 (150), 307 (140). ES-MS (*m*/*z*): 546 ([Tc(9S3)$_2$BF$_4$]$^+$, 30%), 478 ([Tc(9S3)$_2$F]$^+$, 5%), 450 ([Tc(9S3)(L)F]$^+$, 7%), 431 ([Tc(9S3)(L)]$^+$, 25%), 403 ([TcS$_6$(C$_2$H$_4$)$_4$]$^+$, 7%), 375 ([TcS$_6$(C$_2$H$_4$)$_3$]$^+$, 12%), 229.5 ([Tc(9S3)$_2$]$^{2+}$, 100%), 215.5 ([Tc(9S3)L]$^{2+}$, 45%), 201.5 ([TcS$_6$(C$_2$H$_4$)$_4$]$^{2+}$, 7%). HPLC (retention time, area): 3.8 min, 90% ([Tc(9S3)$_2$]$^{2+}$).

Preparation of [Re(9S3)(L)][BF$_4$] (4a). L-Ascorbic acid (0.08 g, 0.45 mmol) was added to a solution of **3a** (0.2 g, 0.27 mmol) dissolved in water (5 mL). After stirring for 2 h a red-brown crystalline solid was collected and dried in vacuo. Recrystallization from water afforded crystalline **4a** (0.14 g, 86%). Found: C, 31.6; H, 5.2. $C_{10}H_{20}BF_4ReS_6$ requires C, 31.7; H, 5.3. IR (Nujol): ν/cm^{-1} 1080 s (BF$_4^-$). UV−vis (MeCN): λ_{max}/nm (ϵ/M^{-1} cm^{-1}) 424 (3129), 331 (477), 288 (1379), 246 (3739), 200 (6783). HPLC retention time: 6.1 min ([Re(9S3)L]$^+$). FAB-MS (*m*/*z*): 519 ([Re(9S3)(L)]$^+$, 30%), 491 ([ReS$_6$(C$_2$H$_4$)$_4$]$^+$, 25%), 463 ([ReS$_6$(C$_2$H$_4$)$_3$]$^+$, 10%). ^{1}H NMR (CD$_3$CN): δ (ppm) 3.41−3.46 (m, 2H, L), 2.92−3.04 (m, 6H, L and 9S3), 2.66−2.81 (m, 6H, L and 9S3), 2.35−2.44 (m, 4H, L and 9S3), 2.07−2.11 (m, 2H, 9S3).

[Tc(9S3)(L)][BF$_4$] (4b). L-Ascorbic acid (0.01 g, 0.055 mmol) was added to a solution of **3b** (0.0198 g, 0.031 mmol) in water (5 mL). After stirring for 5 min the red/orange solution was left to stand overnight. A dark red crystalline solid was collected and dried in vacuo. Recrystallization from water gave **4b** (0.015 g, 94%) in the form of crystals suitable for X-ray analysis. IR (Nujol): ν/cm^{-1} 1072s (BF$_4^-$). UV−vis (MeCN): λ_{max}/nm (ϵ/M^{-1} cm^{-1}) 487 (6731), 376 (1530), 322 (2040), 282 (4581), 213 (15510). HPLC retention time: 6.3 min ([Tc(9S3)L]$^+$). ES-MS (*m*/*z*): 431 ([Tc(9S3)(L)]$^+$, 100%), 403 ([TcS$_6$(C$_2$H$_4$)$_4$]$^+$, 25%), 375 ([TcS$_6$(C$_2$H$_4$)$_3$]$^+$, 46%), 347 ([TcS$_6$(C$_2$H$_4$)$_2$]$^+$, 15%). ^{1}H NMR (CD$_3$CN): δ (ppm) 3.66−3.70 (m, 2H, L), 2.99−3.09 (m, 4H, 9S3 and L), 2.88−2.94 (m, 4H, 9S3 and L), 2.74−2.78 (m, 4H, 9S3), 2.61−2.65 (m, 2H, 9S3), 2.52−2.56 (m, 4H, 9S3).

Re-188 Labeling. All Re-188 radioactive experiments were carried out in the Department of Nuclear Medicine, Kent and Canterbury Hospital. The Re-188 isotope was obtained by elution, with sterile physiological saline, of $^{188}O_4^-$ from a tungsten-188/rhenium-188 radionuclide generator system ($^{188}WO_4^-/^{188}O_4^-$) supplied by Oak Ridge National Laboratory (Oak Ridge, TN).[20] Re-188 is a high-energy β^- emitter (E_{max} 2.1 MeV) with a half-life of 16.9 h and was handled in accordance with local rules governing the use of radioactive substances. OnGuard AG columns were from Dionex Chromatography, U.K.,and anion exchange columns (Isolute SPE, 0.1 g, SAX) were from Jones Chromatography, U.K.

Preparation of [^{188}Re(9S3)(L)][BF$_4$]. The $^{188}WO_4^-/^{188}O_4^-$ generator was eluted with sterile saline solution (10 mL) to provide $^{188}ReO_4$, which was passed through an OnGuard AG column followed by an anion exchange column (SAX).[21] The outlet of the SAX column was briefly attached to a water aspirator to dry the column by passage of air. This procedure gives a quantitative yield of dry, chloride-free $^{188}ReO_4^-$ (7.5 MBq) bound to the column. The SAX column was then eluted with a solution of 9S3 (5 mg, 0.025 mmol) dissolved in glacial acetic acid (500 μL) and HBF$_4$·Et$_2$O (50 μL). This eluate, containing [^{188}ReO$_3$(9S3)]$^+$ (7.0 MBq), was added to a solution of 9S3 (5 mg, 0.025 mmol) dissolved in glacial acetic acid (0.2 mL). Further HBF$_4$·Et$_2$O (50 μL) and SnCl$_2$ (10 mg, 0.04 mmol) were then added and the mixture was vortexed for 10 min and then centrifuged for 5 min at 3000 rpm to pellet any stannous chloride prior to HPLC analysis. The supernatant was removed and diluted with water (1 mL), and L-ascorbic acid (10 mg, 0.055 mmol) was then added to form [^{188}Re(9S3)(L)][BF$_4$]. Yield: 6.5 MBq (87%, based on starting activity of 7.5 MBq). HPLC (retention time, % area), γ detector: 5.16 min, 6.6%; 6.61 min, 90%; 9.32 min, 3.4%. No significant activity remained on the HPLC column.

Results and Discussion

Synthesis, Spectroscopy, and Structure. Scheme 1 summarizes synthetic routes and reaction conditions. Complex **2a** was prepared as described previously[22] by the reaction of [^{n}Bu$_4$N][ReO$_4$] (**1a**) and 9S3 in glacial acetic acid. Upon addition of HBF$_4$·Et$_2$O a yellow precipitate of **2a** formed. The ^{1}H NMR spectrum of **2a** recorded at 600 MHz was sufficiently well resolved to allow simulation and iterative fitting using LAOCOON PC.[23] The two faces of the 9S3 ring are made inequivalent by the presence of the ReO$_3$ fragment, and hence the S−C−C−S fragments appear as three equivalent AA′BB′ systems with vicinal coupling constants (*J* 8.2, *J*′ 4.7) close to those calculated for the expected all-gauche equilibrium mixture (*J* 8.2, *J*′ 3.8).[24] This implies that the 9S3−rhenium linkage in **2a** is relatively inert and any ligand exchange is slow on the NMR time scale.

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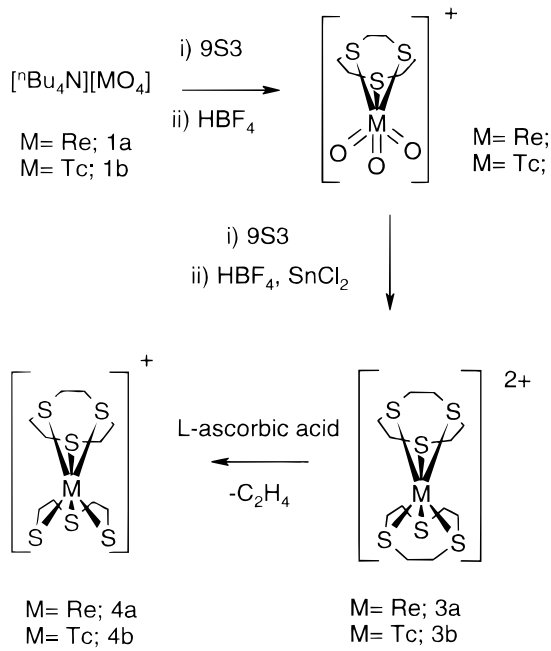
Scheme 1. Summary of Reactions



Addition of a further 1 equiv of 9S3 to **2a** followed by reduction with $SnCl_2$ affords paramagnetic **3a** in high yield, as previously described.[13] Alternatively **3a** can be prepared directly from **1a** without isolation of **2a**. An analogous procedure was used to prepare technetium analogue **3b**.[12] The FAB and electrospray mass spectra of compounds **3** contain isotope envelopes corresponding to $[M(9S3)_2]^+$ but also peaks due to successive losses of ethene. This result is significant in light of subsequent observations (vide infra).

Reduction of **3a** or **3b** with L-ascorbate under aqueous conditions, in an attempt to prepare the putative M(I) complexes $[M(9S3)_2][BF_4]$ led instead to immediate and quantitative loss of ethene and the formation of the complexes $[M(9S3)(L)][BF_4]$ (M = Re (**4a**) or Tc **(4b)**, L = $SC_2H_4SC_2H_4S$) in isolated yields >90%. The reduction of **3a** with L-ascorbate in water to form **4a** was monitored by HPLC over a period of 60 min, demonstrating quantitative conversion of **3a** to **4a**. The identity and quantity of the evolved gas was confirmed by monitoring the atmosphere above the reaction with GC and GC−MS. Formation of compounds **4** could also be achieved by reduction of **3** with $SnCl_2$, Cr, Zn, or Fe. Carbon−sulfur bond cleavage to afford ethene has been reported previously for polynuclear 9S3 complexes at elevated temperature. For example, refluxing $[Ru_3(CO)_7(\mu\text{-CO})(1,1,1\text{-}\eta^3\text{-}9S3)]$ in THF affords $[Ru_3(CO)_9(\mu\text{-}\eta^3\text{-}L)]$[25,26] and heating $[Ru_6(CO)_{14}(\eta^3\text{-}9S3)(\mu_6\text{-C})]$ to 105 °C also eliminates ethene to form $[Ru_6(CO)_{14}(\mu_3\text{-}\eta^3\text{-L})(\mu_5\text{-C})]$.[27]

The structure of **4b** was established by X-ray crystallography (Figure 1) and is similar to that previously described for **4a**.[14] Selected bond lengths and angles for **4a** and **4b** are given in Table 2. The geometry of the MS_6 core is best described as a distorted octahedron. The average Tc−S bond distance to the 9S3 ligand (2.451 Å) is significantly longer than that in **3b** (2.377 Å)[12] and reflects the weaker bonding of 9S3 to Tc(III) compared with Tc(II). The shortest Tc−9S3 bond is trans to a thioether sulfur. The average Tc−thiolate sulfur bond distance (2.263 Å) is significantly shorter than the Tc−thioether bond to L [2.3542(6) Å]. The average 9S3 C−S bond length in **4a** (1.827 Å) is slightly shorter than that in **4b** (1.835 Å), as is the average M−9S3 length (2.430 vs 2.451 Å), suggesting that M→S π back-donation in **4a** is greater than that in **4b**, consistent with well-known periodic trends.

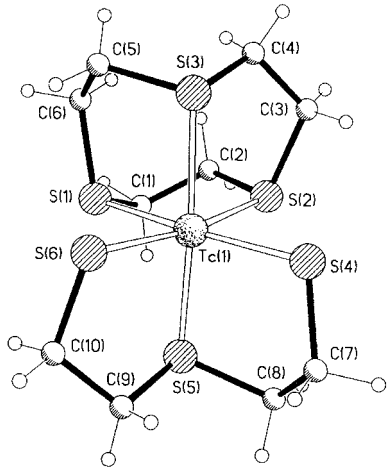


Figure 1. Molecular structure of $[Tc(9S3)L]^+$ (**4b**).

Table 2. Selected Bond Lengths (Å) and Angles (deg) with Estimated Standard Deviations in Parentheses for $[Re(9S3)(L)][BF_4]$ (**4a**) and $[Tc(9S3)(L)][BF_4]$ (**4b**)

bond	**4a**	**4b**	bond	**4a**	**4b**
M−S1	2.436(2)	2.4565(6)	S3−C5	1.828(8)	1.836(2)
M−S2	2.463(2)	2.4815(6)	S4−C7	1.837(9)	1.840(2)
M−S3	2.393(2)	2.4142(6)	S5−C8	1.816(9)	1.833(2)
M−S4	2.256(2)	2.2512(6)	S5−C9	1.817(9)	1.839(3)
M−S5	2.346(2)	2.3542(6)	S6−C10	1.831(9)	1.847(3)
M−S6	2.272(2)	2.2738(6)	C1−C2	1.506(6)	1.504(4)
S1−C1	1.821(8)	1.829(3)	C3−C4	1.507(13)	1.509(4)
S1−C6	1.826(9)	1.837(3)	C5−C6	1.535(11)	1.510(4)
S2−C2	1.819(9)	1.828(3)	C7−C8	1.516(12)	1.503(3)
S2−C3	1.819(9)	1.833(3)	C9−C10	1.531(12)	1.511(4)
S3−C4	1.847(9)	1.849(3)			

angle	**4a**	**4b**	angle	**4a**	**4b**
S4−M−S6	108.52(8)	109.20(3)	C5−S3−M	101.8(3)	100.93(9)
S6−M−S5	87.07(8)	87.42(3)	C4−S3−M	107.4(3)	107.18(9)
S1−M−S2	81.21(7)	80.82(2)	C10−S6−M	106.1(3)	105.59(9)
S3−M−S2	84.53(7)	84.63(2)	C9−S5−M	104.9(3)	103.97(10)
S3−M−S1	85.92(7)	86.12(2)	C8−S5−C9	99.8(4)	100.58(12)
S1−M−S4	164.21(8)	163.89(2)	C1−S1−C6	101.6(4)	102.10(13)
S6−M−S2	167.92(8)	167.13(2)	C9−C10−S6	111.9(6)	111.9(2)
S5−M−S3	175.57(7)	175.47(2)	C10−C9−S5	109.5(6)	109.2(2)
C1−S1−M	105.5(3)	105.59(9)	C5−C6−S1	111.5(6)	112.6(2)
C6−S1−M	106.2(3)	104.96(8)	C1−C2−S2	110.8(6)	110.6(2)

Compound **4a** is diamagnetic and was characterized in solution by ^1H NMR spectroscopy. The 1D spectrum is shown in Figure 2 and shows five multiplets with relative integrated intensities of 2:6:6:4:2, suggesting that conformational mobility of the ligands produces a mirror plane in the molecule on the NMR time scale, rendering the two halves of the 9S3 and L ligands equivalent. In order to assign the multiplets, $^1H/^1H$ DQF-COSY (short-range couplings) and NOESY (long-range couplings) spectra were recorded. The $^1H/^1H$ DQF-COSY of **4a** established the three coupling groups shown in Figure 2. The NOESY spectrum for **4a** revealed long-range coupling between the pairs B/H, H/C, and E/J thus allowing the assignment to 9S3 and also their relative (but not absolute) orientation with respect to the mean plane of the ring. Long-range coupling was also observed between A/G and between

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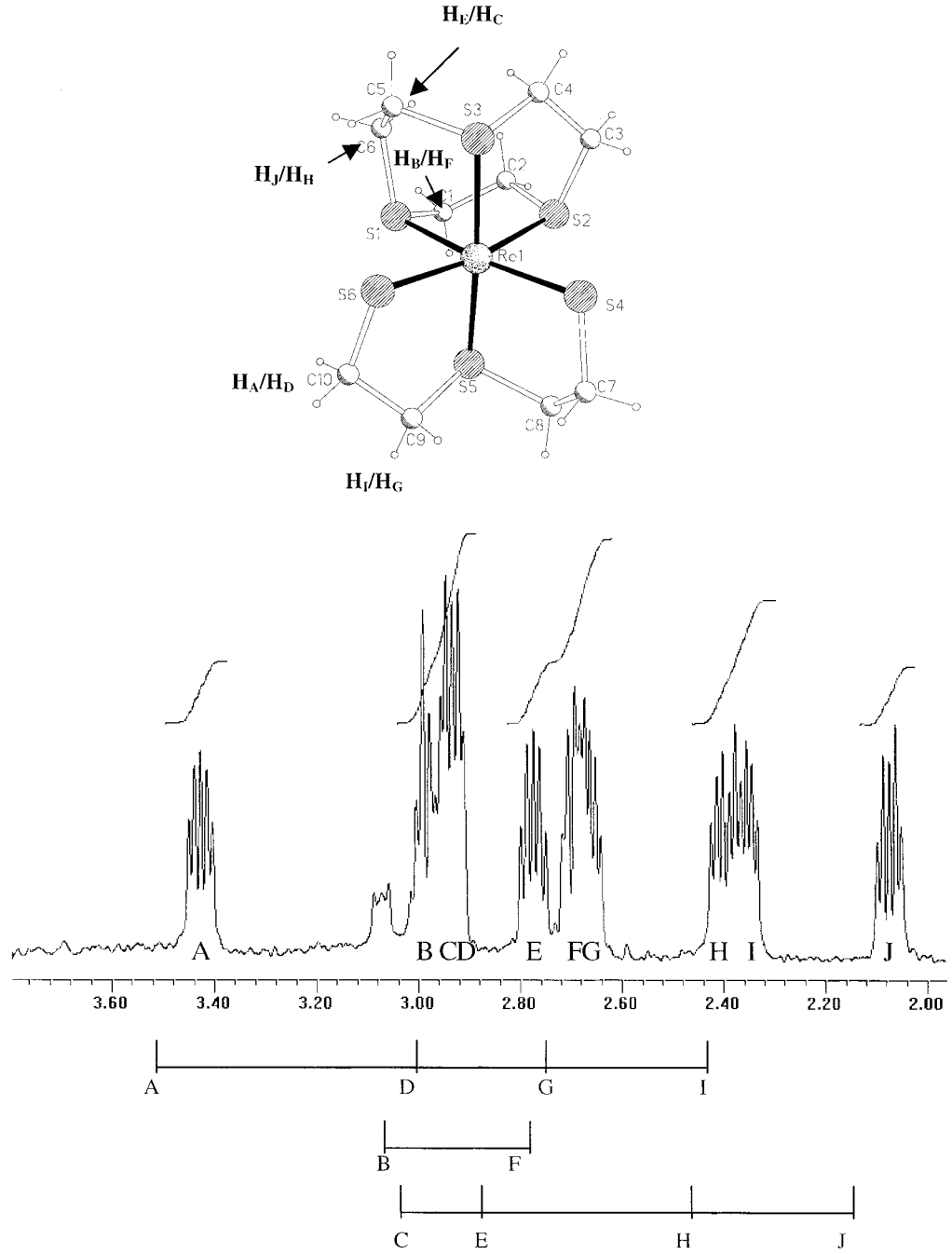


Figure 2. ^{1}H NMR spectrum (600 MHz) of **4a** showing coupling groups derived from COSY and NOESY spectra.

D/I. Assignment of A/D to the thiolate CH_2 was made of the basis of the downfield NMR shifts of protons A/D relative to G/I. The ^{1}H NMR of **4b** was interpreted in an analogous manner.

Electrochemistry. Cyclic voltametry data for compounds **3** and **4** are summarized in Table 3. The results are consistent with the transformations depicted in Scheme 2. Cyclic voltammograms of **3a** and **3b** have been reported previously: for **3a** a reversible oxidation process occurs at +0.47 V corresponding to the Re^{II}/Re^{III} couple.[12] The corresponding reversible redox couple for the analogous **3b** complex was observed at a higher potential of +0.87 V.[12] The cyclic voltammograms of **3a** and **3b** also exhibit irreversible redox couples at around −0.43 and −0.38 V, respectively, which were previously ascribed to the reduction of M^{II} to M^{I}.[12,13] However, in our hands gas evolution is observed in both cases and the short-lived M^{I} species evidently loses ethene to form compounds **4**. The previously reported "Tc(I)" complex[12] has the same UV−vis spectrum as **4b**.

Table 3. Cyclic Voltametry Data for Compounds **3** and **4**

complex	redox couple	$E_{1/2}$ (V) vs $Fc^{+/0}$	E_p (mV)	r/i	ref
4a	Re^{III}/Re^{IV}	+0.015	122	r	this work
	Re^{III}/Re^{II}	−1.350		i	
4b	Tc^{III}/Tc^{II}	−1.08	90	r	this work
	Tc^{II}/Tc^{I}	−1.958		i	
3a	Re^{II}/Re^{III}	+0.47		qr	13
	Re^{II}/Re^{I}	−0.43		i	
3b	Tc^{II}/Tc^{III}	+0.87		qr	12
	Tc^{II}/Tc^{I}	−0.38		qr	

Complex **4a** has a reversible Re^{III}/Re^{IV} redox couple at +0.015 V and an irreversible Re^{III}/Re^{II} couple at −1.350 V (Figure 3). During this reduction process the evolution of gas, presumably ethene, was observed at the working electrode. The analogous technetium complex **4b** does not exhibit an oxidative

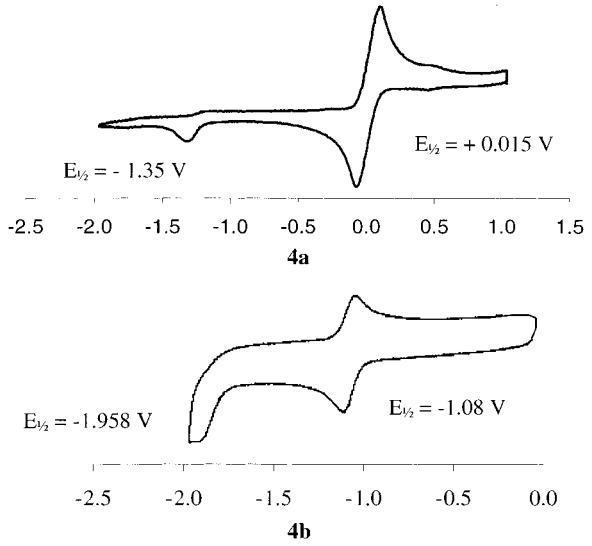
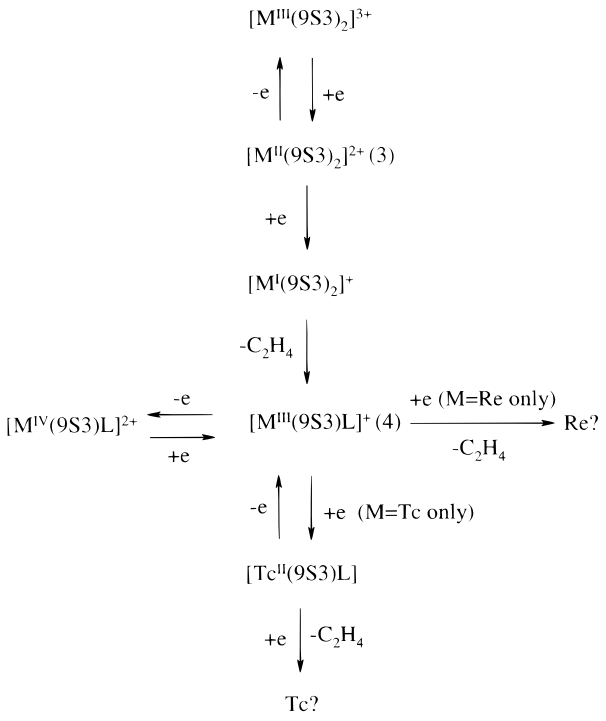


Figure 3. Cyclic voltammograms of $[Re(9S3)L]^+$ (**4a**) and $[Tc(9S3)L]^+$ (**4b**).

Scheme 2. Redox Chemistry of Compounds **3** and **4**



Tc^{III}/Tc^{IV} redox couple. Instead **4b** shows a reversible Tc^{III}/Tc^{II} couple at −1.08 V and an irreversible Tc^{II}/Tc^{I} couple at −1.958 V, which was again accompanied by gas evolution. As expected, reduction of M^{III} to M^{II} is harder for Re than for Tc. This process is irreversible for M = Re, leading to further loss of ethene, while for M = Tc a fully reversible redox couple is observed. These results are consistent with the expected trend that technetium complexes are easier to reduce and harder to oxidize than their rhenium analogues.

Re-188 Labeling. In order to exploit this chemistry as a basis for radiopharmaceutical development, we developed a novel disposable column method for carrier-free synthesis with ^{188}Re. The ^{188}Re radiochemical synthesis of **4a** is achieved by eluting the $^{188}W/^{188}Re$ alumina-based generator with saline solution directly through a halide-removing (OnGuard AG) column and onto a disposable anion exchange column. This procedure serves the twin purposes of conveniently removing chloride ions and changing to nonaqueous solvent. The ^{188}Re is eluted from the anion exchange column by conversion to cationic $[^{188}ReO_3(9S3)]^+$ with a solution of 9S3 and $HBF_4 \cdot Et_2O$ in glacial acetic acid. The reaction of the eluted $[^{188}ReO_3(9S3)]^+$ with further 9S3, $SnCl_2$, and $HBF_4 \cdot Et_2O$ in glacial acetic acid forms $[^{188}Re(9S3)_2]^{2+}$ and other intermediates, and reduction of this complex in aqueous solution with L-ascorbate forms the $[^{188}Re(9S3)(L)]^+$ complex. Even in this prototype, nonoptimized procedure, the yield and purity are high (87% and 90%, respectively). The product and the principal intermediate species were identified by HPLC using an in-line γ detector by coeluting with the spectroscopically characterized nonradioactive samples as standards. This disposable column procedure provides a very convenient means of manipulating radioactive rhenium for purposes of concentration, changing solvents, and general safe handling. It offers the potential, in conjunction with C-functionalized derivatives of 9S3, for facile synthesis of bioconjugates and metal-essential radiopharmaceuticals containing ^{99m}Tc and $^{186/188}Re$.[11]

Conclusions

The ligand 9S3 offers a clean, mild, convenient route from perrhenate and pertechnetate to divalent and trivalent complexes and has potential for use in rhenium and technetium radiopharmaceutical synthesis. The electrochemical or chemical reduction of the divalent species induces a unique ethene-loss reaction to yield the trivalent dithiolate complexes rather than forming stable M(I) species. The M(II) complexes (M = Re or Tc) are relatively stable with respect to ethene loss, but are still much more vulnerable to this process than later transition metal analogues $[M(9S3)_2]^{2+}$.[14] This is supported by the particularly long C−S bonds observed in the crystal structures and the degree of fragmentation these complexes undergo during mass spectroscopy, showing not only the loss of one ethene but sequential loss of up to five ethene molecules from $[Tc(9S3)_2]^{2+}$ and $[Re(9S3)_2]^{2+}$.[28] The radiosynthesis of **4a** can be comfortably completed within 10 min with a radiochemical yield for the overall process in excess of 90%. These complexes thus offer a practical approach to a new Tc/Re core for clinical use.

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Supporting Information Available: X-ray crystallographic files, in CIF format, for **4b**. This material is available free of charge via the Internet at http://pubs.acs.org.

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