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# Structural studies of ReO(V) mixed ligand [SNS][Cl] and [SNS][S] complexes

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#### Abstract

The synthesis, characterization and spectroscopic properties of four oxorhenium complexes, ReO[C<sub>2</sub>H<sub>5</sub>SCH<sub>2</sub>CH<sub>2</sub>N(CH<sub>2</sub>-CH<sub>2</sub>S)<sub>2</sub>][*p*-CH<sub>3</sub>OC<sub>6</sub>H<sub>4</sub>S] (**2**), ReO[(C<sub>2</sub>H<sub>5</sub>)<sub>2</sub>NCH<sub>2</sub>CH<sub>2</sub>N(CH<sub>2</sub>CH<sub>2</sub>S)<sub>2</sub>][*p*-CH<sub>3</sub>C<sub>6</sub>H<sub>4</sub>S] (**3**), and ReO[C<sub>5</sub>H<sub>10</sub>NCH<sub>2</sub>CH<sub>2</sub>N(CH<sub>2</sub>C(CH<sub>3</sub>)<sub>2</sub>S)<sub>2</sub>][*C*<sub>6</sub>H<sub>5</sub>CH<sub>2</sub>SH<sub>2</sub>CH<sub>2</sub>S(H<sub>5</sub>CH<sub>2</sub>S) (**4**) are reported. These neutral and lipophilic complexes are designed according to the '3 + 1' mixed ligand concept. X-ray crystallographic studies show that the coordination geometry around rhenium is distorted trigonal bipyramidal in complexes **2** and **3** and trigonally distorted square pyramidal in complex **4** (C<sub>15</sub>H<sub>24</sub>NO<sub>2</sub>S<sub>4</sub>Re (**2**), triclinic  $P\overline{1}$ , *a* = 9.610(2), *b* = 9.628(2), *c* = 11.791(2) Å, *α* = 108.307(8), *β* = 67.735(6), *γ* = 90.166(8)°, *V* = 950.04 Å<sup>3</sup>, *Z* = 2; C<sub>17</sub>H<sub>29</sub>N<sub>2</sub>OS<sub>3</sub>Re (**3**), monoclinic *P*<sub>21</sub>/*c*, *a* = 13.188(1), *b* = 7.542(1), *c* = 21.193(1) Å, *β* = 103.260(2)°, *V* = 2051.74 Å<sup>3</sup>, *Z* = 4; C<sub>22</sub>H<sub>37</sub>N<sub>2</sub>OS<sub>3</sub>Re · 0.5C<sub>2</sub>H<sub>5</sub>OH (**4**), monoclinic *P*<sub>21</sub>/*c*, *a* = 16.720(6), *b* = 11.013(3), *c* = 16.747(5) Å, *β* = 113.44(1)°, *V* = 2829.08 Å<sup>3</sup>, *Z* = 4). Complete assignments of <sup>1</sup>H and <sup>13</sup>C NMR resonances were made for all complexes and compared to those of analogous technetium complexes. Complex **3** was also prepared at the tracer <sup>186</sup>Re level. © 1999 Elsevier Science S.A. All rights reserved.

Keywords: Crystal structures; Oxorhenium complexes; Mixed ligand complexes; NMR spectroscopy

## 1. Introduction

The relationship between technetium and rhenium coordination chemistry is the focus of much activity because of the importance of the isotopes <sup>99m</sup>Tc, <sup>186</sup>Re and <sup>188</sup>Re in diagnostic and therapeutic nuclear medicine. <sup>99m</sup>Tc labeled pharmaceuticals comprise over 80% of the diagnostic agents used in clinics for imaging of the body. <sup>186</sup>Re and <sup>188</sup>Re labeled pharmaceuticals are being developed for radiotherapy applications with the scope of delivering therapeutically significant radiation doses to malignant lesions [1].

Technetium and rhenium display similarity in their properties which arises from their position in the periodic table combined with the lanthanide contraction which causes the two elements to have almost identical radii [1b,c,2]. As a consequence, analogous Tc and Re complexes are expected to have similar physical properties (size, shape, dipole moment, formal charge, lipophilicity, etc.) and to be indistinguishable by a biological system. On this basis, matched pairs of diagnostic <sup>99m</sup>Tc and therapeutic <sup>186</sup>Re and/or <sup>188</sup>Re radiopharmaceutical complexes are being synthesized and studied. On the other hand, analogous technetium and rhenium complexes present a number of predictable differences in their chemical properties that may provide a basis for biological distinction between analogues. For example, rhenium complexes are more difficult to reduce [1b,c,3] and more substitution inert [4] than their technetium analogues. Differences in spectroscopic parameters between analogous Tc and Re complexes are also widely reported in the literature and are often related to the general chemistry of second-

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and third-row transition metals [5]. Recently [6], the dependence of ligand NMR chemical shifts on the identity of the metal center in analogous technetium and rhenium complexes has been examined for a series of hexacoordinated mono-oxo and di-oxo M(V) and M(III) complexes with the aim of linking qualitatively NMR chemical shift differences to known chemical properties.

We wish to report here on the synthesis and spectroscopic properties of four new oxorhenium complexes,  $ReO[C_2H_5SCH_2CH_2N(CH_2CH_2S)_2]Cl$  (1),  $ReO[C_2H_5 SCH_2CH_2N(CH_2CH_2S)_2[[p-CH_3OC_6H_4S]]$  (2), ReO- $[(C_2H_5)_2NCH_2CH_2N(CH_2CH_2S)_2][p-CH_3C_6H_4S](3)$ , and  $ReO[C_5H_{10}NCH_2CH_2N(CH_2C(CH_3)_2S)_2][C_6H_5CH_2S]$ (4) prepared with the  ${}^{187}\text{Re}/{}^{185}\text{Re}$  mixture of stable rhenium isotopes. The synthesis of complex 3 at tracer <sup>186</sup>Re level is also reported. These complexes belong to the class of [SNS][S] [7] '3 + 1' mixed ligand complexes [8]. The analogues to 2 and 3  $^{99m}$ TcO complexes have shown high brain uptake and significant retention in animals tested [7a,g]. Comparisons of spectroscopic and electrochemical properties of 1-4 to their technetium analogues 1'-4', are made wherever possible with the aim of enriching the existing correlation data on rhenium and technetium chemical properties.

Technetium complexes 1'-4' (prepared with the longlife <sup>99</sup>Tc isotope) are available in our laboratory from previous work, and already reported in the literature [7a,c,f].

## 2. Experimental

#### 2.1. Synthesis

Rhenium-186 is a  $\beta$ - and  $\gamma$ -emitter and special precautions should be taken.

All laboratory chemicals were of reagent grade. Benzylmercaptan, 4-methylthiophenol and 4-methoxythiophenol used as coligands were purchased from Fluka. IR spectra were recorded as KBr pellets on a Perkin-Elmer 1600 FT-IR spectrophotometer and were referenced to polystyrene. Elemental analyses were performed on a Perkin-Elmer 2400/II automatic analyzer. High performance liquid chromatography (HPLC) analysis was performed on a Waters chromatograph equipped with a 600E delivery system and a  $\mu$ -Bondapak C-18 column using 85% methanol as the mobile phase at a 1.0 ml min<sup>-1</sup> flow rate. Rhenium complexes were detected by a Waters 991 PDA photodiode array detector and a Beckman 171 radioisotope detector.

The tridentate ligands N,N-bis(2-mercaptoethyl)-2-(ethylthio)ethylamine and N,N-bis(2-mercaptoethyl)-N',N'-diethylethylenediamine were synthesized by reacting ethylene sulfide with 2-(ethylthio)ethylamine or N,N-diethylethylenediamine in an autoclave at 110°C as described previously [9]. The tridentate ligand 2,6dimethyl-4-(2-piperidin-1-ylethyl)-4-aza-2,6-heptanedithiol was prepared according to the published procedure [7c] by reacting 1-(2-aminoethyl)piperidine with 2,2'-dithiobis(2-methylpropanal) in the presence of sodium cyanohydroborate followed by reduction with Na/NH<sub>3</sub>.

The complex  $\text{ReOCl}_3(\text{PPh}_3)_2$  was prepared according to literature methods [10] while the precursor and Re(O)-citrate were generated in situ by known methods [11] as described in detail below.

The <sup>186</sup>ReO<sub>4</sub><sup>-</sup> salt was a generous gift from Mallinckrodt Medical BV, Petten, Netherlands.

# 2.2. Chloro[N,N-bis(2-mercaptoethyl)-2-(ethylthio)ethylamine]oxorhenium(V) (1)

To a stirred suspension of trichlorobis(triphenylphosphine)rhenium(V) oxide (166 mg, 0.2 mmol) in methanol (10 ml) a 1 N CH<sub>3</sub>COONa solution in methanol (2 ml, 2 mmol) was added. N,N-Bis(2-mercaptoethyl)-2-(ethylthio)ethylamine (45 mg, 0.2 mmol) was added subsequently and the mixture was refluxed until the green-yellow color of the precursor turned to green. After being cooled to room temperature (r.t.), the reaction mixture was diluted with CH<sub>2</sub>Cl<sub>2</sub> (30 ml) and then washed with water. The organic layer was separated from the mixture and dried over MgSO<sub>4</sub>. The volume of the solution was reduced to 5 ml and then 5 ml of methanol were added. Green crystals were formed by slow evaporation. Yield 35%. FT-IR (cm<sup>-1</sup>, KBr pellet): 964 (Re=O). Anal. Calc. for C<sub>8</sub>H<sub>17</sub>NOS<sub>3</sub>ClRe: C, 20.84; H, 3.72; N, 3.04; S, 20.86. Found: C, 21.14; H, 3.67; N, 2.71; S, 19.72%.

2.3. [(4-Methoxy)thiophenolato][N,N-bis(2-mercaptoethyl)-2-(ethylthio)-ethylamine]oxorhenium(V) (2)

#### 2.3.1. Method 1

To a stirred suspension of trichlorobis(triphenylphosphine)rhenium(V) oxide (166 mg, 0.2 mmol) in methanol (10 ml) a 1 N CH<sub>3</sub>COONa in methanol (2 ml, 2 mmol) was added. A mixture of N,N-bis(2-mercaptoethyl)-2-(ethylthio)ethylamine (45 mg, 0.2 mmol) and 28 mg (0.2 mmol) of 4-methoxythiophenol were added under stirring. The solution was refluxed until the green-yellow color of the precursor turned dark green. After being cooled to r.t., the reaction mixture was diluted with CH<sub>2</sub>Cl<sub>2</sub> (30 ml) and then washed with water. The organic layer was separated from the mixture and dried over MgSO<sub>4</sub>. The volume of the solution was reduced to 5 ml and then 5 ml of methanol were added. Green crystals were formed by slow evaporation. Yield 50%. FT-IR (cm<sup>-1</sup>, KBr pellet): 945 (Re=O), 1236 (Ar-O-CH<sub>3</sub>), 832 (arom). Anal. Calc. for

 $C_{15}H_{24}NO_2S_4Re: C, 31.90; H, 4.28; N, 2.48; S, 22.71.$ Found: C, 31.62; H, 4.12; N, 2.35; S, 22.47%.

## 2.3.2. Method 2

To a solution of  $\text{SnCl}_2$  (38.9 mg, 0.2 mmol) in 5 ml of 0.5 M citric acid in water  $\text{KReO}_4$  (57.8 mg, 0.2 mmol) was added. The solution of ReO-citrate was subsequently added to a mixture of *N*,*N*-bis(2-mercaptoethyl)-2-(ethylthio)ethylamine (45 mg, 0.2 mmol) and 4-methoxythiophenol (28 mg, 0.2 mmol) and stirred at r.t. for 30 min. The pH was adjusted to 9 with 0.5 N NaOH and the mixture was extracted with CH<sub>2</sub>Cl<sub>2</sub> and dried over MgSO<sub>4</sub>. Ethanol was added to the solution and after slow evaporation at r.t. green crystals precipitated and were collected by filtration. Yield 45%. Analytical data as above.

## 2.4. [(4-Methyl)thiophenolato][N,N-bis(2-mercaptoethyl)N',N'-diethyl-ethylenediamine]oxorhenium(V) (3)

The complex was prepared as described above, using either the Re(V)O-citrate or ReOCl<sub>3</sub>(PPh<sub>3</sub>)<sub>2</sub> precursor (0.2 mmol) and equimolar quantities (0.2 mmol) of N,N - bis - (2 - mercaptoethyl) - N',N' - diethylethylenediamine and 4-methylthiophenol. The complex was isolated as dark green crystals from a dichloromethanepetroleum ether (40-60°C) solution. Yield 45%. FT-IR (cm<sup>-1</sup>, KBr pellet): 939 (Re=O), 807 (arom) UV-Vis 368, 422. (nm) 230, 294, Anal. Calc. for C<sub>17</sub>H<sub>29</sub>N<sub>2</sub>OS<sub>3</sub>Re: C, 36.47; H, 5.22; N, 5.00; S, 17.18. Found: C, 36.29; H, 4.93; N, 5.29; S, 17.16%.

# 2.5. [Benzylthiolato][N,N-bis(2,2-dimethyl-2-mercaptoethyl)(2-piperidin-1-ylethyl)amine]oxorhenium(V) (4)

The complex was prepared as described above using ReOCl<sub>3</sub>(PPh<sub>3</sub>)<sub>2</sub> as the precursor (0.2 mmol) and equimolar quantities (0.2 mmol) of 2,6-dimethyl-4-(2-piperidin-1-ylethyl)-4-aza-2,6-heptanedithiol and benzylmercaptane. The complex was isolated as green–grey crystals from a dichloromethane–ethanol solution. Yield 42%. FT-IR (cm<sup>-1</sup>, KBr pellet): 954 (Re=O), 700 (arom). *Anal.* Calc. for  $C_{22}H_{37}N_2OS_3Re^*1/2$  CH<sub>3</sub>CH<sub>2</sub>OH: C, 42.44; H, 6.19; N, 4.30; S, 14.77. Found: C, 42.75; H, 6.50; N, 4.22; S, 14.68%.

## 2.6. [(4-Methyl)thiophenolato][N,N-bis(2-mercaptoethyl)N',N'-diethylethylenediamine]oxorhenium-186(V) (<sup>186</sup>Re-**3**)

 $^{186}\text{ReO}_4^-$  (2 mCi, 1 ml) was added to a solution of 1 ml of 0.5 M of citric acid (25 mg, 0.130 mmol) containing 1 mg of SnCl<sub>2</sub>. This solution was transferred to a centrifuge tube containing equimolar quantities (0.02 mmol) of *N*,*N*-bis-(2-mercaptoethyl)-*N'*,*N'*-diethyl-ethylenediamine and 4-methylthiophenol. The mixture

was agitated in a vortex mixer and left to react at r.t. for 10 min. The pH of the reaction mixture was adjusted to 9 with 0.5 N NaOH and the aqueous phase was extracted with two successive 1.5 ml portions of CH<sub>2</sub>Cl<sub>2</sub>. The combined organic extracts were dried over MgSO<sub>4</sub> and filtered. Analysis of the mixture performed by reversed phase HPLC (methanol:water, 85:15, flow rate 1 ml min<sup>-1</sup>) showed a major radioactive peak (>95%) with a retention time similar to that of complex **3**. The identity of <sup>186</sup>Re-complexes was determined by comparative HPLC studies using, as reference samples, the complexes isolated at carrier level.

## 2.7. Crystallography

A green crystal of 2 ( $0.15 \times 0.22 \times 0.50$  mm), a green crystal of 3 ( $0.10 \times 0.20 \times 0.45$  mm) and a green-grey crystal of 4  $(0.10 \times 0.15 \times 0.40 \text{ mm})$  were mounted in air. Diffraction measurements were made on a  $P2_1$ Nicolet diffractometer upgraded by Crystal Logic using Zr-filtered Mo radiation. Unit cell dimensions were determined and refined using the angular settings of 25 automatically centered reflections in the range 11 < $2\theta < 23^{\circ}$  and are shown in Table 1. Intensity data were recorded using a  $\theta - 2\theta$  scan. Three standard reflections monitored every 97 reflections showed less than 3% variation and no decay. Lorentz, polarization and  $\Psi$ -scan absorption corrections were applied using Crystal Logic software. The structures were solved by direct methods using SHELXS-86 [12] and refined by full-matrix least-squares techniques with SHELX-76 [13].

Complex 2:  $2\theta_{\text{max}} = 52^{\circ}$ , scan speed 4.5° per minute, scan range 2.5 +  $\alpha_1 \alpha_2$  separation, reflections collected/ unique/used = 3995/3720 ( $R_{\text{int}} = 0.0204$ )/3458, 265 parameters refined,  $[\Delta \rho]_{\text{max}} / [\Delta \rho]_{\text{min}} = 1.132 / -0.741$  (e Å<sup>-3</sup>),  $[\Delta/\sigma]_{\text{max}} = 0.025$ . Hydrogen atoms of C(1), C(6), C(8), C(14) and C(15) were introduced at calculated positions as riding on bonded atoms, the rest were located by difference maps and refined isotropically. All non-hydrogen atoms were refined anisotropically.

Complex 3:  $2\theta_{\text{max}} = 47^{\circ}$ , scan speed 1.5° per minute, scan range 2.35 =  $\alpha_1 \alpha_2$  separation, reflections collected/ unique/used = 3412/3031 ( $R_{\text{int}} = 0.0349$ )/2382, 269 parameters refined,  $[\Delta \rho]_{\text{max}} / [\Delta \rho]_{\text{min}} = 1.561/-0.916$  (e Å<sup>-3</sup>),  $[\Delta/\sigma]_{\text{max}} = 0.022$ . Hydrogen atoms of C(3), C(4), C(5), C(8), C(9), C(10), C(16) and C(17) were introduced at calculated positions as riding on bonded atoms, the rest were located by difference maps and refined isotropically. All non-hydrogen atoms were refined anisotropically.

Complex 4:  $2\theta_{\text{max}} = 49^{\circ}$ , scan speed 4.5° per minute, scan range 2.7 =  $\alpha_1 \alpha_2$  separation, reflections collected/ unique/used = 4976/4532 ( $R_{\text{int}} = 0.0378$ )/3262, 280 parameters refined,  $[\Delta \rho]_{\text{max}}/[\Delta \rho]_{\text{min}} = 6.722/-0.976$  (e Å<sup>-3</sup>) in the vicinity of the heavy metal,  $[\Delta/\sigma]_{\text{max}} =$ 0.036. All hydrogen atoms were introduced at calcu-

Table 1 Summary of crystal, intensity collection and refinement data for complexes 2, 3, and 4

	2	3	4	
Formula	C <sub>15</sub> H <sub>24</sub> NO <sub>2</sub> S <sub>4</sub> Re	C <sub>17</sub> H <sub>29</sub> N <sub>2</sub> OS <sub>3</sub> Re	C <sub>23</sub> H <sub>40</sub> N <sub>2</sub> O <sub>1.5</sub> S <sub>3</sub> Re	
Formula weight	564.80	559.81	650.98	
a (Å)	9.610(2)	13.188(1)	16.720(6)	
b (Å)	9.628(2)	7.542(1)	11.013(3)	
c (Å)	11.791(2)	21.193(1)	16.747(5)	
α (°)	108.307(8)			
β (°)	67.735(6)	103.260(2)	113.44(1)	
γ (°)	90.166(8)			
$V(Å^3)$	950.04	2051.74	2829.08	
Ζ	2	4	4	
$D_{\text{calc}}/D_{\text{meas}}$ (Mg m <sup>-3</sup> )	1.974/1.96	1.812/1.80	1.528/1.50	
Space group	$P\overline{1}$	$P2_1/c$	$P2_{1}/c$	
Temperature (K)	296	296	296	
Radiation $\lambda$ (Å)	Μο Κα 0.71073	Μο Κα 0.71073	Μο Κα 0.71073	
Absorption coefficient ( $\mu$ ) (cm <sup>-1</sup> )	65.70	59.90	43.50	
Octants collected	$\pm h, -k, \pm l$	$\pm h, -k, l$	$\pm h, k, -l$	
$w = 1/\sigma^2(F_{\rm o}) + gF_{\rm o}^2$	g = 0.0001	unit weights	g = 0.0002	
sig = $[\Sigma w( F_o  -  F_c )^2/(N - P)]^{1/2}$	1.39 <sup>a</sup>	4.21 <sup>b</sup>	3.73°	
$R = \Sigma \ F_{\rm o}  -  F_{\rm c}  / \Sigma  F_{\rm o} $	0.0235ª	0.0392 <sup>b</sup>	0.0732°	
$R_{\rm w} = (\Sigma w ( F_{\rm o}  -  F_{\rm c} )^2 / \Sigma w  F_{\rm o} ^2)^{1/2}$	0.0336ª	0.0454 <sup>b</sup>	0.0950°	

<sup>a</sup> For 3458 reflections with  $F_{o} > 6\sigma(F_{o})$ .

<sup>b</sup> For 2382 reflections with  $F_{o} > 3.6\sigma(F_{o})$ .

<sup>c</sup> For 3262 reflections with  $F_{o} > 6\sigma(F_{o})$ .

lated positions as riding on bonded atoms. All non-hydrogen atoms were refined anisotropically. The ethanolic solvent molecule diffused during data collection and was refined isotropically with occupation factors fixed at 10.50.

#### 2.8. Electrochemistry

Voltammograms were recorded on a PAR model 174A polarographic analyzer operated in conjuction with a model 175 Universal programmer. An undivided three-electrode cell was used with a Pt working electrode ( $0.2 \text{ cm}^2$ ), an Ag wire as the reference and a Pt wire as the counter electrode.

## 2.9. NMR studies

<sup>1</sup>H (250.13 MHz) and <sup>13</sup>C (62.90 MHz) NMR spectra were recorded on a Bruker AC 250E spectrometer. Samples were prepared in CDCl<sub>3</sub>. Chemical shifts were relative to TMS. Spectral parameters have been previously reported in the literature [7b,c,d,e].

## 2.9.1. Calculation of $\Delta G^{\neq}$

The coalescence region for the resonances under investigation was initially determined by obtaining spectra at 5°C intervals. Spectra were then obtained in the coalescence region at 0.5°C intervals in order to determine the coalesence temperature ( $T_{\rm C}$ ).

Complex 3: For C-1/C-4,  $T_{\rm C} = 7^{\circ}$ C (280.0 K),  $\Delta \nu$  in the absence of exchange = 42.8 Hz. For C-2/C-3,  $T_{\rm C} = 16.5^{\circ}$ C (289.5 K),  $\Delta \nu$  in the absence of exchange = 100.2 Hz. Both exchanging pairs give  $\Delta G_c^{\neq}$  values in complete agreement with each other and, since the difference in coalescence temperature is small, the average  $\Delta G_c^{\neq}$  is reported as representative of the complex.

Complex 4: For C-7/C-9,  $T_{\rm C} = -17.0^{\circ}$ C (256.0 K),  $\Delta v$  in the absence of exchange = 11.2 Hz, and for the corresponding protons on C-7/C-9,  $T_{\rm C} = -9.5^{\circ}$ C (263.5 K),  $\Delta v$  in the absence of exchange = 18.3 Hz. Both <sup>13</sup>C and <sup>1</sup>H data give  $\Delta G_c^{\neq}$  data in complete agreement with each other and, since the coalescence temperature is not appreciably affected in going from <sup>13</sup>C to <sup>1</sup>H, the average  $\Delta G_c^{\neq}$  is reported as representative of the complex.

## 3. Results and discussion

Complexes 1-4 are stable in the solid phase and in solution. They are less soluble in CHCl<sub>3</sub> than their technetium analogues. They give green (complexes 1-3) to green-grey (complex 4) crystals as opposed to the technetium complexes that give dark red (complexes 1'-3') to brown (complex 4') crystals.

The Re=O stretch for complexes 1, 2, 3, and 4 occurs at 964, 945, 939, and 954 cm<sup>-1</sup>, respectively. These values are well within the range of the Re=O stretch reported in the literature for some very well character-



Fig. 1. ORTEP diagram of complex 2 with 50% thermal probability ellipsoids showing atomic labeling scheme.

ized Re=O complexes [5]. The Tc=O stretch of the corresponding complexes 1', 2', 3', and 4' occurs at 943 [7a], 920 [7a], 910 [7f] and 934 [7c] cm<sup>-1</sup>, respectively. This difference in oxometal stretching frequency of ca. 20 cm<sup>-1</sup> between analogous ReO and TcO complexes has been reported in the literature for other ligand systems like diaminedithiol [5a,b,e] and diamidedithiol [5f] and has been attributed to the greater orbital overlap of the 5d orbitals of rhenium compared to the 4d orbitals of technetium [5i].

## 3.1. Crystallography

ORTEP diagrams of complexes 2, 3 and 4 are given in Figs. 1-3, respectively. Selected bond distances and angles for the three complexes are given in Table 2. All three complexes have the syn configuration with the side chain on the coordinated nitrogen cis to the oxo group. The oxorhenium moiety is coordinated to a tridentate ligand having an SNS donor set and to a monodentate thiol. The coordination geometry about rhenium(V) in complexes 2 and 3 is distorted trigonal bipyramidal with the sulfur atoms of the tridentate ligand and the oxo group occupying the basal plane while the nitrogen atom of the SNS ligand and the thiol are directed at the apices. Rhenium lies 0.096 Å (for 2) and 0.082 Å (for 3) out of the basal plane toward the monodentate thiol. In the case of complex 4 the coordination sphere can be described as trigonally distorted square pyramidal with the oxo group at the apex. This different description is a result of the calculation of the trigonality index  $\tau$  ( $\tau = 0$  for a perfect square pyramid,



Fig. 2. ORTEP diagram of complex  $\mathbf{3}$  with 50% thermal probability ellipsoids showing atomic labeling scheme.

 $\tau = 1$  for a perfect trigonal bipyramid) which in our complexes is 0.66, 0.63 and 0.48 for **2**, **3**, and **4**, respectively.

The Re=O, Re–S and Re–N bond distances in 2, 3, and 4 were found in the ranges observed in analogous oxorhenium and oxotechnetium complexes. The Re=O bond distance is ca. 1.68 Å. The Re–S bond distances in 2 and 3 range from 2.271(3) to 2.280(1) Å for the



Fig. 3. ORTEP diagram of complex 4 with 50% thermal probability ellipsoids showing atomic labeling scheme.

Table 2 Selected bond distances (Å) and angles (°) for complexes 2, 3, and 4

	2	3	4	
Bond distances (Å)				
Re-S(1)	2.274(1)	2.271(3)	2.261(4)	
Re-S(2)	2.280(1)	2.278(3)	2.273(5)	
Re-S(3)	2.305(1)	2.312(3)	2.259(4)	
Re-N(1)	2.215(3)	2.212(8)	2.24(1)	
Re-O(1)	1.698(3)	1.678(8)	1.68(1)	
Bond angles (°)				
S(1)-Re- $S(2)$	121.0(1)	121.0(1)	127.5(2)	
S(1)-Re- $S(3)$	90.0(1)	87.0(1)	90.1(1)	
S(2)–Re–S(3)	85.0(1)	85.5(1)	84.3(2)	
S(1) - Re - N(1)	84.1(1)	83.6(2)	82.9(3)	
S(2)-Re-N(1)	83.1(1)	83.3(3)	82.1(3)	
S(3) - Re - N(1)	160.8(1)	159.0(3)	156.2(3)	
S(1)-Re-O(1)	118.6(1)	120.1(3)	115.6(5)	
S(2)-Re-O(1)	119.3(1)	118.4(3)	116.5(5)	
S(3)-Re-O(1)	103.8(1)	104.6(3)	103.0(5)	
N(1)-Re- $O(1)$	95.1(1)	96.3(4)	100.5(5)	

bonds in the basal plane, while a reasonable lengthening is observed for the Re–S apical bonds (2.305(1) and 2.312(3) Å for 2 and 3, respectively). In the analogous oxotechnetium complexes 2' and 3' the Tc-S bond lengths observed are in the same ranges. The Re-N bond distance is ca. 2.21 Å in both 2 and 3 a fact that is consistent with the Tc-N bond lengths found in 2' and 3'. In complex 4, the Re-S bond lengths range from 2.259(4) to 2.273(5) Å, as in the case of the analogous oxotechnetium complex 4'. The Re-N bond distance (2.24(1) Å) is slightly longer than usual (2.0-2.21 Å) [14] as was also found in 4' [7c]. The bond angles between the atoms of the basal plane of the trigonal bipyramidal complexes 2 and 3 are close to the ideal value of 120° (118.4(3)-121.0(1)°) but the S(3)-Re-N(1) angles are away from 180° (160.8(1) and 159.0(3)° for 2 and 3, respectively) showing a degree of distortion. In the case of the trigonally distorted square pyramidal complex 4, the angles between the opposite atoms of the basal plane are 156.2(3) and 127.5(2)° for S(3)-Re-N(1) and S(1)-Re-S(2), respectively.

The two five-membered rings defined by the atoms Re, S(1), C(1), C(2), N(1) and Re, S(2), C(3), C(4), N(1) exist in the envelope form. In **2** and **3**, atoms C(2) and C(3) adjacent to nitrogen are ca. 0.60 and ca. 0.65 Å displaced from the mean plane defined by the remaining four. This seems to be the case in a series of analogous oxotechnetium and oxorhenium complexes showing distorted trigonal bipyramidal geometry. But in complex **4**, as in its oxotechnetium analogue **4**', atoms C(2) (which is bonded to the coordinated nitrogen) and C(4) (which carries two methyl substituents) are 0.55 and 0.62 Å displaced from the mean plane of the other four atoms. The torsion angles of the tridentate backbone S(1)–C(1)–C(2)–N(1) and N(1)–C(3)–

C(4)-S(2) are 48.10 and 52.85° for 2 and 47.95 and 51.52° for 3. These angles are different in 4 (-45.54 and 40.06°, respectively) as a result of the different orientation of the tridentate ligand about the oxorhenium group. The piperidine ring in 4, exists in the stable chair form with C(15) and C(12) being 0.70 and 0.61 Å above and below the mean plane defined by the other four atoms.

#### 3.2. Electrochemistry of 3 and 3'

The electrochemical behavior of complex 3 and of its technetium analogue 3' was studied in CH<sub>3</sub>CN at r.t. The cyclic voltammetric data are shown in Fig. 4. Both complexes give rise to (at potential scan rates ranging from 50 to 500 mV s<sup>-1</sup>) voltammograms of little interest with no apparently reversible systems present. Lack of reversibility has been also reported for oxotechnetium complexes with tetradentate Schiff base ligands [15]. The shape of the voltammograms is quite similar for both complexes. In the anodic region, complex 3 displays peaks at 1.01 and 1.33 V while complex 3' displays peaks at 1.00 and 1.41 V. On the reverse scans no cathodic waves were observed even at sweep rates of up to 500 mV s<sup>-1</sup>. The absence of the reverse electron-transfer steps indicates that the oxidized species are unstable.

In the negative potential region complex 3 shows two ill-developed waves at -0.53 and -0.64 V that could be due to reduction to the Re(IV) and Re(III) states. The technetium complex 3' shows reduction waves at



Fig. 4. Cyclic voltammograms of (A) 1 mM of complex 3 in 0.1 M  $Et_4NCIO_4/CH_3CN$  and (B) 1 mM of complex 3' in 0.1 M  $Et_4NCIO_4/CH_3CN$ . Scan rate 100 mV s<sup>-1</sup>. At a Pt working electrode and an Ag pseudo reference.

-0.18 and -0.43 V. These data are in agreement with the existing literature data according to which technetium complexes are easier to reduce than their rhenium analogues with the  $\Delta E^{\circ'}$  (Tc-Re) ranging from 150 to 320 mV for neutral complexes [16]. No anodic waves were observed on the reverse scan suggesting that reductions proceed essentially with decomposition of the complexes.

Electrochemical studies of oxotechnetiun and oxorhenium complexes with bidentate ON Schiff-base or 8-quinolinol ligands [17] as well as tridentate ONN Schiff-base ligands [5g] performed within the voltage range (+1.6 to -0.7 V) used in our study show peaks that are not observed with our complexes. Apparently, the ligating system is determinant in the access and stability of the various oxidation states in these elements.

## 3.3. NMR studies

<sup>1</sup>H and <sup>13</sup>C NMR chemical shifts for complexes 1-4 in CDCl<sub>3</sub> at 25°C are reported in Tables 3 and 4. The chemical shifts of the corresponding oxotechnetium complexes (1'-4') are included in the tables for comparison purposes.

The four complexes display the general characteristics of the class of (3 + 1) mixed ligand complexes with the side chain on nitrogen directed towards the oxygen of the Re=O core (*syn* configuration), as presented in a series of publications from this laboratory [7b,c,e,f].

Chemical exchange occurs between positions 1 and 4 as well as between 2 and 3 due to the conformational mobility of the S1-C1-C2-N-C3-C4-S2 chelated ligand backbone. Temperature studies were conducted in the range of -50 to  $55^{\circ}$ C. At r.t. (25°C) exchange takes place at intermediate rates on the NMR time scale and the resonances of protons and carbons of the S1-C1-C2-N-C3-C4-S2 chelated moieties of complexes 2, 3, and 4 as well as of the benzyl group of complex 4 appear broad. On raising the temperature, the spectra become simpler; the increase in the rate of fluxional mobility of the ligand generates an effective plane of symmetry passing through the Re-O-N atoms so that the S1-C1-C2-N and S2-C4-C3-N parts of the chelated backbone become magnetically equivalent. On lowering the temperature, conformational motion becomes slow and the exchanging protons and carbons on S1-C1-C2-N and S2-C4-C3–N appear as separate spin systems. Fig. 5 displays the temperature dependence of the <sup>13</sup>C spectrum of complex 3 while Fig. 6 displays the temperature dependence of the <sup>1</sup>H spectrum of complex 4.

The  $\Delta G_c^{\neq}$  for the conformational inversion of the chelated S1-C1-C2-N-C3-C4-S2 ligand backbone was determined for complexes **3** and **4** in CDCl<sub>3</sub> [18]. In the case of complex **3** calculation was based on the temperature dependence of the resonances of the C1/C4 and of the C2/C3 exchanging carbons (Fig. 5). In the case of complex **4** calculation was based on the temperature dependence of the <sup>1</sup>H and <sup>13</sup>C resonances of the exchanging C-7/C-9 methyl groups. From the chemical

Table 3

<sup>1</sup>H ( $\delta_{c}$ , ppm) chemical shifts for complexes 1–4<sup>a</sup> and their corresponding technetium analogues 1'–4' in CDCl<sub>3</sub> at 25°C

	1	1′ <sup>b</sup>	2	2′ <sup>b</sup>	3	3′°	4	<b>4</b> ′ <sup>d</sup>
H-1 (H-4)endo	3.60	3.69	3.59	3.57	3.60	3.59		
H-1 (H-4)exo	2.83	3.10	2.90	2.99	2.86	2.98		
H-2 (H-3) endo	3.36	3.65	3.33	3.49	3.44	3.63	3.86	3.90
H-2 (H-3) exo	3.14	3.29	2.71	2.72	2.83	2.82	2.24	2.24
H-5	3.80	3.87	4.01	4.09	3.92	4.02	4.05	4.17
H-6	2.92	2.95	2.95	2.98	2.87	2.89	2.84	2.85
H-7	2.61	2.62	2.62	2.64	2.58	2.58	1.83	1.89
H-8	1.30	1.31	1.30	1.31	1.06	1.07	1.65	1.52
H-9					2.58	2.58	1.83	1.89
H-10					1.06	1.07	1.65	1.52
H-11 (H-15)							2.46	2.49
H-12 (H-14)							1.59	1.60
H-13							1.48	1.60
H-16							4.87	4.94
H-2' (H-6')			7.55	7.56	7.53	7.52	7.41	7.42
H-3' (H-5')			6.94	6.92	7.20	7.19	7.29	7.28
H-4′							7.17	7.18
H-7′			3.84	3.84	2.40	2.39		

<sup>a</sup> Numbering of the atoms is shown in Scheme 1.

<sup>b</sup> Data from Ref. [7b].

<sup>c</sup> Data from Ref. [7f].

<sup>d</sup> Data from Ref. [7c].

Table 4 <sup>13</sup>C ( $\delta_c$ , ppm) chemical shifts for complexes 1–4<sup>a</sup> and their corresponding technetium analogues 1'–4' in CDCl<sub>3</sub> at 25°C

	1	<b>1</b> ′ <sup>b</sup>	2	<b>2</b> ′ <sup>b</sup>	3	3′°	4	<b>4</b> ′ <sup>d</sup>
C-1 (C-4)	43.42	37.25	41.79	36.73	42.07	36.98	61.58	56.66
C-2 (C-3)	65.41	63.05	62.96	61.17	62.91	61.33	76.31	75.15
C-5	66.68	65.26	63.47	62.15	61.36	59.98	61.02	60.04
C-6	25.56	25.49	25.32	25.17	48.16	47.90	54.31	53.97
C-7	26.54	26.64	26.45	26.46	46.94	47.01	30.74	31.11
C-8	14.60	14.63	14.64	14.66	11.74	11.67	31.19	31.55
C-9					46.94	47.01	30.74	31.11
C-10					11.74	11.67	31.19	31.55
C-11 (C-15)							55.05	55.08
C-12 (C-14)							26.02	26.06
C-13							24.03	24.07
C-16							49.28	44.30
C-1′			145.04	138.25	150.05	143.46	142.07	141.65
C-2′(C-6′)			134.50	135.11	133.27	133.75	129.28	129.22
C-3'(C-5')			113.58	113.45	128.79	128.69	128.24	128.29
C-4'			158.54	158.91	136.31	136.86	126.38	126.42
C-7′			55.25	55.26	21.16	21.33		

<sup>a</sup> Numbering of the atoms is shown in Scheme 1.

<sup>b</sup> Data from Ref. [7b].

<sup>c</sup> Data from our laboratory.

<sup>d</sup> Data from Ref. [7c].



Scheme 1.

shift difference of the exchanging peaks in the absence of exchange and from the coalescence temperature,  $\Delta G_c^{\neq}$  was calculated to be  $13.8 \pm 0.1$  kcal mol<sup>-1</sup> for complex 3 and  $13.4 \pm 0.1$  kcal mol<sup>-1</sup> for complex 4. These values are in agreement with the value of  $13.7 \pm$ 0.1 kcal mol<sup>-1</sup> reported from our laboratory for the fluxional motion of the syn isomer of the ReO- $[(C_2H_5)_2NCH_2CH_2N(CH_2CH_2S)_2][SC_6H_4OCH_3]$  [7e] indicating that minor structural changes such as the presence of the methyl groups on the ligand backbone, different substituents on the N-side chain, or different para-substituents on the aromatic thiol do not appreciably affect the mobility of the ligand. On the contrary, the replacement of the aromatic thiol coligand by a smaller group makes the complex more flexible as was evidenced in the case of complex 1 where a chlorine atom is in the place of the aromatic thiol. At r.t., <sup>1</sup>H and <sup>13</sup>C resonances for complex 1 are sharp and no significant change is observed in the spectra down to - 55°C.

The chemical shifts of geminal protons of the S1– C1–C2–N and S2–C4–C3–N chelated backbone are differentiated according to their vicinity to the Re=O core. Protons pointing towards the oxygen (*endo* protons) appear at higher frequencies than those pointing away from the oxygen (*exo* protons). In the present study, the observed differences between *endo* and *exo* protons range from 1.6 (protons on C-2/C-3 of complex 4) to 0.2 ppm (protons on C-2/C-3 of complex 1).

The aromatic ring substituent has little effect on the chemical shifts of protons and carbons of the chelated ligand backbone, since variation of the *para*-substituent

from  $CH_3$  (complex 3) to  $OCH_3$  [7e] to  $NO_2$  [19] produces no significant changes in the chemical shifts of the ligand backbone atoms. This fact indicates that electronic properties of the ring are not transmitted to the chelated part of the ligand through the metal core in this type of complex.

The data in Table 3 show that coordinated ligand protons appear at very similar chemical shifts in analogous Re=O and Tc=O complexes. The observed differences  $\Delta \delta_{\rm H}$  (Re–Tc) range from  $\pm 0.01$  to 0.30 ppm and cannot be associated with specific positions in the molecule. Lack of metal dependence of the proton NMR chemical shifts has been observed in various classes of homologous technetium and rhenium complexes [6]. On the contrary, the <sup>13</sup>C data in Table 4 show metal dependence. Specifically, carbons close to the metal core appear more deshielded in the rhenium complexes compared to the technetium. The difference  $\Delta \delta_{\rm C}$  (Re–Tc) for the carbons that are connected to the metal through a sulfur atom (carbons C-1/C-4 and C-1' in complexes 2 and 3) ranges from 4.9 to 6.8 ppm and is higher than the difference of 1.0 to 2.4 ppm observed for the carbons connected to the metal through a nitrogen atom (carbons C-2/C-3 and C-5). Similar differences are present in the <sup>13</sup>C data reported for homologous technetium and rhenium diaminedithiol [5b] and diamidedithiol [5c] complexes.

As has been previously reported [7e], technetium complexes of the '3 + 1' type are more flexible than their rhenium analogues giving at r.t. sharp, motionally averaged NMR spectra. The  $\Delta G_c^{\neq}$  has been calculated for the TcO[(C<sub>2</sub>H<sub>3</sub>)<sub>2</sub>NCH<sub>2</sub>CH<sub>2</sub>N(CH<sub>2</sub>CH<sub>2</sub>S)<sub>2</sub>][(*p*-CH<sub>3</sub>-



Fig. 5. <sup>13</sup>C NMR spectra (range  $\delta_{\rm C}$  68.1–38.7) of complex 3. At – 20°C exchanging carbons C-1/C-4 and C-2/C-3 appear as separate peaks. As the temperature is raised the peaks coalesce (7°C is the coalesence temperature for C-1 and C-4) and finally give rise to sharp average peaks.

 $OC_6H_4S)$ ] complex and was found to be 1.9 kcal mol<sup>-1</sup> lower than that of the rhenium analogue [7e].

## 4. Concluding remarks

We have shown that the action of the tridentate SN(R)S aminodithiol ligand on a suitable  $ReO^{3+}$  precursor in the presence of a monodentate ligand gives stable, neutral and lipophilic oxorhenium complexes of the '3 + 1' type. The complexes formed have the same structure as those formed with oxotechnetium and the same ligand system. Analogous oxorhenium and oxotechnetium complexes display similar chemical characteristics with a few exceptions. Differences were observed in the frequency of the oxometal stretch (ca. 20 cm<sup>-1</sup> higher for Re=O than Tc=O), the NMR chemical shifts of carbons close to the metal core (rhenium has a deshielding effect relative to technetium) as well as in the fluxional mobility of the ligand backbone (rhenium complexes are less flexible than their



Fig. 6. <sup>1</sup>H NMR spectra (range  $\delta_{\rm H}$  5.30–2.64) of complex 4 at different temperatures. The effect of the fluxional motion of the ligand on the appearance of the benzylic protons (H-16) is clearly displayed. At  $-50^{\circ}$ C the diastereotopic benzylic protons appear as two separate doublet peaks. As the temperature is raised the two peaks broaden and at 25°C they have coalesced into one broad peak. At 50°C one sharp average peak characteristic of fast exchange is present. The rest of the peaks in the spectra are similarly affected by the exchange phenomena.

technetium analogues). In addition, in the electrochemical study the oxorhenium complex 3 proved harder to reduce than its oxotechnetium analogue 3'.

It was shown for complex **3** that the macroscopic chemistry is successfully transferred to the <sup>186</sup>Re tracer level in the same way that the <sup>99</sup>Tc chemistry is transferred to the <sup>99m</sup>Tc level [7g]. Preliminary biodistribution studies show that complex <sup>186</sup>Re-**3** has a similar biodistribution pattern to the <sup>99m</sup>Tc-**3**' complex [20]. Our findings suggest that mixed ligand systems can serve as the basis for the development of target-specific radiopharmaceuticals (<sup>186</sup>Re and <sup>188</sup>Re) for therapeutic purposes.

#### 5. Supplementary material

Tables of crystal data, fractional atomic coordinates and anisotropic thermal parameters, full listings of bond distances and angles (14 pages) are available from the author on request.

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