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Rhenium and technetium-99m complexes with coenzyme M (MESNA)

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Received 6th May 2003, Accepted 18th June 2003
First published as an Advance Article on the web 4th July 2003

New rhenium and technetium-99m complexes with the monodentate thiol $HSCH_2CH_2SO_3Na$ (coenzyme M, MESNA) have been prepared for radiopharmaceutical purposes. Using the '3 + 1' approach, the anionic rhenium complex $[ReO(SCH_2CH_2SCH_2CH_2S)(SCH_2CH_2SO_3)]^-$ was prepared in two different ways: (1) reaction of MESNA with the complex $[ReO(SCH_2CH_2SCH_2CH_2S)Cl]$; and (2) reaction of the tridentate ligand $S(CH_2CH_2SH)_2$ with the MESNA complex $[ReO(SCH_2CH_2SO_3Na)_4]^-$. The structure of this '3 + 1' complex was determined by X-ray crystallographic studies, showing the characteristic $\{ReOS_4\}$ coordination around the metal atom. The sulfonate group of the coordinated MESNA is located far from the rhenium metal and near to the sodium cations. Chromatographic analysis of the reaction products after subsequent addition of MESNA and the tridentate ligand to the 99m-Tc gluconate precursor revealed the formation of a mixture of the '3 + 1' technetium complex $[^{99m}TcO(SCH_2CH_2SCH_2CH_2S)(SCH_2CH_2SO_3)]^-$ and the complex with the monothiol $[^{99m}TcO(SCH_2CH_2SO_3Na)_4]^-$. The limited solubility of the '3 + 1' rhenium complex in water may explain the high yield obtained in the rhenium synthesis compared with the lower yield observed in the same reaction with the homologous technetium-99m complexes.

Introduction

The coordination chemistry of technetium and rhenium plays an important role in the design and synthesis of new radiopharmaceuticals for nuclear medicine. Compounds with the radionuclide ^{99m}Tc are routinely used for diagnostic imaging due to their availability and nuclear properties.[1] Rhenium complexes are structural models of the technetium complexes, since the homologous compounds display very similar coordination parameters and physical properties. In addition, rhenium complexes with the nuclei ^{186}Re and ^{188}Re have attractive properties because they are β-emitters with therapeutically-useful energy.[1,2] Thus, a wide range of complexes with these metals have been reported, some of which are currently used in nuclear medicine.[1]

Sodium 2-mercaptoethane sulfonate (Coenzyme M,[3] MESNA) is a simple compound with pharmaceutical applications. It is a non-toxic drug that exerts a uroprotective effect in cancer chemotherapy by reducing the urotoxic effects of the oxazaphosphorine antineoplastic alkylating agents.[4] It has also been used as a protective drug to reduce the nephrotoxicity of carboplatin.[5] However, the metal complexes with this simple thiol have been poorly studied. Previous reports are limited to the anti-tumor activity of the organotin(IV) compounds and to the interaction with some transition metals *in vitro* and *in vivo*.[6]

In the present study we have synthesised new rhenium and technetium complexes with this ligand. These new anionic complexes could be useful as kidney radiopharmaceuticals in view of: (a) their anionic nature;[7] (b) their low molecular weight,[7] and (c) the properties of small molecules with sulfonate groups, which are substrates for the renal anion transport system.[8]

Ligands with sulfonate groups have scarcely been used to prepare new complexes for radiopharmaceutical applications. However, two noteworthy examples are a sulfonate derivative of mercaptoacetyltriglycine[8] and a ternary ligand system with sulfonated phosphines used to prepare rhenium-labelled biomolecules.[9] The first was fully characterised by X-ray analysis. However, the second group of complexes was characterised only by spectroscopic methods since monocrystals could not be isolated. This is a common occurrence in metallic complexes with uncoordinated sulfonate groups. It is therefore not surprising that, although complexes with sulfonated phosphines have been widely studied, only a few of them have been characterised by X-ray analysis.

In the present study, the '3 + 1' approach[10] was used to prepare new anionic rhenium and technetium complexes with MESNA. This principle can lead to tridentate/monodentate mixed ligand complexes with the monodentate thiol MESNA using an appropriate tridentate ligand such as $HSCH_2CH_2XCH_2CH_2SH$ (HS–X–SH; X = S, NR). Based on the '3 + 1' concept, a wide range of neutral complexes has been studied[10] for radiopharmaceutical uses and a family of cationic[11] complexes has also been described. However, as far as we know no anionic complexes have been reported. In addition, the hydrophobic character of these complexes can be easily modulated by means of the R group when X = NR. If R is a long hydrophobic chain the combination of this characteristic with the hydrophilic properties of MESNA can lead to a family of new amphiphilic rhenium complexes with attracting properties, because these metal complexes can lead to supramolecular arrangements.[12]

Experimental

General

All synthesis and manipulations of rhenium complexes were performed under nitrogen by standard Schlenk tube techniques. The NMR spectra were recorded by the Servei de Ressonància

DOI: 10.1039/b305042d

Magnètica Nuclear de la Universitat Autònoma de Barcelona on a Bruker AC250 instrument. All chemical shifts are reported in ppm and are referenced with respect to residual protons in the solvents for ^{1}H spectra and to solvent signals for ^{13}C spectra. Infrared spectra were recorded on a Perkin-Elmer FT-2000. Electrospray mass spectra were recorded in negative-ion mode in methanolic solutions by the Serveis Científico-Tècnics de la UB using a VG-Quattro (Micromass) instrument. The ligands MESNA and bis(2-mercaptoethyl)sulfide (Fluka) are commercially-available and were used without further purification. The rhenium precursors $[NBu_4][ReOCl_4]$,[13] $[ReO(SCH_2CH_2SCH_2CH_2S)Cl]$[14] and rhenium gluconate[15] were prepared according to previously-published procedures. Sodium pertechnetate was obtained from the commercial ^{99}Mo/^{99m}Tc generators Amertec II (Amersham).

HPLC analysis was conducted on a Waters 600 Millennium chromatography system coupled to both a Waters 486 tunable absorbance detector set and a Gabi γ-detector obtained from Raytest. Separations were achieved on a C-18 Hamilton PRP-1 column (10 μm, 4.1 × 250 mm) eluted with a binary gradient system at a flow rate of 1 mL min^{-1}. Mobile phase A consisted of aqueous 0.01 M NaH_2PO_4 and 0.01 M tetrabutylammonium bromide, while mobile phase B was pure methanol. The elution profile was a linear gradient from 50% B to 95% B from 0–14 min, this composition being held for 3 min. This was followed by a linear gradient from 95% B to 50% B for 3 min, and the column was reequilibrated with this composition for 20 min prior to the next injection.

Thin-layer chromatography (TLC) was performed on 200 mm PALL ITLC-SG plates developed with dichloromethane : acetone (65 : 35). In the technetium studies, the plates were analysed in a BIOSCAN System 200 Imaging Scanner.

Rhenium complexes

Synthesis of Na[ReO(SCH$_2$CH$_2$SCH$_2$CH$_2$S)(SCH$_2$CH$_2$SO$_3$)]. *Method A.* A solution of MESNA (70 mg, 0.45 mmol) in water (1 mL) was added to a suspension of $[ReO(SCH_2CH_2SCH_2CH_2S)Cl]$ (142 mg, 0.36 mmol) in water (5 mL). The resulting solution was stirred at room temperature for 12 h and it slowly darkened to yield a dark brown solution. The resulting solution was filtered to eliminate any residual insoluble material and cooled to 4 °C. A solid precipitated as crystalline brown needles was formed. This solid was separated by filtration, washed with cold water and dried *in vacuo*. Yield: 119 mg (59%).

Method B. A solution of MESNA (1.11 g, 6.8 mmol) in water (3 mL) was added to 25 mL of a rhenium gluconate solution (1.7 mmol). The resulting solution was stirred at room temperature for 3 h and a brown solution was formed. A solution of bis(2-mercaptoethyl)sulfide (147 μL, 1.53 mmol) in acetone (20 mL) was then added dropwise and the resulting solution was stirred at room temperature for 12 h. The HPLC analysis of the resulting solution showed two main signals at the retention times of 7.7 and 9.8 min, assigned to the complexes $[ReO(SCH_2CH_2SCH_2CH_2S)(SCH_2CH_2SO_3)]^-$ and $[ReO(SCH_2CH_2SO_3Na)_4]^-$, respectively. The integration of the two signals led to a similar value. This solution was cooled at 4 °C and brown needle crystals were separated, collected, washed with cold water and dried *in vacuo*. Yield: 0.61 g (74%).

The spectroscopic data of the products prepared by methods A and B were identical.

Elemental analysis. Found: C, 13.67; H, 2.65; S, 28.22. $C_6H_{16}NaO_6ReS_5$ requires C, 13.00; H, 2.91; S, 28.96%. IR (KBr, cm^{-1}): 1190, 1052 (SO_3); 954 ($\nu_{Re=O}$). NMR data. ^{1}H NMR (250 MHz, D_2O): δ 2.10 (2H, $SCH_2CH\mathit{H}_{exo}SCH\mathit{H}_{exo}CH_2S$), 3.11 (2H, $SCH\mathit{H}_{exo}CH_2SCH_2CH\mathit{H}_{exo}S$), 3.25 ($SCH_2\mathit{C}H_2SO_3$), 4.05 ($SC\mathit{H}_2CH_2SO_3$), 4.10 (2H, $SCH_2CH\mathit{H}_{endo}SCH\mathit{H}_{endo}CH_2S$), 4.32 (2H, $SCH\mathit{H}_{endo}CH_2SCH_2CH\mathit{H}_{endo}S$). ^{13}C{^{1}H} NMR (250 MHz, D_2O): δ 30.1 ($SCH_2CH_2SO_3$), 43.8 ($SCH_2CH_2SCH_2\mathit{C}H_2S$), 46.8 ($SCH_2\mathit{C}H_2S\mathit{C}H_2CH_2S$), 54.1 ($SCH_2\mathit{C}H_2SO_3$). ES-MS (*m*/*z*): 495 ([M − Na]$^-$, 54%). TLC data: R_f = 0.7. HPLC data: t_R = 7.7 min.

^{1}H NMR simulation: The ^{1}H NMR spectrum was simulated with the gNMR 4.0 computer program[16] using the following set of values (δ/ppm, *J*/Hz): δ_A = 2.15, δ_B = 3.16, $\delta_C = \delta_{C'}$ = 3.30, $\delta_D = \delta_{D'}$ = 4.04, δ_E = 4.09, δ_F = 4.38. J_{AB} = 10.7, J_{AE} = 14.3, J_{AF} = 4.9, J_{BE} = 4.7, J_{BF} = 12.7, $J_{CC'}$ = 15.1, J_{CD} = 4.8, $J_{CD'}$ = 10.9, $J_{C'D}$ = 10.8, $J_{C'D'}$ = 4.9, $J_{DD'}$ = 15.4.

(A = $SCH_2CH\mathit{H}_{exo}SCH\mathit{H}_{exo}CH_2S$, B = $SCH\mathit{H}_{exo}CH_2SCH_2CH\mathit{H}_{exo}S$, C = $CH_2C\mathit{H}_2SO_3$, D = $SC\mathit{H}_2CH_2SO_3$, E = $SCH_2CH\mathit{H}_{endo}SCH\mathit{H}_{endo}CH_2S$, F = $SCH\mathit{H}_{endo}CH_2SCH_2CH\mathit{H}_{endo}S$).

Preparation of [ReO(SCH$_2$CH$_2$SO$_3$Na)$_4$]$^-$ solution. A solution of MESNA (0.112 g, 0.68 mmol) in MeOH was added to a solution of $[NBu_4][ReOCl_4]$ (0.100 g, 0.17 mmol) in $CHCl_3$. The resulting solution was stirred at room temperature for 3 h and a brown solution was formed. Solvents were evaporated to dryness under vacuum and the residual solid was dissolved in water (8 mL) to yield a brown solution.

This complex was also prepared from rhenium gluconate solution (1.7 mmol, 25 mL) by addition of a solution of MESNA (1.11 g, 6.8 mmol) in water (3 mL) and subsequent stirring for 3 h.

NMR data. ^{1}H NMR (250 MHz, D_2O): δ 2.95 (m, 2H, $SCH_2\mathit{C}H_2SO_3$), 3.18 (m, 2H, $SC\mathit{H}_2CH_2SO_3$). ^{13}C{^{1}H} NMR (250 MHz, D_2O): δ 33.3 ($SCH_2CH_2SO_3$), 51.9 ($SCH_2\mathit{C}H_2SO_3$). ES-MS (*m*/*z*): 855 (M$^-$). TLC data: R_f = 0. HPLC data: t_R = 9.8 min.

Technetium-99m labelling. Technetium-99m labelling was performed by addition of 10 μL of an aqueous solution of MESNA 0.055 M (0.55 μmol) to [^{99m}Tc]gluconate (1 mCi/100 μL) at room temperature and pH was subsequently adjusted to 9 by addition of NaOH solution. The labelling mixture was stirred for 30 min and the ligand $S(CH_2CH_2SH)_2$ was then added (0.55 μmol) in 10 μL of acetone, the pH being adjusted to 9. Analysis by TLC and HPLC methods equipped with γ-radiometric detector showed two peaks, assigned to the '3 + 1' complex and the complex $[^{99m}TcO(SCH_2CH_2SO_3Na)_4]^-$ by comparison with the R_f and t_R values of the homologous rhenium complexes.

TLC data (R_f): 0 ($[^{99m}TcO(SCH_2CH_2SO_3Na)_4]^-$), 0.7 ($[^{99m}TcO(SCH_2CH_2SCH_2CH_2S)(SCH_2CH_2SO_3)]^-$). HPLC data ($t_R$, min): = 7.3 ($[^{99m}TcO(SCH_2CH_2SCH_2CH_2S)(SCH_2CH_2SO_3)]^-$), 9.5 ($[^{99m}TcO(SCH_2CH_2SO_3Na)_4]^-$).

X-Ray crystallography. A prismatic crystal (0.1 × 0.1 × 0.2 mm) was selected and mounted on a MAR345 diffractometer with image plate detector. Pertinent details for the structure determination are presented in Table 1. Unit-cell parameters were determined from automatic centring of 4211 reflections ($2 < \theta < 33°$) and refined by least-square methods. Intensities were collected with graphite monochromatised Mo-Kα radiation. Lorentz-polarization and absorption corrections were made. The structure was solved by direct methods (SHELXS97)[17] and refined with the SHELXL97[17] program using 1400 reflections. Atomic scattering factors were taken from International Tables of X-ray Crystallography.[18] All hydrogen atoms were computed and refined with an overall isotropic temperature factor using a riding model. Maximum and minimum peaks in final difference synthesis were 0.784 and −0.365 e Å^{-3}.

CCDC reference number 171988.

See http://www.rsc.org/suppdata/dt/b3/b305042d/ for crystallographic data in CIF or other electronic format.

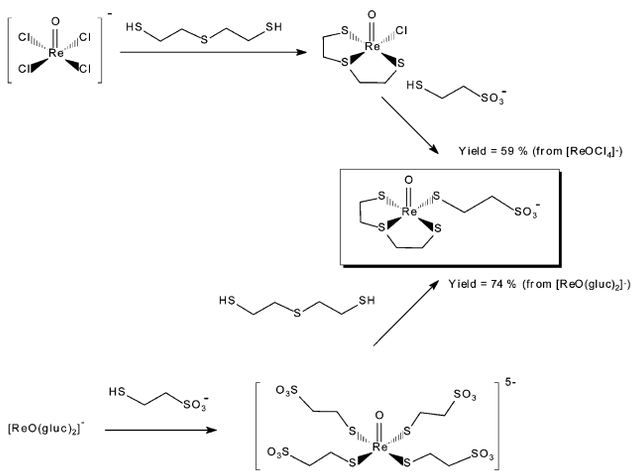
Results and discussion

(a) Rhenium complexes

The target '3 + 1' rhenium complex Na[ReO(SCH$_2$CH$_2$SCH$_2$CH$_2$S)(SCH$_2$CH$_2$SO$_3$)] was prepared by two different methods, as shown in Scheme 1. Both routes have been previously used

Table 1 Crystal data and structure refinement parameters for $Na[ReO(SCH_2CH_2SCH_2CH_2S)(SCH_2CH_2SO_3)]$

Empirical formula	$C_6H_{16}NaO_6ReS_5$
Formula mass	553.68
Crystal system	Monoclinic
Space group	$P2_1/n$
a/Å	7.702(1)
b/Å	10.009(1)
c/Å	20.625(1)
β/°	93.124(1)
V/Å^3	1587.6(3)
Z	4
T/K	293
D_c/Mg m^{-3}	2.316
Reflections total, observed ($I > 2\sigma(I)$)	3321, 1173
Parameters refined	172
R, Rw	0.0354, (0.1005)



Scheme 1

for the synthesis of '3 + 1' complexes[10,11] but, whereas reported syntheses were performed in organic solvents the present study used water as the solvent. In the first method, the complex was prepared by the simple stoichiometric reaction between a water solution of MESNA and the complex $[ReO(SCH_2CH_2SCH_2CH_2S)Cl]$ at room temperature. Although this neutral complex is not soluble in water, the initial suspension of the solid complex in the water solution of MESNA slowly changes to a dark brown solution. Brown needles of the target complex were separated from this solution by crystallisation after cooling at 4 °C. The same complex was prepared from a water solution of the precursor rhenium(V) gluconate,[15] as shown in Scheme 1. The addition of an excess of $HSCH_2CH_2SO_3Na$ to an aqueous solution of rhenium(V) gluconate led to the formation of a dark brown solution that presumably contains the substitution product of the labile gluconate ligand by the monothiol.[19] Despite several attempts the pure solid sodium salt of this anion could not be isolated because it is very soluble in water. The formation of this anion was demonstrated by ES-MS, showing the signal of the $[ReO(SCH_2CH_2SO_3Na)_4]^-$ anion and the agreement between the calculated and experimental isotopic distribution for this stoichiometry (see Fig. 1). The same complex was also synthesised from the $[ReOCl_4]^-$ precursor by reaction with 4 mol equiv. of MESNA. The HPLC analysis of the obtained solutions revealed that the complex prepared in this way was identical to the compound prepared by reaction with rhenium(V) gluconate, since a peak at a retention time of 9.8 min was observed for both complexes. The ^{1}H and ^{13}C NMR spectra in D_2O of the complex obtained from $[ReOCl_4]^-$ show the signals of the two methylene groups and is consistent with the presence of coordinated MESNA.

As is shown in Scheme 1, the reaction of an aqueous solution of $[ReO(SCH_2CH_2SO_3Na)_4]^-$ with an acetone solution of $HSCH_2CH_2SCH_2CH_2SH$ led to the target '3 + 1' complex. The

Table 2 Selected bond distances (Å) and angles (°) for $Na[ReO(SCH_2CH_2SCH_2CH_2S)(SCH_2CH_2SO_3)]$

Re–O1	1.71(1)	Re–S3	2.311(5)
Re–S1	2.294(3)	Re–S4	2.296(5)
Re–S2	2.360(5)		
O1–Re–S1	114.9(4)	S1–Re–S3	134.1(2)
O1–Re–S2	103.5(5)	S1–Re–S4	88.3 (2)
O1–Re–S3	111.0(4)	S2–Re–S3	83.5 (2)
O1–Re–S4	104.2(5)	S2–Re–S4	152.0 (2)
S1–Re–S2	83.9(1)	S3–Re–S4	82.8(2)

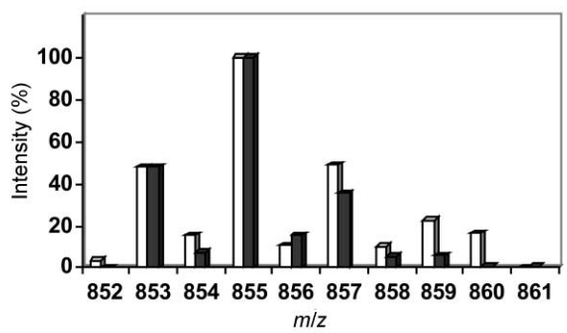


Fig. 1 Negative-ion ES mass spectrum: Calculated (white) and observed (grey) isotope pattern for the $[ReO(SCH_2CH_2SO_3Na)_4]^-$ ion.

final products synthesised by the two paths displayed in Scheme 1 exhibit identical spectroscopic parameters, in agreement with the proposed structures. Hence, the IR spectrum displays the characteristic signals of the $[Re{=}O]^{3+}$ and $[SO_3]^-$ fragments. The first is illustrated by a sharp and intense band at 954 cm^{-1}, assigned to the ν(Re=O) band, and the second by the particular group of intense signals at 1052, 1190 and 1213 cm^{-1}. The ^{1}H and ^{13}C NMR spectra at room temperature show the signals of all methylene groups. The ^{1}H spectrum shows different multiplets and the assignment of ^{1}H and ^{13}C NMR signals was based on the COSY and HMQC spectra and the previously-reported data in the literature.[20] The protons of the chelated backbone are differentiated as *endo* (those facing the Re=O bond) and *exo* (those remote from the Re=O bond), and it is well known that protons close to the Re=O bond are deshielded relative to those remote from this bond. The ^{1}H NMR spectrum was simulated (Fig. 2) using an appropriate set of values for the coupling constants, band width and chemical shift. The obtained coupling constants are consistent with the proposed structure,[21] with the exception of the absence of coupling between the endo hydrogens, which is also not observed in the COSY spectrum. The ES-MS of a water solution of the complex is also consistent with the proposed structure, since an intense peak assigned to $[ReO(SCH_2CH_2SCH_2CH_2S)(SCH_2CH_2SO_3)]^-$ (m/z 495) was observed in the negative-ion ES mass spectrum.

Crystals of $Na[ReO(SCH_2CH_2SCH_2CH_2S)(SCH_2CH_2SO_3)]$ were obtained from concentrated aqueous solutions cooled at 4 °C and their X-ray structure was determined. The structure consists of discrete $[ReO(SCH_2CH_2SCH_2CH_2S)(SCH_2CH_2SO_3)]^-$ anions and charge-balancing sodium cations. An ORTEP view of the anion is shown in Fig. 3 and selected bond distances and angles are shown in Table 2. The rhenium atom is coordinated to the tridentate ligand by the three sulfur atoms of the tridentate ligand and to the monodentate MESNA ligand by the thiolate group. The coordination geometry around the metal atom is distorted square pyramidal, the four sulfur atoms being located in the basal plane and the oxo group occupying the apical position. When compared with related '3 + 1' complexes with the $\{ReO\}^{3+}$ core and the [(SSS)(S)] donor atom system,[10,11] the bond distances were found to be similar to the published data and the distortion from regular square pyramidal geometry was also in the reported range. Thus, the

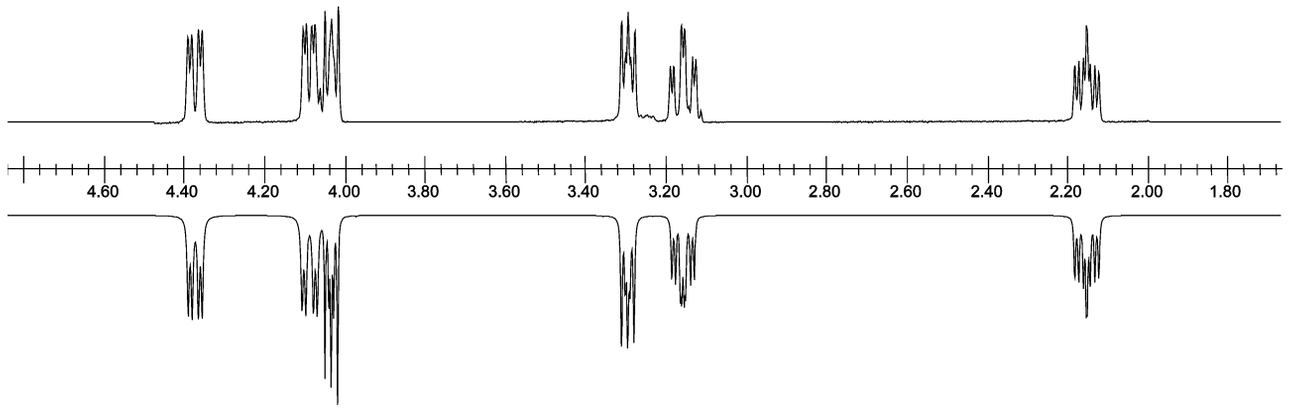


Fig. 2 The ^{1}H NMR spectrum of Na[ReO($SCH_2CH_2SCH_2CH_2S$)($SCH_2CH_2SO_3$)]. Top: experimental. Bottom: simulated.

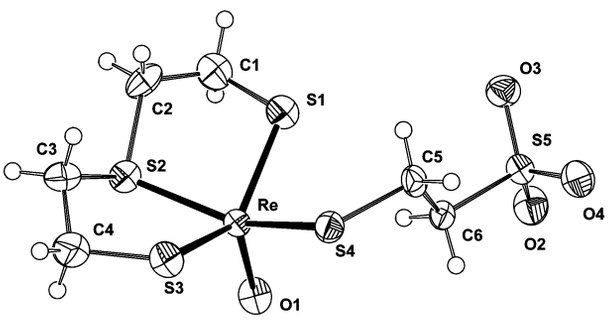


Fig. 3 ORTEP diagram of [ReO($SCH_2CH_2SCH_2CH_2S$)($SCH_2CH_2SO_3$)]$^-$ showing 50% probability ellipsoids.

value of the calculated geometric parameter† $\tau = 0.298$ shows that the arrangement around the metal in this anion is similar to those reported complexes closer to the square pyramidal geometry.[11] The sulfonate group is located away from the metal atom, whereas in reported metal complexes with the ethanesulfonate fragment the sulfonate group is frequently coordinated to the metal atom by oxygen atoms.[23] This result is relevant with regard to radiopharmaceutical applications, since the sulfonate group serves as the primary recognition site for renal tubular transport.[8] Likewise, intermolecular interactions between the sulfonate and the metal are not possible in the solid state because, as can be seen in the crystal packing (Fig. 4), all sulfonate groups face a layer of sodium cations and water molecules.

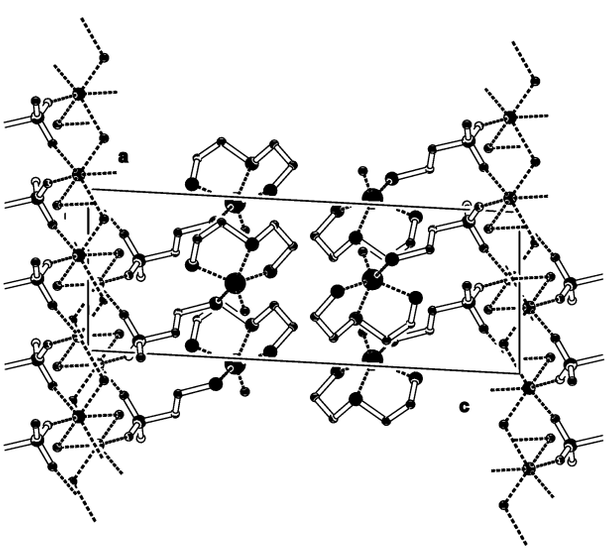


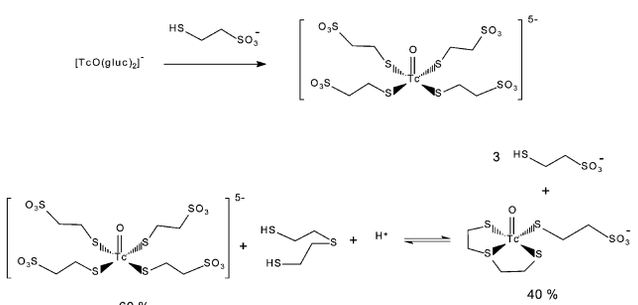
Fig. 4 Crystal packing of Na[ReO($SCH_2CH_2SCH_2CH_2S$)($SCH_2CH_2SO_3$)].

† This value is equal to zero for a square pyramidal geometry. It becomes unity for a trigonal bipyramidal geometry.[22]

Thus, the arrangement in the crystal cell can be described as alternative hydrophobic and hydrophilic layers. The hydrophilic region is formed by sodium cations, water molecules and sulfonate groups. Sodium atoms are located in a pseudo-octahedral arrangement of oxygen atoms of sulfonate groups and water molecules. The hydrophobic region can be defined by the nonpolar {$ReOS_4$} fragments which are facing each other. This result is consistent with the idea that MESNA can be used to prepare new amphiphilic rhenium complexes by the simple addition of a hydrophobic chain to the tridentate ligand.

(b) Technetium-99m complexes

The preparation of the homologous technetium-99m complexes was studied in no-carrier-added conditions by ligand substitution from the 99m-Tc gluconate precursor, as shown in Scheme 2. The 99m-Tc gluconate was prepared by reduction of $^{99m}TcO_4^-$ with stannous chloride in the presence of sodium D-gluconate and checked by HPLC analysis. An aqueous solution of MESNA was added to this solution and the pH adjusted to 9 by means of a NaOH solution. The HPLC analysis of the reaction mixture showed the presence of a single peak with a retention time of 9.5 min, in agreement with the formation of the complex with the monothiol [$^{99m}TcO(SCH_2CH_2SO_3Na)_4]^-$ since the homologous rhenium complex exhibits a similar retention time (t_R = 9.8 min). The addition of the tridentate ligand to this solution led to the formation of the expected '3 + 1' complex (see Scheme 2), the TLC and HPLC analyses showing the formation of a new compound with identical values to those of the homologous rhenium complex (R_f = 0.7, t_R = 7.7 min). However, this is not the only complex formed in these conditions and the signal assigned to the [$^{99m}TcO(SCH_2CH_2SO_3Na)_4]^-$ complex is also observed (see Fig. 5). This reaction was studied by changing the reaction conditions (pH, temperature, reaction time and reagents concentration) and, in all studied conditions, the complex with the monothiol MESNA was formed in a percentage of 60% or higher. In contrast, previous studies with neutral '3 + 1' complexes have shown the formation of the target complexes in similar conditions.[24] The different behaviour observed in the



Scheme 2

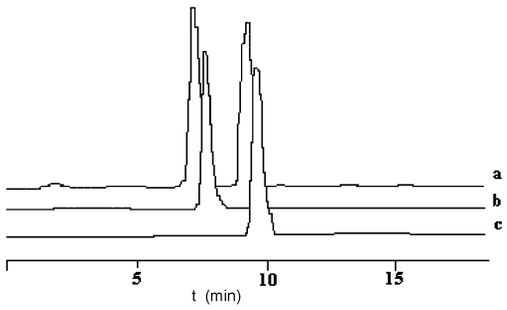


Fig. 5 HPLC traces of: (a) Reaction products of 99m-Tc gluconate with MESNA and $S(CH_2CH_2SH)_2$ (radiometric detector), (b) $[ReO(SCH_2CH_2SCH_2CH_2S)(SCH_2CH_2SO_3)]^-$, (c) $[ReO(SCH_2CH_2SO_3Na)_4]^-$.

present study may be related to the hydrophilic character of MESNA. In the synthesis of the '3 + 1' rhenium complex from rhenium gluconate (Scheme 1), after addition of the tridentate ligand there is also an equilibrium between the '3 + 1' complex and the complex with MESNA, similar to that observed with the technetium complexes (Scheme 2). This point has been corroborated by means of HPLC analysis of the reaction mixture obtained in the synthesis of the rhenium '3 + 1' complex before precipitation. This analysis shows that in this solution there is a mixture of the rhenium complexes $[ReO(SCH_2CH_2SO_3Na)_4]^-$ and $[ReO(SCH_2CH_2SCH_2CH_2S)(SCH_2CH_2SO_3)]^-$ in an almost 1 : 1 ratio, a value not very different to that observed in the technetium complexes. Therefore, in the synthesis of the rhenium '3 + 1' complex from the rhenium gluconate, the equilibrium between the two complexes is shifted to the '3 + 1' complex since it is more lipophilic and crystallises in the water medium. The technetium-99m complexes are prepared at very low concentrations, and consequently the mixture between the '3 + 1' complex and the complex with the monothiol was found under these conditions.

Acknowledgements

The authors would like to thank the Spanish Direccion General de Investigacion for financial support and Dr J. Real for helpful comments regarding use of the gNMR program.

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