SYNTHESIS OF THE SULPHONATE AND PHOSPHONATE DERIVATIVES OF MERCAPTOACETYLTRIGLYCINE. X-RAY CRYSTAL STRUCTURE OF Na₂[ReO(MERCAPTOACETYLGLYCYLGLYCYL-AMINOMETHANESULPHONATE)]·3H₂O

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Abstract

Mercaptoacetyltriglycine forms complexes with ¹⁸⁶/¹⁸⁸Re and ⁹⁹ᵐTc radionuclides that are useful in nuclear medicine because they are substrates of the renal anion transport system. However, the renal clearance of [MO(MAG₃)]²⁻ (MAG₃ = penta-anionic form of mercaptoacetyltriglycine, M = Re, Tc) complexes are less than ideal. Organic sulphonates are also transported by the renal anion transport system and phosphonates are similar to sulphonates in size and shape. In an effort to develop new ligands that form Re and Tc complexes and have improved renal clearances compared to [MO(MAG₃)]²⁻ complexes, the sulphonate and phosphonate derivatives of mercaptoacetyltriglycine were synthesized. The dianion [ReO(MAG₂-AMS)]²⁻ (MAG₂-AMS = penta-anionic form of mercaptoacetylglycylglycylaminomethanesulphonic acid) was prepared for characterization by exchange reaction of ReOCl₃(Me₂S)(OPPh₃) and isolated as the disodium salt. The structure of Na₂[ReO(MAG₂-AMS)]·3H₂O (8) was determined by X-ray diffraction. The coordination geometry is pseudo square pyramidal, with the nitrogen and sulfur donor atoms forming a square base and the oxo ligand at the apex. The deprotonated sulphonate group has a syn conformation with respect to the oxo ligand. The renal clearances of [⁹⁹ᵐTcO(MAG₂-AMS)]²⁻ and [⁹⁹ᵐTcO(MAG₂-AMP)]³⁻ were similar in rats and suggest that the difference in total charge between the SO₃⁻ and PO₃²⁻ groups is not important to renal clearance. However, their renal clearances were 40-50% less than that of [⁹⁹ᵐTcO(MAG₃)]²⁻ suggesting that the size and shape of the large tetrahedral SO₃⁻ and PO₃²⁻ groups of [⁹⁹ᵐTcO(MAG₂-AMS)]²⁻ and [⁹⁹ᵐTcO(MAG₂-AMP)]³⁻ inhibit recognition by the renal transport system compared to the small planar CO₂⁻ group of [⁹⁹ᵐTcO(MAG₃)]²⁻.

Introduction

Mercaptoacetyltriglycine (MAG₃H₅) forms complexes with Re and Tc that are substrates of the renal transport system for organic anions. In fact, derivatives of [⁹⁹ᵐTcO(MAG₃)]²⁻ and [¹⁸⁶ReO(MAG₃)]²⁻ (MAG₃ = penta-anionic form of MAG₃H₅) are being used to radiolabel antibodies in investigational cancer diagnosis and therapy, in part because the radiolabeled catabolites and metabolites are rapidly excreted by the kidneys.¹,² [⁹⁹ᵐTcO(MAG₃)]²⁻ is also used in nuclear medicine to evaluate renal tubular function. However, the renal clearance of [⁹⁹ᵐTcO(MAG₃)]²⁻ is only 50-60% that of radiolabeled [¹³¹I]-o-iodohippurate (OIH)³ which is also used clinically to evaluate renal function. Since therapeutic applications for ¹⁸⁶Re and ¹⁸⁸Re radiolabeled antibodies are under investigation and ⁹⁹ᵐTc is the preferred diagnostic radionuclide in nuclear medicine procedures, it is important to develop new ligands that not only form Re and Tc chelates but are also superior substrates for the renal anion transport system.

Organic sulphonates are also substrates for the renal anion transport system. A sulphonate group is similar to a carboxylate group in that both are mono-anionic oxo acids at physiological pH and both serve as the primary recognition site for renal tubular transport. However, a sulphonate is a large tetrahedral group while a carboxylate is a smaller planar group. The charge on a sulphonate group is also more diffuse than that of a carboxylate group because the sulphonate has an additional oxo group participating in electron delocalization.
Previously, Nosco and coworkers reported that the total clearance of \( {\text{\[^{99m}\text{TcO} \text{(MAG}_2\text{-taurine)}\]}}^2\) (MAG2 = mercaptoacetylglycylglycyl) was slower than that of \( {\text{\[^{99m}\text{TcO} \text{(MAG}_3\text{)}\]}}^2\) in the rat. (Renal clearance was not reported.) Hepatobiliary excretion was evidently significant with the taurine analogue. However, the reasons for the differences in the biological properties of \( {\text{\[^{99m}\text{TcO} \text{(MAG}_3\text{)}\]}}^2\) and \( {\text{\[^{99m}\text{TcO} \text{(MAG}_2\text{-taurine)}\]}}^2\) were unclear because the tauryl residue in \( {\text{\[^{99m}\text{TcO} \text{(MAG}_2\text{-taurine)}\]}}^2\) is a \( \beta \)-amino sulphonate. The renal clearance of \( {\text{\[^{99m}\text{TcO} \text{(MAG}_2\beta\text{-alanine)}\]}}^2\) is also inferior to that of \( {\text{\[^{99m}\text{TcO} \text{(MAG}_3\text{)}\]}}^2\).

In an effort to determine the properties that best facilitate rapid renal transport, two derivatives of MAG3H5 were synthesized. Mercaptoacetylglycylglycylaminomethanesulphonate (MAG2-AMSH5) was designed to determine the effect of the differences between a carboxylate and sulphonate group (size, shape and charge distribution) on renal clearance. However, the presence of amine and sulphonate groups on the same carbon presented synthetic problems which required a new synthetic approach. Mercaptoacetylglycylglycylaminomethylphosphonic acid (MAG2-AMPH6) was also synthesized to determine if a difference in the formal charge of the anionic group had an effect on renal clearance. The phosphonate group is similar to a sulphonate group in size and shape but it is diatomic at physiological pH. Like MAG3H5, these ligands form \( \text{[Tc(V)O]}^3+\) and \( \text{[Re(V)O]}^3+\) complexes in which the mercapto and amide donor groups are deprotonated; the terminal anionic groups are also fully deprotonated at physiological pH. Comparisons between \( {\text{\[^{99m}\text{TcO} \text{(MAG}_2\text{-AMSH)}\]}}^2\) (MAG2-AMS = penta-anionic form of MAG2-AMSH5), \( {\text{\[^{99m}\text{TcO} \text{(MAG}_2\text{-AMP)}\]}}^3\) (MAG2-AMP = hexa-anionic form of MAG2-AMPH6) and \( {\text{\[^{99m}\text{TcO} \text{(MAG}_3\text{)}\]}}^2\) are straightforward because in all three complexes the terminal residues are \( \alpha \)-amino acids.

The renal clearances of the \( {\text{\[^{99m}\text{TcO} \text{complexes with the new ligands have been measured in rats.}}^2\) The renal clearances of the sulphonate, \( {\text{\[^{99m}\text{TcO} \text{(MAG}_2\text{AMS)}\]}}^2\), and phosphonate, \( {\text{\[^{99m}\text{TcO} \text{(MAG}_2\text{-AMP)}\]}}^3\), complexes are comparable suggesting that for both complexes the stereoelectronic interaction with the renal anion transport receptor is similar. A representative Re(V) oxo complex was prepared with the sulphonate ligand for characterization and the solid-state structure of Na2[ReO(MAG2-AMS)]·3H2O was determined by X-ray diffraction methods. The structure of [ReO(MAG2-AMS)]2- is important because the terminal anionic group (SO3-) (which is expected to be conformationally flexible in solution) is syn to the oxo ligand. A syn conformation is generally believed to be important for efficient renal clearance since syn-[\[^{99m}\text{TcO} \text{(map)}\]2- (map = penta-anionic form of 2,3-bis(mercaptopetiamido)propanoate) is excreted at twice the rate of anti-[\[^{99m}\text{TcO} \text{(map)}\]2- (The carboxylate groups of the \( {\text{\[^{99m}\text{TcO} \text{(map)}\]}}^2\) complexes are bound to chelate ring carbons and do not show conformational flexibility.) Although [Ph4As][\[^{99m}\text{TcO} \text{(MAG}_3\text{H)}\] (MAG3H = tetra-anionic form of MAG3H5 in which the carboxyl group is protonated) has a syn conformation in the solid-state the structural details have not been reported. Others, [Bu4N][ReO(MAG3H)] and [Ph4P][ReO(MAG3-oABAH)] adopt anti conformations in the solid-state. Furthermore, the structure of [ReO(MAG2-AMS)]2- is unique in that the terminal anionic group (SO3-) is in its deprotonated, physiologically relevant from. All other MO(N3S) and MO(N2S2)(M=Re,\(^{99m}\text{Tc}) complexes for which crystal data are available have protonated carboxyl groups.

**Materials and Methods**

NMR spectra were obtained at 300 MHz for \(^1\text{H}\) and 75 MHz for \(^{13}\text{C}\) with a General Electric QE-300 spectrometer. The spectra were recorded in Me2SO-d6 or D2O. Chemical shifts (ppm) in Me2SO-d6 were referenced to the solvent peak 2.49 ppm \(^1\text{H}\) and 39.9 ppm \(^{13}\text{C}\) vs. TMS (tetramethylsilane). Chemical shifts in D2O were referenced to dioxane 3.53 ppm \(^1\text{H}\) and 66.5 ppm \(^{13}\text{C}\) vs TMS. Elemental analyses were performed by Atlantic Microlabs Inc., Atlanta, GA. FTIR spectra were recorded with a Bruker IFS 66 instrument. Yields are based on purified, air-dried material.

**Ligand Synthesis.**
Phthaloylglycyl chloride (PGC) mp 83-85 °C (lit. 83-85 °C), succinimyld-N-(S-
benzoylthioacetate)\(^\text{\textsuperscript{13}}\) \(\text{SbzMA-OSucc}\) \(\text{\textsuperscript{1}}\text{H NMR (MeSO-\text{d}_6)}\): 7.93 (d, 2H, SbzH), 7.69 (t, 1H, SbzH), 7.56 (t, 2H, SbzH), 3.89 (s, 2H, SCH\(_2\)), and succinimidyl-N-(S-benzoylthioacetyl)glycinate\(^\text{\textsuperscript{8}}\) \(\text{SbzMAG-OSucc}\) \(\text{\textsuperscript{1}}\text{H NMR (MeSO-\text{d}_6)}\): 8.87 (t, 1H, CONH), 7.93 (d, 2H, SbzH), 7.71 (t, 1H, SbzH), 7.57 (t, 2H, SbzH), 4.30 (d, 2H, NCH\(_2\)), 3.89 (s, 2H, SCH\(_2\)), 2.80 (s, 4H, COCH\(_2\)CH\(_2\)CO) were prepared by literature methods.

**Glycinylaminomethane sulphonate (1).** Aminomethanesulphonic acid (15.3 g, 0.14 mol) and MgO (2.8 g, 0.07 mol) were suspended in H\(_2\)O (300 ml) and cooled to 5 °C. 

**Na[S-(Benzoylthioacetyl)glycylglycylaminomethanesulphonate]-2H\(_2\)O (2).** 1 (2.0 g, 0.01 mol) was dissolved in 80% MeOH/H\(_2\)O (100 ml) by warming and adjusting the pH to 7 with 1 N NaOH. SbZMAG-OSucc (4.0 g, 0.01 mol) was added to the solution and the solution was heated at reflux for 2.5 h. The reaction mixture was left at room temperature overnight. A white solid was collected and washed with hot CH\(_3\)CN. Yield 2.5 g (50%).

**Succinimidyl-N-(S-benzoylthioacetyl)glycylglycinate (3).** SbZMA-OSucc (7.3 g, 25 mmol) was dissolved in warm EtOH (100 ml). Glycylglycine (3.3 g, 25 mmol) was dissolved in H\(_2\)O (30 ml) and the pH of the solution was brought to 7 with 1 N NaOH. The aqueous solution was added to the alcoholic solution and heated at reflux for 2 h. The solution was left at room temperature overnight. A white solid was collected and washed with MeOH. Yield 5.1 g (96%) for N-(S-benzoylthioacetyl)glycylglycine (SbZMAG\(_2\)). SbZMAG\(_2\) (5.0 g, 16 mmol) was dissolved in THF (200 ml) along with N-hydroxysuccinimide (1.9 g, 16 mmol). The solution was cooled to 0 °C. Dicyclohexylcarbodiimide (4.1 g, 20 mmol) in THF (30 ml) and added dropwise over 30 min. The reaction mixture was stirred for an additional 2 h at 0 °C and then left at room temperature overnight. Dicyclohexylurea was removed by filtration and the filtrate evaporated to dryness. The residue was crystallized from ethyl acetate and iPrOH. Yield: 5.3 g (81%; 53% overall).
Synthesis of Rhenium(V) Complexes.

ReOCl₃(Me₂S)(OPPh₃) (5): This complex was prepared by the method of Grove and Wilkinson.¹⁴ᵃ FTIR in KBr: 992 cm⁻¹ [Re=O], 1139 cm⁻¹ [P-O] (lit. 992 cm⁻¹ [Re=O], 1140 cm⁻¹ [P-O]).¹⁴ᵇ

Na₂[ReO(mercaptoacetylglycylglycylaminomethanesulphonate)]·3H₂O (6). 2 (0.37 g, 0.85 mmol) was dissolved in 63% MeOH/H₂O (16 ml) and the pH of the solution was brought to 8 with 1 N NaOH. 6 (0.55 g, 0.85 mmol) was added to the solution to give a green suspension which was heated to 85-70 °C. As the reaction proceeded, a pH of 8 was maintained by dropwise addition of 1 N NaOH. The green suspension gradually cleared to give an orange solution after 1 h. The solution was cooled to room temperature, filtered and extracted twice with CHCl₃. Ammonium hydroxide (5 ml) was added to the solution along with acetone (100 ml) and the resulting solution left to stand at 5 °C overnight. Orange microcrystals were collected and washed with acetone. Yield 0.31 g (61%). X-ray quality crystals were obtained by slow diffusion of EtOH into a saturated solution of the complex in H₂O. Anal. Cacld for C₇H₁₄Na₂N₃O₁₀ReS₂: C, 14.10; H, 2.37; N, 7.04. Found: C, 14.23; H, 2.40; N, 7.03. ¹H NMR (Me₂SO-d₆): 5.48, 4.39 (dd, 2H, J = 12 Hz, NCH₂), 4.53, 4.08 (dd, 2H, J = 18 Hz, NCH₂), 4.13, 4.06 (dd, 2H, J = 18 Hz, NCH₂), 3.75, 3.63 (dd, 2H, J = 17 Hz, SCH₂). ¹³C NMR: 192.43 (CO), 191.38 (CO), 188.58 (CO), 69.14 (NCH₂), 56.18 (NCH₂), 53.19 (NCH₂), 38.78 (SCH₂). FTIR in KBr: 972 cm⁻¹ [Re=O].

X-ray Crystallography.

An orange prism of 6 having approximate dimensions of 0.26 x 0.42 x 0.58 mm was used for data collection on a Siemens P4 diffractometer. The crystal system and cell dimensions were determined by least-squares refinement of 30 centered reflections, 10 of which were > 2σ in 2θ. Two check reflections were measured every 48 reflections and there was no significant deviation in intensities. Intensities were corrected for Lorentz and monochromator polarization effects and a semi-empirical absorption correction was applied based on azimuthal scans of 8 reflections. Systematic absences were consistent with the unique space group Pbc a. The structure was solved by Patterson methods and all non-hydrogen atoms were refined anisotropically by full-matrix least-squares procedures using SHELXTL PLUS (VMS). The water hydrogen atoms were located from difference maps and the methylene hydrogen atoms were generated at calculated (d(C-H) = 0.98 Å) positions. The hydrogen atoms were constrained using a riding model with isotropic thermal parameters fixed at 0.08. Crystallographic data are summarized in Table I.

Results

The synthesis of S-benzoyl (SBz) protected [SBzMAG₂-AMPH₄]^+ (2) using a standard activated ester coupling procedure¹⁰ was moderately successful (33% yield) at room temperature. Heating the reaction gave product that contained an impurity (by NMR) that was difficult to remove. The synthesis of [SBzMAG₂-AMSH₃]^+ (4) was completely unsuccessful using

Table I. Crystallographic Data for Na₂[ReO(MAG₂-AMS)]·3H₂O (6).

| chemical formula | C₇H₁₄Na₂N₃O₁₀ReS₂ |
|------------------|------------------|
| fw               | 596.5            |
| space group      | Pbc a            |
| Z                 | 8                |
| a (Å)            | 18.039 (3)       |
| b (Å)            | 9.774 (2)        |
| c (Å)            | 18.474 (3)       |
| volume (Å³)      | 3257.2 (10)      |
| dcalcd (g/cm³)   | 2.43             |
| μ (mm⁻¹)         | 7.91             |
| λ (Å)            | 0.71073 (Mo Kα)  |
| T (K)            | 298              |
| min./max. transm.| 0.0005 /0.0066   |
| R (%)            | 5.97             |
| Rw (%)           | 6.98             |
| goodness-of-fit  | 1.86             |

Synthesis of the Sulphonate and Phosphonate Derivatives of Mercaptoacetylgliglycine. X-Ray Crystal Structure of Na₂[ReO(Mercaptoacetylglycylglycylaminomethanesulphonate)]·3H₂O
the activated ester coupling procedure. α-Amino sulphonic acids decompose to aldehyde, sulfur dioxide and ammonia under acidic and alkaline conditions apparently because the free electron pair on the nitrogen participates in the formation of an intermediate imine followed by loss of a proton and hydrogen sulfite.15

\[
\text{NH}_2\text{-CH(R)}\text{-SO}_3\text{H} \rightarrow \text{NH=CH(R)} + \text{SO}_3\text{H}^+ + \text{H}^+ \rightarrow R\text{-CH}=\text{O} + \text{SO}_2 + \text{NH}_3
\]

Undoubtedly, the tendency of α-amino sulphonic acids to undergo such an electronic shift reduces their nucleophilicity and the lack of any reactivity between aminomethanesulphonic acid (AMS) and the relatively stable succinimidyld ester (SBzMAG2-OSucc) was unanticipated but not surprising.

N-(carbobenzoxy)glycine and AMS were coupled using isobutylchloroformate by Frankel and Moses16 in the late 1950’s (43% yield). However, removal of the protecting group by treating with HBr to give glycyaminomethanesulphonic acid (1) resulted in an overall yield of 8%. In the present study, phthaloylglyclyl chloride (PGC) and AMS were coupled based on the method of Sheehan and Frank.12 The phthaloyl protecting group was readily removed with hydrazine giving 1 in an overall yield of 38%. 1 was then coupled with SBzMAG-OSucc by the usual activated ester procedure to give [SBzMAG2-AMSH3]+. Both [SBzMAG2-AMSH3]+ and [SBzMAG2-AMPH4]+ were isolated as mono-sodium salts.

[SBzMAG2-AMSH3]+ (2) reacted smoothly with ReOCl3(Me2S)(OPPh3) in aqueous methanol resulting in a clear orange solution from which Na2[ReO(MAG2-AMS)] (6) was isolated. The presence of a Re=O group was confirmed by a strong absorption in the FTIR spectrum at 972 cm⁻¹.9-11 The coupling between geminal protons in the ¹H NMR spectrum is consistent with a square-pyramidal coordination environment.10 The ¹³C NMR signals are shifted significantly downfield from the corresponding signals in the free ligand. Similar downfield shifts were observed for the ¹³C NMR signals of the ortho, meta and para isomers of [ReO(MAG2-ABAH)]+. (MAG2-ABAH = tetra-anionic form of mercaptoacetamidoglycylglycylaminobenzoic acid). 10

[SBzMAG2-AMPH4]+ (4) also reacted smoothly with ReOCl3(Me2S)(OPPh3) in aqueous methanol resulting in a clear orange solution. However, the product could only be obtained in poor yield as a crude oil. The FTIR spectrum in KBr of the crude product showed a strong band at 975 cm⁻¹ characteristic of a Re=O stretch.9-11 The ¹H NMR spectrum included signals similar to those observed in the spectrum of Na2[ReO(MAG2-AMS)]=[3H2O (6) except that two of the signals attributable to the geminal NCH2P protons were split into triplets due to coupling with each other and phosphorus.

The structure of Na2[ReO(MAG2-AMS)]=3H2O (6) was determined by X-ray diffraction. A perspective drawing of the dianion of 6 is presented in Figure 1. Final atomic coordinates are listed in Table II and selected bond distances and angles are given in Table III. The coordination geometry is square pyramidal with Re displaced 0.75 Å out of the ligand coordination plane (S(1), N(1), N(2), N(3), mean deviation = 0.02 Å) toward the apical oxo ligand. The Re bond distances and angles are similar to those in the structures of other Re(V)O(N₃S) species: [Bu₄N][ReO(MAG₃H)],9 [Ph₄P][ReO(MAG₂-pABAH)]=H₂O,10 and [Ph₄P][ReO(MAG₂-oABAH)].10

The sulphonate group in 6 is deprotonated and adopts a syn conformation with respect to the oxo ligand. Both the protonation state and the conformation of the terminal group are important for the renal anion transport system because (1) the terminal group, in its anionic form, serves as the primary recognition site for renal tubular transport and (2) the oxo ligand is considered to be a secondary recognition site (at least in the related carboxylate species).11,17

Since syn-[⁹⁹ᵐTcO(map)]²⁺ is excreted at twice the rate of anti-[⁹⁹ᵐTcO(map)]²⁺ simultaneous recognition of the primary anionic group and the oxo ligand may be most effective when the primary anionic and secondary (oxo) recognition sites are on the same side of the metal coordination plane.11 The structure of 6 is the first example of a Re(V)ON₃S complex that satisfies the charge and conformational criteria for renal tubular transport in the solid-state. In the reported crystal structures of other renal agents ([Bu₄N][ReO(MAG₃H)],9 [Ph₄P][ReO(MAG₂-pABAH)]=H₂O,10 [PPP₄][ReO(MAG₂-oABAH)],10 [Ph₄As][⁹⁹ᵐTcO(mapH)],11
Synthesis of the Sulphonate and Phosphonate Derivatives of Mercaptoacetyltriacylglycerine. X-Ray Crystal Structure of $\text{Na}_2(\text{ReO(Mercaptoacetyl-glycyclylaminomethanesulphonate)})\cdot 3\text{H}_2\text{O}$

Figure 1. Perspective drawing of $\text{Na}_2[\text{ReO(MAG}_2\text{-AMS)}]\cdot 3\text{H}_2\text{O}$ (dianion of 6) with 50% probability for the thermal ellipsoids.

Table II. Atomic Coordinates ($x\times 10^4$) and Equivalent Isotropic Displacement Coefficients ($\text{Å}^2 \times 10^3$) for $\text{Na}_2[\text{ReO(MAG}_2\text{-AMS)}]\cdot 3\text{H}_2\text{O}$ (6).

| atom | $x$  | $y$  | $z$  | U(eq) |
|------|------|------|------|-------|
| Re   | 8547(1) | 1935(1) | 4256(1) | 52(1) |
| S(1) | 7540(2) | 710(3)  | 4629(2) | 62(1) |
| S(2) | 8499(2) | -1090(3) | 2779(2) | 57(1) |
| N(1) | 8400(6) | 2876(10) | 5212(6) | 54(3) |
| N(2) | 9595(6) | 2322(12) | 4567(6) | 61(4) |
| N(3) | 9087(5) | 195(11) | 3938(6) | 56(3) |
| O(1) | 8282(5) | 2941(9) | 3566(5) | 67(3) |
| O(2) | 7683(5) | 3543(10) | 6142(5) | 63(3) |
| O(3) | 10346(5) | 3529(10) | 5303(5) | 67(3) |
| O(4) | 10242(5) | -717(10) | 3719(6) | 76(4) |
| O(5) | 8154(5) | -2419(10) | 2674(5) | 64(3) |
| O(6) | 9160(5) | -888(11) | 2351(5) | 73(3) |
| O(7) | 7972(5) | 18(6)  | 2700(5) | 60(3) |
| C(1) | 7194(7) | 1835(13) | 5329(8) | 61(4) |
| C(2) | 7772(8) | 2845(14) | 5588(7) | 60(5) |
| C(3) | 9026(7) | 3689(16) | 5458(7) | 62(5) |
| C(4) | 9733(8) | 3185(13) | 5106(7) | 57(5) |
| C(5) | 10176(8) | 1508(17) | 4228(8) | 66(5) |
| C(6) | 9851(7) | 263(16)  | 3929(7) | 62(5) |
| C(7) | 8756(7) | -1084(13) | 3716(7) | 58(4) |
| Na(1) | 6714(3) | 307(6)  | 3024(3) | 69(2) |
| Na(2) | 8103(3) | 2250(5)  | 2272(3) | 64(2) |
| O(8) | 6653(5) | -512(9)  | 1804(5) | 67(3) |
| O(9) | 5489(5) | 273(10)  | 3358(5) | 74(3) |
| O(10) | 9409(6) | 2239(11) | 2384(6) | 82(4) |

* Equivalent isotropic U defined as one third of the trace of the orthogonalized Uij tensor.
Table III. Selected Bond Distances (Å) and Angles (deg) for Na₂[ReO(MAG₂-AMS)]·3H₂O (6).

| Bond distances (Å)     | Re-O(1)       | 1.680(9)     | Re-N(2)       | 2.011(10)    | Re-S(1)       | 2.282(3)     | Re-N(3)       | 2.046(10)    |
|------------------------|--------------|--------------|--------------|--------------|--------------|--------------|--------------|--------------|
| Bond angles (deg)      | S(1)-Re-O(1) | 108.0(3)     | N(3)-Re-O(1) | 113.8(4)     | N(1)-Re-N(2) | 82.5(3)      | Re-N(1)-C(1) | 124.1(9)     |
|                        | S(1)-Re-N(1) | 139.5(3)     | S(1)-Re-N(2) | 91.7(3)      | Re-N(1)-C(3) | 77.7(4)      | Re-N(2)-C(4) | 115.0(8)     |
|                        | S(1)-Re-N(2) | 134.1(4)     | N(1)-Re-N(3) | 78.0(4)      | Re-N(2)-C(5) | 111.2(4)     | Re-N(3)-C(6) | 116.7(9)     |
|                        | N(1)-Re-N(3) | 111.2(4)     | N(1)-Re-O(1) | 112.0(5)     | N(2)-Re-N(3) | 111.2(4)     | Re-N(3)-C(7) | 127.2(8)     |

[Ph₄P][⁹⁹TcO(mapH)]¹¹ and [Ph₄As][ReO(mapH)]¹¹ the terminal carboxyl groups are protonated and the orientation of the carboxyl group is anti to the oxo ligand in [Bu₄N][ReO(MAG₃H)]⁹ and [PPh₄][ReO(MAG₂-oABAH)].¹⁰ However, although the solid-state structure of 6 is in its deprotonated, physiologically relevant form, the observed syn conformation could be due to lattice interactions. Therefore, we examined possible interactions in the solid.

Within the crystal lattice there is an O(1), O(5), O(7), O(8) bridging network (Figure 2) that creates four Na⁺ channels with interatomic Na-Na distances of 3.3-3.4 Å running parallel to the b axis. Na(1) is surrounded in a pseudo-octahedral manner by S(1), O(7), two water oxygen atoms (O(6) and O(9)), and two oxygen atoms from symmetry related dianions (O(1a) symmetry position (1.5-x, -0.5+y, z) and O(5a) symmetry position (1.5-x, 0.5+y, z)). Na(2) is also surrounded in a pseudo-octahedral manner by O(1), O(7), two water oxygen atoms (O(10) and O(8a) symmetry.

Figure 2. Na⁺ coordination in the crystal lattice of Na₂[ReO(MAG₂-AMS)]·3H₂O (6).
position (1.5-x, 0.5+y, z), and two oxygen atoms from symmetry related dianions \(O(2a)\) symmetry position \((x, 0.5-y, -0.5+z)\) and \(O(5a)\) symmetry position \((1.5-x, 0.5+y, z)\). Na(1) and Na(2) are bridged by \(O(7)\) and \(O(5a)\) with a Na-Na distance of 3.4 Å. Na(1) is bridged to Na(2a) symmetry position \((1.5-x, -0.5+y, z)\) by \(O(1)\) and Na(2) is bridged to Na(1a) symmetry position \((1.5-x, 0.5+y, z)\) by \(O(8)\) with Na-Na distances of 3.3 Å. The syn conformation of the dianion is evidently important in the solid state since Na(2) is coordinated by both \(O(1)\) and \(O(7)\) and three out of the four bridging oxygen atoms are sulphonate and oxo species.

**Discussion**

The predominant difference between \([MO(MAG2-AMS)]^2^-\) and \([MO(MAG3)]^2^-\) (\(M = \text{Tc, Re}\)) appears to be the size and shape of the terminal anionic group (SO₃\(^-\) vs CO₂\(^-\)) based on solid-state models. The bond distances and angles associated with the metal coordination spheres of Na₂[ReO(MAG2-AMS)]·3H₂O and [Bu₄N][ReO(MAG3H)]\(^9\) are not significantly different and those of [Ph₄As][\(^{99}\)TcO(MAG3H)]\(^9\) are comparable. Although there is a difference in the conformation of the terminal anionic group of Na₂[ReO(MAG2-AMS)]·3H₂O and [Bu₄N][\(^{99}\)TcO(MAG3H)]\(^9\), there is evidence that suggests the conformation is influenced by lattice interactions involving coordination of both the oxo ligand (O(1)) and the sulphonate oxygen atoms (O(5) and O(7)) to the Na⁺ ions in an extended bridging network. Furthermore, these complexes should be conformationally flexible in solution. \([^{99m}\text{TcO}(	ext{MAG2-AMS})]^2^-\) and \([^{99m}\text{TcO}(	ext{MAG2-AMP})]^3^-\) are also expected to be structurally similar since a phosphonate group is similar in size and shape to a sulphonate group.

The renal clearances (in rats) of \([^{99m}\text{TcO}(	ext{MAG2-AMS})]^2^-\) and \([^{99m}\text{TcO}(	ext{MAG2-AMP})]^3^-\) were approximately equal\(^5\) but showed a 40-50% decrease in renal clearance compared to \([^{99m}\text{TcO}(	ext{MAG3})]^2^-\). These results suggest that the difference in total charge between the sulphonate group and phosphonate group is not important for renal clearance. If the total charge had been an important parameter, a significant difference in the clearance rates for \([^{99m}\text{TcO}(	ext{MAG2-AMS})]^2^-\) and \([^{99m}\text{TcO}(	ext{MAG2-AMP})]^3^-\) would have been observed. However, the similar decrease in the renal clearance of \([^{99m}\text{TcO}(	ext{MAG2-AMS})]^2^-\) and \([^{99m}\text{TcO}(	ext{MAG2-AMP})]^3^-\) compared to \([^{99m}\text{TcO}(	ext{MAG3})]^2^-\) suggest that the size and shape of a small planar CO₂ group is more easily recognized by the renal anion transport system than the larger tetrahedral SO₃\(^-\) and PO₃²^- groups.

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