Technetium(V) and Rhenium(V) Complexes of 2,3-Bis(mercaptoacetamido)propanoate. Chelate Ring Stereochemistry and Influence on Chemical and Biological Properties

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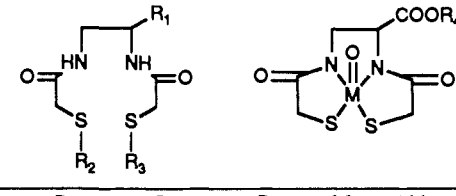
Abstract: Monoxo complexes of technetium(V) and rhenium(V) with 2,3-bis(mercaptoacetamido)propanoate (map) have been synthesized. The complexes with general formula $[Ph_4X][MO(map)]$ (where X = As, P; M = Tc, Re) were characterized by IR, visible-UV spectra, and negative ion fast atom bombardment spectroscopy. The chelate ring epimers were separated by HPLC (semipreparative reverse-phase C_{18}) isolated and crystallized as salts of $[Ph_4X][MO(map)]$. The structures of the two epimers (syn and anti) of technetium and one of the epimers (syn) of the rhenium complexes were determined by single-crystal X-ray analyses. All three complexes crystallize in the space group $P2_1/c$ and have four formula units in the unit cell. The crystal data for $[Ph_4As][syn\text{-}TcO(map)]$ are as follows: a = 12.729 (1) Å, b = 13.225 (2) Å, c = 18.318 (2) Å, β = 91.67 (1)°, v = 3082.4 (6) Å^3, and R = 0.059. For the complex, $[Ph_4P][anti\text{-}TcO(map)]$, the crystal data are as follows: a = 11.260 (2) Å, b = 23.622 (3) Å, c = 11.834 (3) Å, β = 94.52 (2)°, v = 3138 (1) Å^3, and R = 0.057. The corresponding parameters for $[Ph_4As][syn\text{-}ReO(map)]$ are 12.749 (4) Å, 13.189 (2) Å, 18.311 (6) Å, 91.63 (3)°, 3078 (2) Å^3, and 0.049. In all of the three complexes, the metal (Tc, Re) is coordinated to one oxygen (yl) atom, two sulfur (thiolate) atoms, and two nitrogen atoms (amide) in a distorted square-pyramidal geometry. The position trans to the oxygen (yl) atom is vacant. The metal atom is 0.747 ± 0.005 Å above the basal plane (N_2S_2). The mean M-O, M-N, and M-S bond lengths are 1.654, 1.979, and 2.283 Å, respectively, and are in good agreement with the bond lengths in similar complexes. There is no bonding between the carboxylic acid group of the ligand and the metal or yl oxygen atom. The tetrafluorophenyl ester derivatives of the complexes were prepared by the carbodiimide coupling method. The HPLC profile of the complexes and their ester derivatives are consistent with the polarity of the complexes and the nature of column material. Even though the structures of syn epimers of Tc and Re complexes are similar, contrary to expectations, the order of elution of the Tc and Re epimers is reversed on the C_{18} reverse-phase column with the anti Tc complex epimer significantly retarded. The influence of the chelate ring stereochemistry on the rates of renal excretion and the applications of the chelates for the radiolabeling of monoclonal antibodies are discussed.

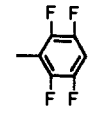
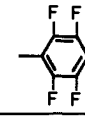
Introduction

The increased recent interest in the coordination chemistry of technetium is due to its radionuclide-based application in radiopharmaceuticals.[3-5] ^{99m}Tc is the radioisotope of choice for imaging in diagnostic nuclear medicine due to its ideal γ photon energy of 140 keV, lack of particulate radiation dose, half-life of 6 h and convenient availability.[6] A number of complexes of technetium with a wide variety of chelating agents containing O, S, N, P, and isonitrile donor atoms and groups have been evaluated as dynamic and static imaging agents for various organ systems.[7] *o*-Iodohippurate (OIH) labeled with iodine-131 is actively secreted by the renal tubular cells and as such is routinely used to evaluate renal function.[8] Due to the inferior nuclear properties of ^{131}I and high cost of production of the preferable alternative iodine radioisotope, ^{123}I, there has been a need to develop a technetium-(^{99m}Tc-) based radiopharmaceutical that can be used as a renal tubular function agent.

Davison and co-workers prepared and characterized the technetium-99 complex of 1,2-(mercaptoacetamido)ethane [DADS, for diamide disulfur, abbreviated as mae in this paper, (Table I)] as one of a series of N_2S_2 diamide/dithiolate ligands designed to coordinate the TcO^{3+} center.[9,10] The complex was formed in high yield and in high stability with the ligand forming a 5,5,5-membered set of chelate rings about the TcO^{3+} core.[10] With respect to nuclear medicine application, the ^{99m}Tc complex was found to be rapidly excreted by the kidney in a manner consistent with active tubular secretion, but was inferior to OIH in rate and

Table I



R_1	R_2	R_3	R_4	M	Abbreviations
H	H	H			mae
COOH	COC_6H_5	COC_6H_5			bmap
COOH	H	H			map
			H	Tc	$[TcO(map)]^-$
			H	Re	$[ReO(map)]^-$
				Tc	$[TcO(TFPmap)]^-$
				Re	$[ReO(TFPmap)]^-$

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specificity for renal excretion.[11] To overcome the disadvantages of Tc-mae complexes, a series of N_2S_2 ligands were synthesized by Kasina et al.,[12] Fritzberg et al.,[13] and Schneider et al.[14] These compounds included a variety of functional groups that modified the ethylene bridge portion of the parent ligand. Addition of a carboxylate group to give 2,3-bis(mercaptoacetamido)propanoate (map) and complexation by Tc resulted in the production of two complexes separable only by HPLC. Mass spectral studies showed that both components had the same molecular weight and thus were chelate ring epimers.[15] These stereoisomers, referred to as [Tc(CO_2DADS)]-A and -B (A and B denote the order of elution on reverse-phase C_{18} HPLC, abbreviated as [TcO(map)]-A and -B in this paper) differ in the disposition of the COOH group on the chelate ring syn or anti to the Tc=O group.

Studies of the renal handling of the complexes in mice showed that the A epimer has a higher excretion rate than the B epimer. Importantly, the A epimer showed a higher clearance rate than the parent TcO(mae) complex, which was comparable to OIH.[16] Moreover, nearly complete specificity for renal excretion was seen. The complexes (A and B) behaved similarly in dogs and humans, but with more pronounced differences between epimers.[17] For example, in humans 58% of [^{99m}TcO(map)]-A was excreted at 30 min as compared to only 19% of B, a remarkable difference due to the stereochemical disposition of the carboxylate group attached to the chelate ring.

In order to correlate the stereochemistry of the complexes with rate of renal excretion, we prepared, isolated, and characterized the two epimers of TcO(map) complexes using macroscopic amounts of long-lived ^{99}Tc isotope.

Because of the recent interest in the use of monoclonal antibodies in cancer therapy and diagnosis,[7,18] we have developed methods to label antibodies with ^{99m}Tc using these N_2S_2 chelating agents. The carboxylate groups on the TcO(map) chelates have been shown to not be involved in coordination to technetium, by HPLC determination of the pK_a values of the carboxylic acid group, and thus were available for conjugation to protein amine groups.[19] By derivatizing this group to an active ester group, the ^{99m}Tc chelate could be thus covalently attached to monoclonal antibodies.[20] Due to the interest in correlations of rhenium and technetium chemistry and potential radiotherapy applications of ^{186}Re and ^{188}Re,[21] we have also prepared and characterized the carboxylic acid and ester derivatives of corresponding rhenium complexes. Despite the similarities of structures and the biological properties of the carboxylate complexes of Tc and Re, subtle differences in the HPLC behavior have been observed.

Experimental Section

All chemicals used were of reagent grade. ^{99}Tc was obtained as NH_4TcO_4 from New England Nuclear. Caution! Technetium-99 is a weak β emitter (E = 0.292 meV, $t_{1/2} = 2.12 \times 10^5$ years). All the work with the isotope was performed in laboratories approved for the use of low-level radioactive materials. Precautions necessary for its use as a weak β emitter have been described elsewhere.[22-25] NH_4ReO_4 was obtained from Aldrich Chemical Co. Radioactive rhenium was obtained as $^{186/188}ReO_4^-$ from the University of Missouri Research Reactor in Columbia, MO. Infrared spectra were recorded in the range 4000–200 cm^{-1} in Nujol mulls by a Perkin-Elmer P2A3 instrument. Visible–UV spectra were recorded with a HP 8451A diode array spectrophotometer. Mass spectra (FAB, negative ion) were recorded on a Varian 731 instrument in glycerol matrix with $CHCl_3$ as solvent. HPLC was performed using Beckman Models 110 and 113 equipped with UV and γ radiation detectors. Columns used were Ultrasphere C_{18} (5 μm, 4.6 × 250 mm) and Ultrasil-AX (10 μm, 10 × 250 mm) (Beckman) and PRP-1 (Hamilton). Radiochemical detection was by a Beckman Model 170 radioisotope detector. The detectors were equipped with Hewlett-Packard 3390A integrating recorders. The pK_a values of the carboxylic acid complexes were determined by anion-exchange HPLC as described.[19]

Preparation of 2,3-Bis[(*S*-benzoylmercapto)acetamido]propanoic Acid. This compound was prepared as described.[26]

Preparation of [ReO_2(en)$_2$Cl]. The complex was prepared from $ReOCl_3(PPh_3)_2$ as described.[27]

Preparation of a Mixture of TcO(map) Epimers. A solution of 2,3-bis(mercaptoacetamido)propanoate was prepared by the addition of 57 mg (0.12 mmol) of, 2,3-bis[(*S*-benzoylmercapto)acetamido]propanoic acid to 2 mL of 1:1 ethanol/H_2O mixture and 2 mL of 1 N NaOH. Then 0.17 mL of 0.44 M $NH_4{}^{99}TcO_4$ (0.074 mmol) was added to the above solution followed by 30 mg (0.172 mmol) of sodium dithionite. The solution was heated at 80 °C for 15 min. During that time the solution turned yellow in color. The pH of the solution was adjusted to 3.0 by the addition of 1 N HCl. The precipitated benzoic acid was filtered, and the pH of the solution was adjusted to 7.0 for the HPLC separation of the A and B chelate ring epimers. The yield based on Tc was 98%. The complexes using ^{99m}Tc were prepared as described.[11]

Separation of the TcO(map)-A and -B Epimers. Aliquots of the solutions of the epimeric mixture were injected onto a semipreparative HPLC column, (5-μm C_{18} Ultrasphere, Beckman, 10.0 × 250 mm). The mobile phase used was 2% CH_3CN/0.01 M phosphate (pH = 7.0) at 3.0 mL/min flow rate. The A and B epimers were collected separately. After 40 injections, the fractions collected for each epimer were combined, concentrated, and pH adjusted to 3.0 with 1 N HCl.

Isolation of the [TcO(map)]-A Epimer. To 3.6 mg (9.9 μmol) of the complex in 1 mL of H_2O (pH = 3.0) was added 4.2 mg (9.2 μmol) of tetraphenylarsonium chloride (in 1 mL of H_2O). The precipitated tetraphenylarsonium salt was centrifuged, washed with H_2O and ether, and dried under vacuum. Crystals suitable for X-ray diffraction studies were grown by the solution-diffusion method, using ethanol and ether as solvent and precipitant, respectively.

Isolation of the [TcO(map)]-B Epimer. The procedure was the same as described for the A epimer except that tetraphenylphosphonium chloride was used instead of tetraphenylarsonium chloride. Crystals suitable for X-ray studies were grown by diffusing ether vapors onto a solution of the complex in *N*,*N*-dimethylformamide. The crystals obtained with tetraphenylarsonium as countercation were not suitable for X-ray studies.

Preparation of a Mixture of ReO(map) Epimers. 2,3-Bis[(*S*-benzoylmercapto)acetamido]propanoic acid (26 mg, 0.05 mmol) was dissolved in 2 mL of ethanol/H_2O (1:1) mixture and 2 mL of 1 N NaOH. The solution was boiled for 10 min and added dropwise with stirring to a solution of 20 mg (0.060 mmol) of ReO_2(en)$_2$Cl dissolved in 1 mL of H_2O. The reaction mixture was heated for 30 min at 90 °C, whereupon an orange solution of the complex was formed. The pH of the solution was adjusted to 3.0 with 1 N HCl. The precipitated benzoic acid was filtered, and the pH of the solution was adjusted to 7.0 for HPLC separation of the chelate ring epimers. The yield based on Re was 90%.

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Table II. Crystal Data

	$Ph_4As[TcO(map)]$-A (syn)	$Ph_4P[TcO(map)]$-B (anti)	$Ph_4As[ReO(map)]$-B (syn)
formula	$[Tc(C_7H_8O_5N_2S_2)^-][AsPh_4^+]$	$[Tc(C_7H_8O_5S_2N_2)^-][PPh_4^+]$	$[Re(C_7H_8O_5S_2N_2)^-][AsPh_4^+]$
cryst size, mm	0.2 × 0.18 × 0.1	0.25 × 0.25 × 0.08	0.32 × 0.2 × 0.05
FW	744.63	700.68	833.83
space group	$P2_1/c$	$P2_1/c$	$P2_1/c$
a, Å	12.729 (1)	11.260 (2)	12.749 (4)
b, Å	13.225 (2)	23.662 (3)	13.189 (2)
c, Å	18.318 (2)	11.834 (3)	18.311 (6)
β, deg	91.67 (1)	94.53 (2)	91.69 (3)
v, Å^3	3082.4 (6)	3138 (1)	3078 (2)
Z	4	4	4
λ(Mo Kα), Å	0.7107	0.7107	0.7107
μ, mm^{-1}	1.749	0.66	5.73
no. of measd intensities	5400	5505	4850
no. of obsd intensities	2437	3387	3082
R	0.059	0.057	0.049
R_w	0.033	0.051	0.022

Separation of the [ReO(map)]-A and -B Epimers. The procedure was identical with that used for the Tc chelate epimers except that 1% CH_3CN/0.01 M phosphate (pH = 7.0) was used as mobile phase.

Isolation of the [ReO(map)]-A Epimer. To a solution containing 4.5 mg (10 μmol) of the A epimer (pH = 3.0) was added 4.2 mg (9.2 μmol) of tetraphenylarsonium chloride dissolved in 1 mL of H_2O. The precipitated orange compound was centrifuged and washed with H_2O and ether. Attempts to grow the crystals of this epimer were not successful.

Isolation of the [ReO(map)]-B Epimer. The procedure was identical with that for A epimer. Crystals suitable for X-ray studies were grown by the solution-diffusion method using ethanol and ether as solvent and precipitant, respectively.

Preparation of [$^{186/188}$ReO(map)]. $^{186/188}ReO_4^-$ (1 mCi, 100 μL) was added to a solution of 1 mL of 0.130 M citric acid (25 mg, 0.130 mmol) containing 1 mg of $SnCl_2 \cdot 2H_2O$ (5 μmol). A 200-μL aliquot of 2,3-bis(mercaptoacetamido)propanoate (1 mg/mL, 0.79 μmol) was added to the above solution. The reaction mixture was heated for 15 min at 90 °C. The radiochemical yield of the complex was 90%.

Preparation of the 2,3,5,6-Tetrafluorophenyl (TFP) Esters of [TcO(map)] Complexes. To a solution containing 2.0 mg (5.5 μmol) of the [TcO(map)]-A or -B epimer in 0.2 M phosphate buffer at pH = 6.0 were added 18 mg (0.11 mmol) of 2,3,5,6-tetrafluorophenol (in 0.2 mL of CH_3CN) and 20 mg (0.10 mmol) of 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride (also in CH_3CN). The reaction mixture was heated at 75 °C for 30 min. The solution was cooled to room temperature and analyzed by HPLC. The yield of the ester was 25%.

Preparation of the TFP Ester of [ReO(map)]. The same procedure as above was used. Yield of the active ester was 20%.

X-ray Crystallographic Studies of [TcO(map)]-A and -B and [ReO(map)]-B. Preliminary space group and cell constant information were obtained from Weissenberg and precession photographs. Accurate cell dimensions were obtained from the angular settings of 15–20 reflections on a CAD-4F diffractometer. Intensities of three reflections were monitored periodically and there was no significant decay. Empirical corrections for absorptions were applied on the basis of azimuthal scans of three reflections whose χ angle is close to 90°. No absorption correction was applied for [TcO(map)]-A. Other relevant experimental details are given in Table II.

The structures were solved by Patterson and Fourier methods and all the non-hydrogen atoms were refined anisotropically by full-matrix least-squares procedures. The hydrogen atoms were placed geometrically and refined. The carboxyl proton for the [TcO(map)]-B epimer was located from a difference map, but could not be located in the case of [TcO(map)]-A and [ReO(map)]-B. Refinement was based on $|F|$ with weights of the form $w^{-1} = \sigma(F_0)^2$ where $(\sigma|F_0|)$ is derived from counting statistics. The function minimized was $\sum w(|F_0| - |F_c|)^2$. The highest peaks in the final difference map were 0.3 e/Å^3 for [TcO(map)]-A and -B and 0.5 e/Å^3 for [ReO(map)]-B. They were close to the heavy atom and are of no chemical significance.

X-ray 76 System computer programs were used for structure solutions and refinement. Neutral scattering factors were those of Cromer and Mann[29] for non-hydrogen atoms and Stewart, Davidson, and Simpson[30] for hydrogen atoms. Anomalous dispersion corrections for rhenium, technetium, arsenic, phosphorus, and sulfur atoms were included.[31]

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Table III. Visible–UV Spectrophotometric Data

complex	solvent	λ_{max}, nm (ϵ, M^{-1} cm^{-1})
[*syn*-TcO(map)$^-$][a]	CH_3CN	480 (sh), 366 (3550), 280 (sh)
[TcO(map)$^-$], syn + anti mixture[a]	CH_3CN	480 (sh), 366 (3550), 280 (sh)
[ReO(map)$^-$], syn + anti mixture[a]	CH_3CN	480 (40), 400 (200), 230 (sh)
[TcO(mae)$^-$][b]	CH_3CN	434 (sh), 363 (4300), 290 (sh)

[a] This study. [b] Reference 10.

Table IV. Infrared Spectral Data

complex	M=O stretch, cm^{-1}
[*syn*-TcO(map)$^-$][a]	945
[*anti*-TcO(map)$^-$][a]	950
[*anti*-ReO(map)$^-$][a]	970
[*syn*-ReO(map)$^-$][a]	970
[TcO(mae)$^-$][b]	940

[a] This study. [b] Reference 10.

Results

Synthesis. The technetium complexes were prepared readily by the reduction of TcO_4^- by sodium dithionite in the presence of the map ligand. The corresponding rhenium complexes cannot be prepared in this manner as ReO_4^- is more difficult to reduce than TcO_4^-. The [ReO(map)] complexes were prepared by exchange reactions of intermediate Re^V complexes like $ReO_2(en)_2Cl$ or Re^V–citrate with the map ligand. The citrate intermediate was not, however, isolated and characterized, but was used when formed in situ by the reduction of ReO_4^- by Sn^{2+} in citric acid. The A epimer of the technetium complex mixture was easier to crystallize than the B epimer, while the reverse was true for the rhenium pair.

The amount of the A epimer formed over the B was dependent on the pH and temperature of the reaction. By modification of reaction conditions a maximum ratio of A to B of 6:1 and 8:1 was observed for Tc and Re complexes, respectively. Once the epimers were formed they were found to be very stable from 25 to 100 °C over a pH range of 1–11.0. The conversion of one epimer to the other was not observed under these conditions and in the presence of excess ligand in free thiol form. The complexes as Ph_4X (X = As, P) salts are very stable and soluble in nonaqueous solutions. The technetium complexes are yellow and the rhenium complexes are orange. The esters were not isolated but characterized by HPLC properties and by reactions with amino acids such as lysine or hydrolysis back to the corresponding carboxylate complexes. The complexes of Tc and Re at carrier added level coelute on C_{18} reverse-phase HPLC with complexes prepared at the no carrier added level. This indicates correspondence of chemistry at high (to 10^{-3} M) and low (less than 10^{-6} M) concentrations of Tc and Re.

Spectroscopy. The visible–UV spectroscopic data are presented in Table III. The technetium complexes exhibit a strong band

Table V. Mass Spectral Data

complex	M^- ion
[*syn*-TcO(map)$^-$][a]	363
[*anti*-TcO(map)$^-$][a]	363
[*anti*-ReO(map)$^-$][b]	449, 451
[*syn*-ReO(map)$^-$][b]	449, 451

[a] Reference 15. [b] This study.

Table VI. Bond Lengths and Bond Angles of the Anion (M = Tc, Re)

	[TcO(map)]-B	[TcO(map)]-A	[ReO(map)]-B
	Bond Lengths, Å		
M-S(1)	2.290 (2)	2.276 (4)	2.282 (2)
M-S(2)	2.281 (2)	2.286 (4)	2.284 (3)
M-N(1)	2.000 (5)	2.012 (9)	2.006 (7)
M-N(2)	2.007 (6)	1.890 (10)	1.959 (7)
M-O(1)	1.644 (5)	1.656 (7)	1.662 (5)
S(1)-C(2)	1.815 (10)	1.786 (16)	1.831 (10)
S(2)-C(3)	1.830 (11)	1.780 (19)	1.808 (11)
C(2)-C(1)	1.506 (12)	1.501 (20)	1.510 (15)
C(3)-C(4)	1.484 (14)	1.482 (23)	1.515 (16)
C(1)-O(2)	1.217 (9)	1.229 (13)	1.233 (11)
C(4)-O(3)	1.242 (10)	1.216 (18)	1.209 (13)
N(1)-C(1)	1.345 (9)	1.342 (14)	1.371 (11)
N(1)-C(6)	1.465 (10)	1.447 (15)	1.467 (12)
N(2)-C(4)	1.336 (10)	1.441 (18)	1.392 (13)
N(2)-C(5)	1.462 (10)	1.470 (17)	1.464 (11)
C(6)-C(5)	1.483 (11)	1.538 (20)	1.523 (12)
C(6)-C(7)	1.595 (12)	1.489 (18)	1.512 (14)
C(7)-O(4)	1.257 (11)	1.307 (19)	1.341 (13)
C(7)-O(5)	1.201 (11)	1.236 (17)	1.191 (12)
	Bond Angles, deg		
S(1)-M-S(2)	90.8 (1)	87.1 (1)	88.4 (1)
S(1)-M-N(1)	82.2 (2)	82.6 (3)	83.0 (2)
S(1)-M-N(2)	141.0 (2)	140.9 (3)	139.9 (2)
S(1)-M-O(1)	107.7 (2)	109.8 (3)	109.0 (2)
S(2)-M-N(1)	136.5 (2)	135.4 (3)	136.5 (2)
S(2)-M-N(2)	81.6 (2)	84.1 (3)	82.8 (2)
S(2)-M-O(1)	109.9 (2)	111.5 (3)	110.0 (3)
N(1)-M-N(2)	77.8 (2)	77.5 (3)	77.1 (2)
N(1)-M-O(1)	113.1 (2)	112.8 (4)	113.2 (3)
N(2)-M-O(1)	110.8 (2)	108.9 (4)	110.8 (3)
M-S(1)-C(2)	97.9 (3)	97.9 (5)	98.3 (3)
M-S(2)-C(3)	98.7 (4)	97.7 (6)	100.4 (4)
M-N(1)-C(6)	117.5 (4)	120.1 (7)	121.0 (5)
M-N(1)-C(1)	124.8 (5)	123.1 (8)	124.5 (6)
C(1)-N(1)-C(6)	115.8 (6)	116.6 (9)	114.2 (7)
M-N(2)-C(4)	124.1 (5)	127.0 (8)	126.5 (6)
M-N(2)-C(5)	116.3 (5)	119.8 (8)	117.3 (5)
C(4)-N(2)-C(5)	119.2 (6)	113.0 (10)	116.1 (8)
N(1)-C(1)-C(2)	113.9 (7)	114.5 (10)	113.7 (8)
N(1)-C(1)-O(2)	125.1 (7)	124.6 (10)	124.6 (9)
C(2)-C(1)-O(2)	121.0 (7)	120.9 (10)	121.7 (8)
C(1)-C(2)-S(1)	112.4 (6)	112.7 (10)	112.8 (6)
S(2)-C(3)-C(4)	112.1 (8)	116.2 (12)	113.4 (7)
C(3)-C(4)-O(3)	122.6 (8)	123.9 (14)	121.6 (10)
C(3)-C(4)-N(2)	115.6 (8)	109.7 (13)	113.0 (9)
O(3)-C(4)-N(2)	121.8 (8)	125.8 (12)	125.3 (10)
N(2)-C(5)-C(6)	105.7 (6)	107.2 (11)	109.2 (7)
C(5)-C(6)-N(1)	109.3 (6)	106.8 (10)	106.1 (7)
C(5)-C(6)-C(7)	106.6 (7)	109.9 (11)	111.7 (7)
N(1)-C(6)-C(7)	109.0 (7)	116.5 (11)	115.2 (8)
C(6)-C(7)-O(4)	112.7 (7)	113.4 (11)	113.1 (8)
C(6)-C(7)-O(5)	121.1 (8)	121.6 (14)	122.0 (10)
O(4)-C(7)-O(5)	126.0 (9)	124.8 (14)	124.7 (9)

at 366 nm, while the Re complexes absorb weakly around 480 and 400 nm and much more strongly at 230 nm. The infrared spectra show M=O stretch absorptions around 950 and 970 cm^{-1} (Table IV) for Tc and Re complexes, respectively. The negative-ion fast atom bombardment mass spectra show the expected molecular ion peaks at M^- (Table V) for the carboxylic acid complexes of Tc and Re. The molecular ion peak at M^- observed for Tc complexes is in agreement with earlier work.[15]

Crystal Structures. The bond lengths and bond angles involving the atoms of the anion are given in Table VI. The bond lengths

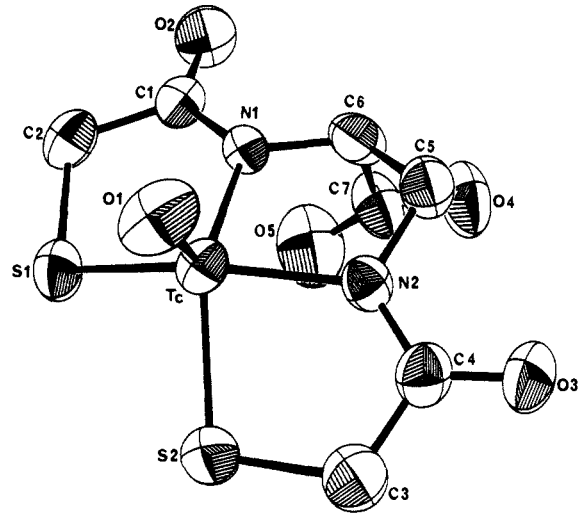

Figure 1. Perspective view of the [Tc($C_7H_8O_5N_2S_2$)] anion (isomer B). Thermal ellipsoids are drawn at the 50% probability level. Hydrogen atoms are not shown.

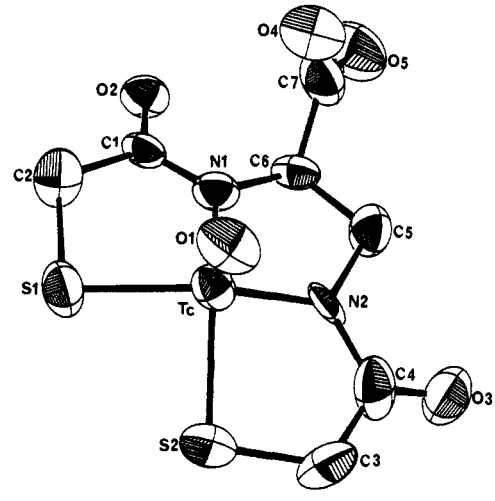

Figure 2. Perspective view of the [Tc($C_7H_8O_5N_2S_2$)] anion (isomer A). Thermal ellipsoids are drawn at the 50% probability level. Hydrogen atoms are not shown.

and bond angles between the atoms in the cations (Ph_4As^+, Ph_4P^+) are normal and are available as supplementary material. Positional parameters and U_{eq} values for the non-hydrogen atoms of the three compounds are available as supplementary material. Perspective drawings of the three complexes are shown in Figures 1-3. In all three complexes, the metal atom is coordinated to five atoms (S1, S2, N1, N2, and O1) in an approximately square-pyramidal geometry. The atoms N_1, N_2, S_1 and S_2 form a perfect basal plane in all three complexes. The average distance of Tc and Re atoms from the basal plane is 0.747 ± 0.005 Å. The structure determinations establish the identities of the [TcO(map)]-A and [ReO(map)]-B as "syn" epimers based on the metal-oxo and carboxylate group relationship and [TcO(map)]-B as the "anti" epimer.

HPLC Properties. The carboxylic acid complexes of both technetium and rhenium are very polar, but can be retained significantly on C_{18} reverse-phase HPLC columns (Table VII, supplementary material) when eluted with 2-10% organic solvent and 0.01 M phosphate buffer (pH = 7). The separation between the two epimers is greater in the case of technetium than rhenium (Figure 4). The resolution and the retention time are dependent on the pH of the mobile phase and the ionic strength of the buffer. This dependence is expected since these complexes contain ionizable carboxylic acid groups. On an anion-exchange column the difference in the retention times of the A and B epimers of both the Tc and Re complexes is the same. The ester complexes are

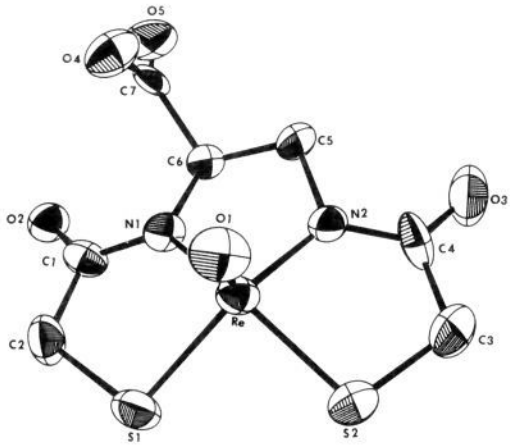

Figure 3. Perspective view of the $[Re(C_7H_8O_5N_2S_2)]$ anion (isomer B). Thermal ellipsoids are drawn at the 50% probability level. Hydrogen atoms are not shown.

very lipophilic (organic solvent 34–38% for comparable retention volume), and the differences between Tc and Re complexes in reverse-phase retention times of the epimer pairs are insignificant. The pK_a values of the Tc and Re carboxylic acid complexes were determined from the plot of the retention time versus the pH of the mobile phase. The values for all the epimers are in the range 3.1–3.2. Variation of ~0.5 pH unit in the values have been observed, depending on the column used and the ionic strength of the mobile phase. However, under the same conditions, the pK_a values of all four epimers are within 0.1 pH unit.

Discussion

The ligand, 2,3-bis(mercaptoacetamido)propanoate (map), forms stable complexes with both technetium and rhenium at oxidation level five consistent with the parent ligand, 1,2-bis(mercaptoacetamido)ethane.[10] The complexes contain a metal–monooxo core with no atom or group binding to the metal in the sixth position trans to the oxygen. The absence of a sixth group or an atom is due to the strong trans effect of oxygen and is generally observed when the ancillary donor atoms are negatively charged and function as good π donors.[32] On the other hand, the sixth position is occupied when the donor atoms are neutral and poor π donors.[23,33]

The infrared spectra of the complexes of technetium show the Tc=O stretch in the range 945–950 cm^{-1} as expected for typical complexes containing the $Tc{=}O^{3+}$ core.[10,23,32] The Re=O stretch was found 20 cm^{-1} higher than the corresponding Tc complexes, but well within the range of several well-characterized Re(V) complexes containing the $Re{=}O^{3+}$ core.[23] This difference in the stretching frequency between analogous Tc and Re complexes has been previously observed.[23,34,35] The visible–UV spectra of the technetium complexes are identical with those of the parent complex, [TcO(mae)].[10] The spectra are also similar to those of low-spin d^2 oxotechnetium complexes.[23,32a,b] The weak bands observed in the visible spectra of rhenium complexes are in the same range as observed for several low-spin d^2 rhenium complexes.[23]

The crystal structures of the complexes show that the COOH group has no interaction with the central metal atom or the metal–oxo group in any of the three complexes. The distance between O(5) and Tc in TcO(map)-B (Figure 1) is 3.81 Å while O(4) and O(1) are separated by 4.22 and 4.24 Å in [TcO(map)]-A and [ReO(map)]-B, respectively (Figures 2 and 3). The COOH hydroxyl group forms an intermolecular hydrogen bond in all three compounds. In [TcO(map)]-A and [ReO(map)]-B the H bond is with the O(2) of the symmetry-related molecule $(2 - x, 1 - y, -z)$ and the O(4)···O(2) separations are 2.68 and 2.63 Å, respectively. In [TcO(map)]-B the H bond is with O(3) at $(x, {}^1/_2 - y, -{}^1/_2 + z)$ and the O(4)···O(3) distance is 2.55 Å.

It is possible that in solution an intramolecular hydrogen bond between the COOH hydroxyl and the carbonyl oxygen O(2) could form in all three complexes. In the TcO(map)-A and ReO(map)-B structures, the O(4)···O(2) distances are 3.22 and 3.21 Å, respectively, while in TcO(map)-B the O(5)···O(2) distance is 3.17 Å. Rotation of the carboxylic acid group about the C(6)–C(7) bond could reduce all three intramolecular O···O separations to values commensurate with hydrogen-bonding interactions.

The metal–oxygen bond distances are 1.644–1.662 Å, well within the range of several well-characterized monooxo complexes of technetium and rhenium.[36,37] The metal–sulfur bond distances are in the range 2.276–2.290 Å, also consistent with other Tc and Re–thiolate complexes.[25,32a,b,35–38] The Tc–N(1) bond distances are in the range 2.000–2.012 Å. All of these parameters are in general agreement with the structural parameters reported for the TcO(mae) complex and for a large number of complexes containing the same donor atoms.[36,37,38b,d,39] The Tc–N(2) and Re–N(2) bond distances, 1.890 (10) Å in [TcO(map)]-A and 1.959 (7) Å in [ReO(map)]-B, are significantly shorter than the corresponding distance of 2.007 (6) Å in the [TcO(map)]-B and the Tc–N bond lengths reported so far in the literature. One possible reason for this shortening could be the high anisotropic thermal motion associated with the N(2) atom in [ReO(map)]-B and [TcO(map)]-A.

Of the three torsion angles that are of interest, the S(1)–C(2)–C(1)–N(1) angle is nearly equal in all three compounds, the average value being $-21.4 \pm 2°$. The torsion angle S(2)–C(3)–C(4)–N(2) shows some differences. This angle is 20(2)° for [TcO(map)]-A, but for [TcO(map)]-B and [ReO(map)]-B it is almost equal, the average angle being $11.4 \pm 1°$. The significant differences lie in the ring where the COOH group is substituted at the atom C(6). The torsion angle N(1)–C(6)–C(5)–N(2) in the syn epimers [TcO(map)]-A and [ReO(map)]-B is $21.6 \pm 7°$, whereas in the anti isomer [TcO(map)]-B it is 36.2 (8)°. This difference is also reflected in the different puckering of this five-membered ring. The ring formed by the atoms M(Tc, Re) N(1), C(6), C(5), and N(2) has a perfect envelope conformation in all of the three compounds studied. In [TcO(map)]-B (anti epimer), the atom C(5) is off the plane defined by the atoms N(1), Tc, N(2), and C(6) by 0.503 (8) Å, whereas in [TcO(map)]-A and [ReO(map)]-B (syn epimers), the atom N(2) is off by 0.440 (8) Å from the plane of the other four atoms. Thus, in addition

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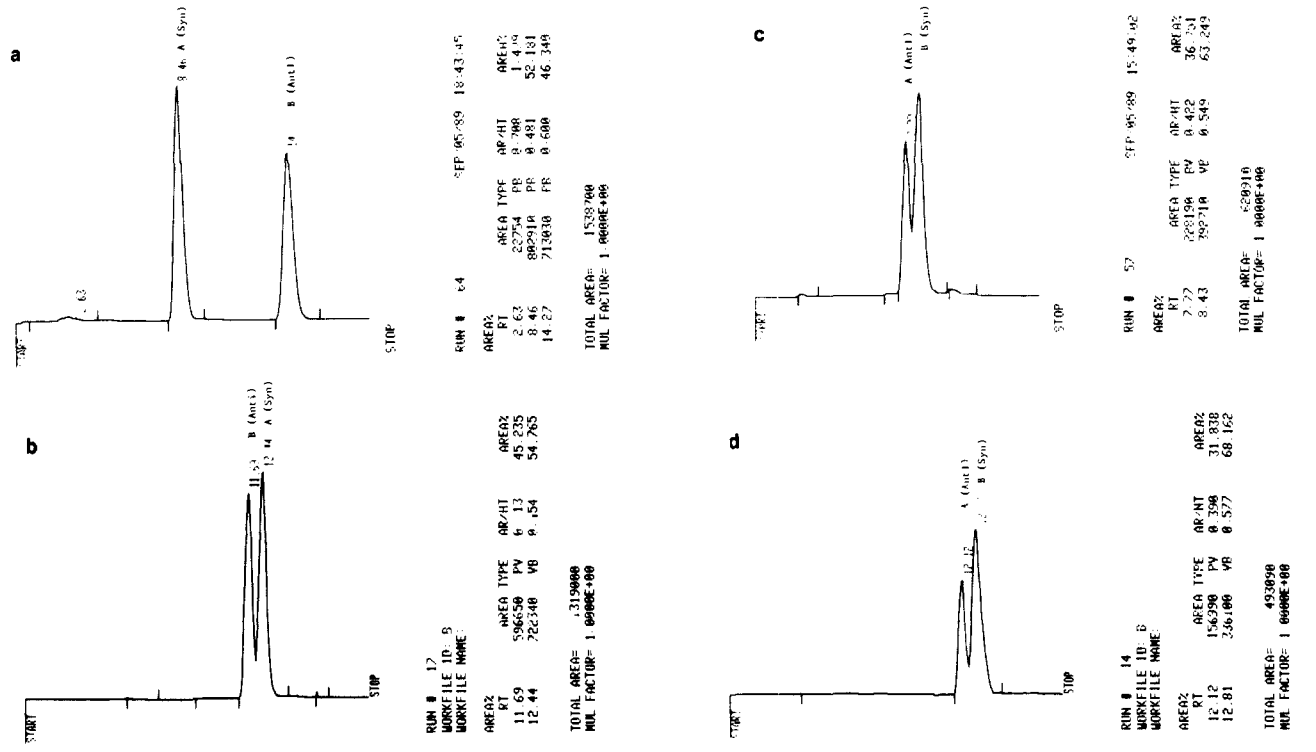

Figure 4. HPLC traces of TcO(map) and ReO(map) complexes on C_{18} reverse-phase and anion-exchange (Ax) columns. HPLC conditions are given in Table VII (supplementary material). (a) TcO(map) on C_{18} column; (b) TcO(map) on Ax column; (c) ReO(map) on C_{18} column; (d) ReO(map) on Ax column.

to the differences in the orientation of the COOH group in the syn and anti epimers, significant structural differences between the epimers are also observed in the conformation of this five-membered ring.

The HPLC profiles of Tc complexes are consistent with the polarity of the complexes and the nature of the column material interaction. For the carboxylic acid complexes the syn (A) epimer elutes first followed by anti on the C_{18} column, but anti (B) is (Table VII) eluted first followed by syn on the anion-exchange column. Conversely, when the anti carboxylic acid is esterified, the anti ester (Figure 5) elutes first followed by the syn ester. This is expected because in the syn epimer the disposition of the nonpolar ester group is more available for interaction with the alkyl groups on the C_{18} column.

In the case of map complexes of rhenium, the epimer that is retained longer on the C_{18} column was found by crystal structure analysis to be the syn in contrast to the technetium complexes. Based on the crystal structure of the B epimer, the stereochemistry of the A epimer can be assigned as "anti". Unlike the technetium complexes, the order of elution of syn (B) and anti (A) epimers of rhenium on the anion-exchange HPLC (Figure 4) was the same as on the C_{18} reverse-phase column. The order of elution of the rhenium ester complexes on C_{18} reverse-phase HPLC is the same as that of the corresponding carboxylic acid complexes. This is also in contrast to the case of technetium, where the order of elutions is inverted between the acid and ester complexes on C_{18} reverse-phase HPLC.

It was surprising that the anti epimer of the [ReO(map)] complex eluted first on the C_{18} reverse-phase column followed by the syn epimer. On the all-organic PRP column, however, the syn epimer eluted first (Table VII, supplementary material), which was consistent with the [TcO(map)] complexes. The crystal structure data and the similarity of the pK_a values indicate that there is no interaction between the COOH group and the M=O group or the metal either in solid state or in solution in all four epimers. There are no discernible qualitative or quantitative differences in the three-dimensional structures of the Tc and Re complexes that can be invoked to explain their differences in elution behavior. The difference in the elution behavior can possibly be explained on the basis of the substitution inertness of rhenium complexes compared to technetium complexes.[45] The sixth coordination site trans to the metal–oxo group in the technetium complexes is probably more labile toward substitution reactions in solution while it is inert in the rhenium complexes. Thus, the technetium complexes can interact with the solvent molecules and the column, while the rhenium complexes are inert on the time scale of HPLC.

However, this relationship cannot account for the observed retention times of the syn complexes on the C_{18} column. If the interaction of the sixth coordination position trans to the M=O group in the complexes with the stationary and mobile phases is possible, it would be more likely to happen in the syn epimers rather than in the anti epimers. In the anti epimers the proximity of the COOH group to the sixth coordination position might hinder that interaction. Based on the relative kinetic inertness of Re complexes toward substitution reactions, the interaction with the stationary and mobile phases would be slower compared to the technetium complexes and hence the retention times of the Tc and Re syn epimers would be quite different. However, the observed retention times of the syn epimers (Figure 4) are approximately the same on the C_{18} column. On the other hand, the retention times of the anti epimers are quite different, as the technetium complex is retained 7.31 min longer (Figure 4) than the rhenium complex. Without the structural data of the *anti*-ReO(map) complex, it is difficult to rationalize the inversion of the order of elution of Tc and Re complexes based solely on the difference in the substitution labilities of the complexes. In addition to the kinetics of substitution reactions, minor differences in the polarity of the $Re{=}O^{3+}$ and the $Tc{=}O^{3+}$ cores and the interactions of the complexes with the residual silica groups on the column under low percentage organic modifier conditions are also likely to affect the order of elution of the epimers.

The Tc epimer A (syn) of the carboxylic acid is excreted faster than B (anti) in humans, the former probably being more easily recognized by the kidney receptors because the COOH is on the same side of the Tc=O group above the chelate plane. Animal studies of rhenium complexes have shown stereochemical agreement with the Tc series in that the [^{186}ReO(map)]-B epimer (syn)

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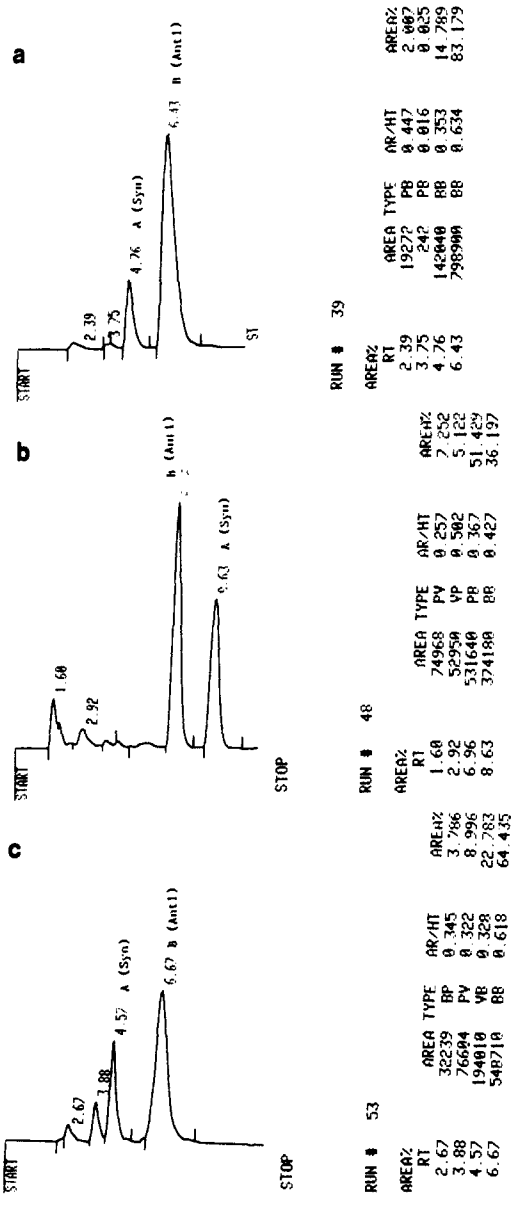
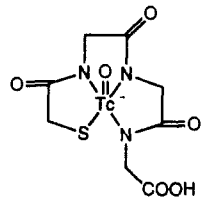


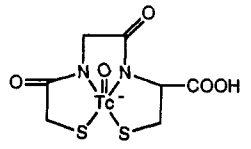
Figure 5. HPLC traces of acid and TFP ester complexes of technetium on C_{18} column. Conditions are given in Table VII (supplementary materials). (a) TcO(map); (b) TcO(TFPmap); (c) hydrolyzed TcO-(TFPmap).

is excreted more rapidly than the A epimer (anti).[40]

Without structural knowledge of the membrane transport proteins of the proximal tubular cells of the kidneys, and thus the ability to model binding interactions, it is difficult to correlate the stereochemical relationships and differences in renal handling



oxo(mercaptoacetylglycyl glycylglycine)technetate (V)
TcO(MAG$_3$)



oxo(mercaptoacetylglycylcysteine) technetate (V)

Figure 6. Structures of oxo(mercaptoacetylglycylglycylglycine)technetate(V) and oxo(mercaptoacetylglycylcysteine)technetate(V) complexes.

of the epimers in animals and humans. In a simplistic view, the syn epimer may allow more effective interaction of the carboxylate and oxo groups with the transport system, an interaction consistent with the Despopolous model.[41] This relationship of oxo and carboxylate groups is similar in the oxo(mercaptoacetylglycyl-glycylglycine)technetate(V) complex in which stereoisomers involving the carboxylate group are precluded.[42] In fact, the ^{99m}Tc(MAG$_3$) complex (Figure 6) is handled even more efficiently by the renal tubular system and is now in routine clinical use.[43] More subtle considerations will be ultimately needed to understand the structure–renal handling relationship, however, as the renal handling of the positional ^{99m}Tc-N_2S_2 carboxylate isomer, oxo-(mercaptoacetylglycylcysteine)technetate(V) (Figure 6) exhibited nearly identical renal handling of chelate ring epimers in mice, rabbits, and dogs, but not in humans.[13] Further understanding of the structure–renal handling relationship awaits crystal structure determinations of related complexes.

The results of the structural characterization of the Tc and Re complexes of 2,3-bis(mercaptoacetamido)propanoate provide information that may be useful in eventual understanding of the active transport of metal complexes by the kidneys and other in vivo interactions. Further, as ^{186}Re and ^{188}Re radiopharmaceuticals become developed for therapy, as evidenced by the development of ^{186}Re-labeled antibodies,[44] the understanding of the chemical, structural, and reactivity properties between Tc and Re become important. The structural correlations reported here provide support for the development of agents as diagnostic (^{99m}Tc)/therapeutic (^{186}Re/^{188}Re) matched pairs.

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Supplementary Material Available: HPLC data (Table VII), fractional atomic coordinates and equivalent isotropic factors (Table VIII), and bond lengths and bond angles (Table IX) of cations in [TcO(map)]-A, [TcO(map)]-B, and [ReO(map)]-B (4 pages). Ordering information is given on any current masthead page.