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$Re(CO)_3$ Complexes Synthesized via an Improved Preparation of Aqueous *fac*-$[Re(CO)_3(H_2O)_3]^+$ as an Aid in Assessing ^{99m}Tc Imaging Agents. Structural Characterization and Solution Behavior of Complexes with Thioether-Bearing Amino Acids as Tridentate Ligands

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Parallel studies of the preparation of Re and ^{99m}Tc agents aid in interpreting the nature of tracer ^{99m}Tc radiopharmaceuticals. Aqueous solutions of the *fac*-$[^{99m}Tc(CO)_3(H_2O)_3]^+$ cation are gaining wide use and are readily prepared, but such solutions of the *fac*-$[Re(CO)_3(H_2O)_3]^+$ cation (**1**) are not so easily accessible. Herein we describe a new, reliable, and straightforward preparation of aqueous solutions of **1**, characterized by HPLC and ESI-MS. Treatment of solutions of **1** with thioether-bearing amino acids, AAH = *S*-methyl-L-cysteine (MECYSH), *S*-propyl-L-cysteine (PRCYSH), and methionine (METH), gave high yields of *fac*-$Re(CO)_3$AA complexes. X-ray crystallographic and NMR analyses indicated that $MECYS^-$, $PRCYS^-$, and MET^- were bound in *fac*-$Re(CO)_3$AA complexes as tridentate monoanionic ligands through amino, thioether, and α-carboxyl groups. In CD_3OD, ^1H NMR spectra have broad signals but have two sets of signals at –10 °C, consistent with two isomers with different configurations at the pyramidal sulfur; these interconvert slowly on the NMR time scale at low temperatures. Indeed, the crystal structure of the *fac*-$Re(CO)_3$(PRCYS) reveals a mixture of the two possible diastereoisomers. *S*-(Carboxymethyl)-L-cysteine ($CCMH_2$) and **1** gave two products, **5A** (kinetically favored) and **5B** (thermodynamically favored). X-ray crystallographic analyses of a crystal of **5B** and of a 1:1 cocrystal of **5A** and **5B** showed that **5A** and **5B** are diastereoisomers with the $CCMH^-$ α-carboxyl group dangling. In addition to the amino and thioether groups, the *S*-(carboxymethyl) carboxyl group is coordinated, a feature that slows interconversion of diastereoisomers relative to the other *fac*-$Re(CO)_3$AA complexes because interconversion can now occur only after the rupture of Re–ligand bonds. These N, O, and S tridentate adducts are quite stable, and the grouping has promise in $^{99m}Tc(CO)_3$ tracer development.

Introduction

Technetium-99m (^{99m}Tc), the most prevalent diagnostic radionuclide in nuclear medicine,[1−8] has ideal nuclear properties that make it the radionuclide of choice for diagnostic imaging. Radiopharmaceutical synthesis utilizing a $\{^{99m}Tc^{V}O\}^{3+}$ core has received the most attention.[2,9−12]

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For example, the $\{^{99m}Tc^{V}O\}^{3+}$ core is used in renal imaging agents such as ^{99m}TcO(MAG3) (MAG3 is mercaptoacetylglycylglycylglycine)[13−16] and ^{99m}TcO(EC) (EC is ethylenedicysteine).[17] Recently, the numerous synthetic advantages of the $^{99m}Tc^{I}$ precursor $[^{99m}Tc(CO)_3(H_2O)_3]^+$ have shifted the focus of ^{99m}Tc radiopharmaceutical development to agents with a $\{^{99m}Tc(CO)_3\}^+$ core.[18−22]

Nonradioactive Re analogues are useful for understanding the chemistry of the radioactive ^{99m}Tc species and for ligand design. This analogue approach has been used widely to develop and to evaluate agents with the $\{^{99m}Tc^{V}O\}^{3+}$ core.[11,23,24] The preparations of $Tc^{V}O$ and $Re^{V}O$ species are analogous; however, the method of preparation of $[^{99m}Tc(CO)_3(H_2O)_3]^+$, reduction of $^{99m}TcO_4^-$ in the presence of CO in water,[25,26] is inefficient for preparing the precursor of the Re^{I} congener. $[Re(CO)_3(H_2O)_3]^+$ has been obtained mainly by the hydrolysis of $(NEt_4)_2[Re(CO)_3Br_3]$,[27,28] prepared by a tedious reaction of $Re(CO)_5Br$ with NEt_4Br that may lead to other products such as $(NEt_4)[cis\text{-}Re(CO)_4Br_2]$,[29] $(NEt_4)_2[Re_2(CO)_6Br_4]$,[28] and $(NEt_4)[Re_2(CO)_7Br_3]$.[29] Obtaining reasonable yields of $(NEt_4)_2[Re(CO)_3Br_3]$ requires the use of a large volume of dry diglyme under N_2, strict control of the reaction temperature, and removal of the excess of NEt_4Br. The need for these demanding experimental conditions prompted us to seek a better preparation of aqueous solutions of the $[Re(CO)_3(H_2O)_3]^+$ precursor, bypassing the $(NEt_4)_2[Re(CO)_3Br_3]$ step by solvating a rhenium pentacarbonyl synthon. Our initial studies showed that solvation of $Re(CO)_5Br$ in water was slow. Indeed, a report published after this phase of our work was completed indicates that $[Re(CO)_3(H_2O)_3]Br$ is formed from $Re(CO)_5Br$ directly in boiling water only after 24 h.[30] At a 2003 ACS meeting[31] we presented a simple, straightforward method for preparing solutions of $[Re(CO)_3(H_2O)_3]^+$ from $Re(CO)_5OTf$[32] (OTf = trifluoromethanesulfonate), and here we report all details of this preparation as well as the use of the solution in synthetic studies.

We have been interested in developing radiopharmaceuticals possessing high renal clearance.[22,24,33−40] ^{99m}Tc-labeling of peptides and ligands designed to target the organic anion tubular transporter has generally led to agents with high clearance.[13,14,16,17] Small peptides are easy to synthesize and modify, are less likely than typical ligands to be immunogenic, and are more likely to exhibit rapid blood clearance. In most cases, the primary sites of interactions of the peptides are specific receptors on the outer surface of the cell membrane (extracellular). All these factors make small peptides excellent candidates for the development of target-specific radiopharmaceuticals.[41]

As a relatively soft receptor, the $\{^{99m}Tc(CO)_3\}^+$ core prefers ligands with soft sp^2 aromatic nitrogen and thioether donors.[42−45] A bifunctional approach that incorporates ligating groups such as pyridyl groups into amino acids or peptides has proved successful in labeling the $\{^{99m}Tc(CO)_3\}^+$ core.[21] However, designing pyridine rings into ligands to enhance labeling also raises the overall lipophilicity, which usually leads to labeled agents with undesirably high hepatobiliary uptake.[46] We chose to explore the direct $\{^{99m}Tc(CO)_3\}^+$ labeling of amino acids. Obviously, to form stable $^{99m}Tc(CO)_3$ complexes, the best choices in ligands are chelates that bind as tridentates. Past studies have shown that $^{99m}Tc(CO)_3$ agents with tridentately coordinated ligands exhibit better clearance characteristics in vivo than agents

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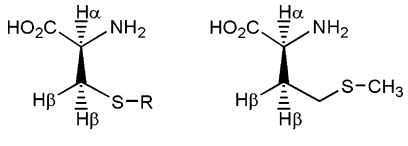
Chart 1



MECYSH, R = Me
PRCYSH, R = Pr
CCMH$_2$, R = CH_2CO_2H

L-METH

with mono- or bidentate ligands.[47] Derivatives of cysteine with a thioether function and providing a set of N, S, and O chelating rings for the $\{^{99m}Tc(CO)_3\}^+$ core are ideal candidates. Amino acids (AAH) with a thioether group, such as *S*-methyl-L-cysteine (MECYSH) and methionine (METH), are good model compounds for this approach. However, only a few examples showing methionine or *S*-methylcysteine tridentate coordination in metal complexes have been reported;[48−51] moreover, reports of investigations into the coordination chemistry of metal carbonyl compounds made from MECYSH and METH are quite rare.[52]

We describe here the complexes formed by $[Re(CO)_3(H_2O)_3]^+$ with MECYSH, METH, *S*-propyl-L-cysteine (PRCYSH), and *S*-(carboxymethyl)-L-cysteine ($CCMH_2$) (Chart 1); all contain the monoanionic deprotonated amino acid bound in a tridentate fashion. The last ligand has a second carboxylic acid group, offering the potential of a dangling carboxyl group for interaction with the renal receptor, a desirable feature often present in promising renal diagnostic agents with rapid clearance.[16] A dangling carboxyl group could also be used for bioconjugation of the agent to a peptide or protein, a nucleic acid, etc.;[53] this design would allow the radionuclide to clear when the bioconjugate is enzymatically hydrolyzed.

Experimental Section

General Methods. All reagents and organic solvents used were reagent grade and were used without further purification. $Re(CO)_5OTf$[32] and *S*-propyl-L-cysteine[54] were prepared by known methods. 1D NMR spectra were recorded on a Varian 600 MHz spectrometer. COSY experiments were performed on a Bruker 500 MHz spectrometer, and chemical shifts were referenced with the residual solvent signal. FTIR spectra were obtained (KBr pellets) with a Nicolet 510M instrument. HPLC analyses were performed on a Waters Breeze system equipped with a Waters 2487 dual wavelength absorbance detector, Waters 1525 binary pump, and XTerra MS C18 column (5 μm; 4.6 × 250 mm). HPLC solvents consisted of the buffer [0.05 M TEAP (aqueous triethylammonium phosphate) at pH 2.5, solvent A] and methanol (solvent B). The HPLC system started with 100% of A from 0 to 3 min. The eluent switched at 3 min to 75% A/25% B, at 6 min to 66% A/34% B, and remained for 3 more min, followed by linear gradients: 66% A/34% B to 34% A/66% B from 9 to 20 min; 34% A/66% B to 100% A from 20 to 30 min. The flow rate was 1 mL/min. The electrospray ionization MS experiments were performed by using the first two sectors of a JEOL SX102/SX102/E five-sector mass spectrometer (configuration BEBEE). The ion source was a JEOL Generation 2 ESI source operated at 5 kV. Water was introduced through a needle at flow rates of approximately 10 μL/min. Care was taken to ensure that all other solvents were flushed from the system by rinsing pure water through the system several times. The needle was maintained at ground potential, while the front entrance to the capillary in the source was used to apply the electrospray potential (2−4 kV). A pneumatic nebulizer helped with the electrospray process. A heated capillary at approximately 100 °C was used for desolvation. All of the skimmer and capillary voltages were optimized for the signal. Elemental analyses were performed by Atlantic Microlabs, Atlanta, GA.

$[Re(CO)_3(H_2O)_3]OTf$ (1). A suspension of $Re(CO)_5OTf$ (2.38 g, 5 mmol) in water (50 mL) was maintained at reflux. Upon boiling, the mixture became a clear solution, which was cooled to room temperature after 1 h. HPLC analysis showed only one sharp peak (retention time (RT) = 3.6 min) and no change upon further heating. This 0.1 M solution was analyzed directly by ESI-MS: *m*/*z* 325 ($[Re(CO)_3(H_2O)_3]^+$, 70%), 307 ($[Re(CO)_3(H_2O)_2]^+$, 71%), 289 ($[Re(CO)_3(H_2O)]^+$, 100%), and 271 ($[Re(CO)_3]^+$, 62%). This 0.1 M solution was used as a stock solution for the following reactions.

$Re(CO)_3$(MECYS) (2). An aqueous solution (total 20 mL) of *S*-methyl-L-cysteine (0.040 g, 0.30 mmol) and **1** (2.5 mL, 0.1 M) at pH 5 (adjusted with aqueous 2 M NaOH) was heated at 70−80 °C for 1 h. HPLC analysis of the solution showed only one sharp peak (RT = 14.4 min). The solution was concentrated to 2−3 mL by rotary evaporation and passed down a column of Sephadex G-15 (eluting with deionized water) to remove salt. The fractions collected were evaporated to dryness and dried under vacuum to give pure **2**. Yield: 0.090 g (89%). Anal. Calcd for $C_7H_8NO_5SRe$: C, 20.79; H, 1.99; N, 3.46; S, 7.93. Found: C, 20.94; H, 2.17; N, 3.58; S, 7.96. IR (KBr, ν/cm^{-1}): 2026, 1920, and 1878.

$Re(CO)_3$(PRCYS) (3). *S*-Propyl-L-cysteine (0.09 g, 0.55 mmol) was dissolved in dilute aqueous NaOH (25 mL). The solution was adjusted to pH 8 with 1 M HCl and added to **1** (5 mL, 0.1 M). The solution (pH 5−6) was heated at 70 °C for 90 min; HPLC analysis showed that the precursor was consumed and one sharp peak (RT = 20.7 min) was observed (precipitate which started to form during the reaction was dissolved by adding methanol before the HPLC analysis). The solution was concentrated to 3−5 mL by rotary evaporation. The precipitate formed was collected by filtration, washed with a small amount of water, and dried under vacuum. Yield: 0.14 g (65%). Anal. Calcd for $C_9H_{14}NO_5SRe$: C, 25.00; H, 2.79; N, 3.24; S, 7.41. Found: C, 25.15; H, 2.98; N, 3.40; S, 7.54. IR (KBr, ν/cm^{-1}): 2029 and 1898. Crystals suitable for X-ray crystallography were obtained by slow evaporation of the CH_3OH-H_2O solution of **3**. To test the stability of **3**, crystals of **3** (17 mg) were dissolved in 5 mL of a methanol/water mixture (2:3) and this solution was heated at 70 °C for 90 min. HPLC analysis showed only one peak (RT = 20.7) corresponding to the original **3**.

$Re(CO)_3$(MET) (4). An aqueous solution (total 20 mL) of L-methionine (0.16 g, 1.1 mmol) and **1** (10 mL, 0.1 M) was adjusted to pH 5.7 with aqueous 2 M NaOH and heated under reflux for 1 h. The solution was concentrated to 3−5 mL by rotary evaporation.

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Table 1. Crystal and Structure Refinement Data for **3**, **4**, **5B**, and Cocrystals of **5A** and **5B**

parameter	**3**	**4**	**5B**·0.5H_2O	**5A** + **5B**·H_2O
formula	$C_9H_{12}NO_5ReS$	$C_8H_{10}NO_5ReS$	$C_{16}H_{18}N_2O_{15}Re_2S_2$	$C_{16}H_{18}N_2O_{15}Re_2S_2$
fw	432.46	418.43	914.86	914.86
space group	C_2	$P2_1/c$	C_2	$P2_1$
a (Å)	31.371(2)	14.1703(2)	12.6341(12)	7.3324(1)
b (Å)	6.1718(4)	7.9202(1)	8.0536(7)	21.4514(3)
c (Å)	29.357(2)	10.9282(2)	23.669(2)	7.4827(1)
α (deg)	90	90	90	90
β (deg)	117.122(3)	106.9530(10)	100.343(6)	100.619(1)
γ (deg)	90	90	90	90
V (Å^3)	5058.9(6)	1173.19(3)	2369.1(4)	1156.80(3)
Z	16	4	4	4
T (K)	173(2)	173(2)	100(2)	173(2)
λ (Å)	0.710 73	1.541 78	1.541 78	1.541 78
d_{calcd} (g cm^{-3})	2.271	2.369	2.565	2.626
μ (mm^{-1})	9.781	22.022	22.066	22.596
F(000)	3264	784	1720	860
R [$I > 2\sigma(I)$]				
R_1[a]	0.0484	0.0439	0.0502	0.0396
wR_2[b]	0.0909	0.1121	0.1261	0.1011
R (all data)				
R_1[a]	0.0551	0.0456	0.0523	0.0397
wR_2[b]	0.0930	0.1139	0.1273	0.1011

[a] $R_1 = \Sigma||F_o| - |F_c||/\Sigma|F_o|$. [b] $wR_2 = [\Sigma(w(F_o^2 - F_c^2)^2)/[\Sigma(w(F_o^2)^2)]^{1/2}$.

The white solid formed was collected, washed with water, and dried under vacuum. Yield: 0.31 g (74%). Anal. Calcd for $C_8H_{10}NO_5SRe$: C, 22.96; H, 2.41; N, 3.35; S, 7.66. Found: C, 23.33; H, 2.56; N, 3.45; S, 7.66. IR (KBr, ν/cm^{-1}): 2028, 1914, and 1888. Attempts to obtain crystals suitable for X-ray crystallography failed. However, by using D,L-methionine instead of L-methionine, crystals suitable for X-ray crystallography were obtained directly from the reaction solution as it was allowed to cool slowly to room temperature.

$Re(CO)_3$(CCMH) (5). An aqueous solution (total 10 mL) of *S*-(carboxymethyl)-L-cysteine (0.093 g, 0.54 mmol) and **1** (5 mL, 0.1 M) adjusted to pH 5 with 2 M NaOH was heated at reflux for 1 h. After the solution was allowed to cool to room temperature, white crystals formed; these were collected (0.095 g) by filtration. HPLC analysis for the crystals showed only one peak (RT = 13.1 min) (isomer **5B**). The crystals were suitable for X-ray crystallography. The filtrate [two HPLC peaks, RT = 13.1 min (isomer **5B**) and 13.6 min (isomer **5A**)] was evaporated to dryness, and the solid (0.09 g) was washed with a small amount of water. Total yield (**5A** + **5B**): 82%. Anal. Calcd for **5B** ($C_8H_8NO_7SRe$): C, 21.43; H, 1.80; N, 3.12; S, 7.15. Found: C, 21.11; H, 1.96; N, 2.99; S, 7.00. ^{1}H NMR [δ (ppm), DMSO-d_6]: 13.49 (b, 1H), 5.71 (dd, 1H), 5.08 (t, 1H), 3.60 (d, 1H), 3.43 (d, 1H), 3.35 (dd, 1H), 3.23 (m, 1H), 2.72 (t, 1H). IR (KBr, ν/cm^{-1}): 2029 (s), 1923 (s), 1875 (vs).

Attempts to isolate pure **5A** failed. An aqueous solution of *S*-(carboxymethyl)-L-cysteine and **1** at pH 5 kept overnight in the refrigerator (5 °C) yielded white crystals. HPLC and X-ray analysis showed the crystals consisted of **5A** and **5B** in a 1:1 ratio. ^{1}H NMR spectra of the crystals dissolved in DMSO-d_6 exhibited two sets of signals with a similar pattern; one set is attributed to **5B**, and the other set, to **5A** (see below).

To examine the conversion of **5A** into **5B**, a separate experiment was carried out. A mixture of *S*-(carboxymethyl)-L-cysteine (0.093 g, 0.54 mmol) and **1** (5 mL, 0.1 M) in H_2O (total 20 mL) at pH 5 was heated at 50 °C (under mild conditions) and analyzed over time by HPLC. With exclusion of a small impurity, the following relative distributions of **5B** and **5A** were found: 30 min, **5B**, 40%, and **5A**, 60%; 70 min, **5B**, 67%, and **5A**, 33%; 130 min, **5B**, 80%, and **5A**, 20%. The temperature was then raised to 70 °C, and the sample was heated for an additional 210 min; subsequent analysis showed that the distribution of the two isomers was virtually unchanged: **5B**, 81%; **5A**, 19%.

Crystal Structure Analysis. Suitable crystals of **3**, **4**, **5B**, and the 1:1 cocrystal of **5A** and **5B** were coated with Paratone N oil, suspended in a small fiber loop, and placed in a cooled nitrogen gas stream on a Bruker D8 SMART APEX CCD sealed tube diffractometer with graphite-monochromated Mo Kα radiation for **3** and Cu Kα radiation for **4**, **5B**, and the 1:1 cocrystal of **5A** and **5B**. Crystals of **4** were thin plates, limiting the completeness of the data set. Data were obtained by using a series of combinations of ϕ and ω scans with 10-s (30 s for **5B**) frame exposures and 0.3° frame widths. Data collection, indexing, and initial cell refinements were all carried out by using SMART software (version 5.55 for the 1:1 cocrystal of **5A** and **5B**; version 5.625 for **4** and **5B**; version 5.628 for **3**).[55] SAINT software was used for frame integration and final cell refinements (version 6.02 for the 1:1 cocrystal of **5A** and **5B**; version 6.36A for **3**, **4**, and **5B**).[56] SADABS was used for absorption corrections (1996 version for the 1:1 cocrystal of **5A** and **5B**; version 2.08 for **3**, **4**, and **5B**).[57]

The structures were solved by direct methods and difference Fourier techniques (SHELXTL: version 5.10 for the 1:1 cocrystal of **5A** and **5B**; version 6.12 for **3**, **4**, and **5B**).[58] All the hydrogen atoms were located in a difference Fourier map and were included in the final cycles of least squares with isotropic U_{ij}'s or as riding atoms. All non-hydrogen atoms were refined anisotropically only in **3** and **4**. All non-hydrogen atoms for structures in the cocrystal of **5A** and **5B** were refined isotropically. Scattering factors and anomalous dispersion corrections were taken from ref 59. Structure solution, refinement, graphics, and generation of publication

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Table 2. Selected Bond Distances of **3**, **4**, and **5A** and **5B**

	3	4	5A	5B
Re−O(carboxyl)	**3A**, 2.159(5)	2.166(6)	2.171(8)[a]	2.148(9)
	3B, 2.180(5)			2.158(10)
	3C, 2.182(5)			2.160(9)[a]
	3D, 2.170(5)			
Re−S	**3A**, 2.5005(18)	2.499(2)	2.455(3)[a]	2.469(4)
	3B, 2.4956(18)			2.459(4)
	3C, 2.500(2)			2.454(3)[a]
	3D, 2.504(2)			
Re−N	**3A**, 2.215(6)	2.194(11)	2.228(10)[a]	2.244(12)
	3B, 2.201(6)			2.265(12)
	3C, 2.194(6)			2.247(10)[a]
	3D, 2.215(6)			
Re−C	1.88−1.92	1.91−1.94	1.90−1.94[a]	1.92−1.93
				1.89−1.92
				1.89−1.94[a]

[a] Data from the **5A** and **5B** cocrystal.

materials were performed by using SHELXTL software as described above.[58] Crystal data of all complexes are presented in Table 1; selected bond distances appear in Table 2.

Results and Discussion

Crystal Structures of 3, 4, 5A, and 5B. Interesting details of the crystal structures and molecular parameters are presented below after the synthetic and solution studies are discussed. All complexes show a molecular structure consisting of a distorted octahedron with three carbonyl ligands occupying one face. The other three remaining coordination sites are occupied by one N, one S, and one O of the chelate ligands. The Re−C, Re−O, Re−N, and Re−S bond distances of all complexes are normal (Table 2), compared with those found in previously reported Re tricarbonyl complexes.[60,61]

α-Amino acids can commonly act as bidentate ligands, including a number of metal complexes with the bidentate methionine or *S*-methylcysteine coordinated through N, O[62−64] or N, S[65−67] donor atoms. In particular, the product in a report on the reaction of $Re(CO)_5Br$ with METH was $Re(CO)_3Br$(METH), in which METH acts as a bidentate ligand, leaving an uncoordinated carboxylic acid.[68] However, our methods lead to complexes with the amino acids acting as capping tridentate ligands with amino, carboxylate, and thioether groups occupying the three available sites on the $\{Re(CO)_3\}^+$ core.

Synthesis and Characterization of 1. $[Re(CO)_3(H_2O)_3]^+$ (**1**) is a useful precursor for the preparation of $Re(CO)_3$ complexes because the three water molecules are readily substituted by a variety of ligands. Traditionally, this precursor was obtained by the hydrolysis of $(NEt_4)_2[Re(CO)_3Br_3]$.[27,28] The disadvantages of preparing $(NEt_4)_2[Re(CO)_3Br_3]$ by using $Re(CO)_5Br$ and an excess of NEt_4Br have been outlined in the Introduction. A much easier procedure would be to solvate the rhenium pentacarbonyl synthon, bypassing the $(NEt_4)_2[Re(CO)_3Br_3]$ step. Because $Mn(CO)_5OTf$ can be converted to $[Mn(CO)_3(acetone)_3]^+$,[69] and because OTf^- is a weakly coordinating hydrophilic anion,[70] we explored a one-pot reaction to prepare $[Re(CO)_3(H_2O)_3]^+$ (**1**) from $Re(CO)_5OTf$ in water. A clear solution of **1** was formed when an aqueous suspension of $Re(CO)_5OTf$ was boiled for 1 h. HPLC analysis showed a sharp peak and no change upon further heating. ESI-MS analysis of this solution confirms that the reaction forming **1** goes to completion: The predominant fragments in the MS spectra are $[Re(CO)_3(H_2O)_3]^+$ (70%), $[Re(CO)_3(H_2O)_2]^+$ (71%), $[Re(CO)_3(H_2O)]^+$ (100%), and $[Re(CO)_3]^+$ (62%); no fragments containing $[Re(CO)_5]^+$ or $[Re(CO)_4]^+$ are present. This preparative method (1) leads readily to formation of the desired rhenium tricarbonyl precursor **1** in water in 1 h, (2) requires no further purification steps, and (3) provides a stock solution of **1** suitable for the synthesis of the rhenium tricarbonyl complexes reflective of the procedures used to prepare ^{99m}Tc radiopharmaceuticals.

Synthesis and Characterization of 2−4. Reactions of **1** with MECYSH, PRCYSH, or METH gave high yields of the neutral complexes, $Re(CO)_3$(MECYS) (**2**), $Re(CO)_3$(PRCYS) (**3**), and $Re(CO)_3$(MET) (**4**), respectively. HPLC analysis showed the presence of only one product for each reaction mixture. All of these pure complexes are only slightly soluble in water but are easily soluble in polar organic solvents such as methanol and DMSO. The IR spectra of these complexes contain two or three strong bands in the 2029−1878 cm^{-1} region, typical of rhenium tricarbonyl complexes.[71−73]

Solution Behavior of 2−4. Treatment of solutions of **1** with thioether-bearing amino acids gave high yields of *fac*-$Re(CO)_3$AA complexes. Although HPLC analyses of all products showed a single sharp peak, the ^1H NMR spectra of all these complexes in D_2O or CD_3OD recorded at room temperature have broad signals. However, at low temperature (−10 °C) in CD_3OD sharp spectra (Table 3) showing two sets of signals indicated the presence of two interconverting species. Because sulfur has two lone pairs of electrons and because each ligand has a chiral carbon, the formation of diastereoisomers upon coordination is clearly possible. Two isomers can equilibrate by inversion of the sulfur configu-

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Table 3. Important Chemical Shifts of All Complexes with Coupling Constant for Comparison[a]

complex	N−H (cis to Hα)	N−H (trans to Hα)	Hα	Hβ (trans to Hα)	Hβ (cis to Hα)	S−R[b]
2 (major) CD_3OD, −10 °C	6.18 $J_{gem} = 9$	4.95 $J_{gem} = 9$	4.31 (b)	2.94 $J_{vic} = 3$; $J_{gem} = 12$	2.69 $J_{gem} = 12$	2.45 (s)
2 (minor) CD_3OD, −10 °C	6.26 $J_{gem} = 9$	5.15 $J_{gem} = 9$	4.20 (b)	2.52 $J_{vic} = 5$; $J_{gem} = 14$	3.26[c]	2.78 (s)
3 (major) CD_3OD, −10 °C			4.31 $J_{vic} = 4$	2.90 $J_{vic} = 4$; $J_{gem} = 14$	2.77[d]	
3 (minor) CD_3OD, −10 °C			4.20 $J_{vic} = 3$	2.54 $J_{vic} = 3$; $J_{gem} = 13$	3.22 $J_{gem} = 13$	
PRCYSH ligand CD_3OD			3.66 $J_{vic} = 3.6$; $J_{vic} = 9$	3.14 $J_{vic} = 3.6$; $J_{gem} = 15$	2.87 $J_{vic} = 9$; $J_{gem} = 15$	
5A DMSO-d_6	6.21 $J_{gem} = 9.6$	3.98 $J_{vic} = 12.0$; $J_{gem} = 9.6$	3.49[e] (m)	2.34 $J_{vic} = 13.8$; $J_{gem} = 13.8$	3.49[e] (m)	3.65, 3.40 $J_{gem} = 17.4$
5B DMSO-d_6	5.71 $J_{vic} = 3.6$; $J_{gem} = 10.8$	5.08 $J_{vic} = 11.1$; $J_{gem} = 10.8$	3.23 (m)	2.72 $J_{vic} = 12.9$; $J_{gem} = 13.8$	3.35 $J_{vic} = 4.2$; $J_{gem} = 13.8$	3.60, 3.43 $J_{gem} = 18$
5B CD_3OD	5.58 $J_{vic} = 3.6$; $J_{gem} = 10.8$	5.05 $J_{vic} = 11.1$; $J_{gem} = 10.8$	3.50 (m)	2.88 $J_{vic} = 11.4$; $J_{gem} = 13.8$	3.37 $J_{vic} = 4.2$; $J_{gem} = 13.8$	3.68, 3.51 $J_{gem} = 17.4$

[a] Chemical shifts (ppm), coupling constants (Hz). [b] R = CH_3 for **2** and R = CH_2CO_2 for **5A** and **5B**. [c] Signal overlaps with the signal of methanol. [d] Signal overlaps with the signals of S−CH_2 protons. [e] Signals overlap with each other.

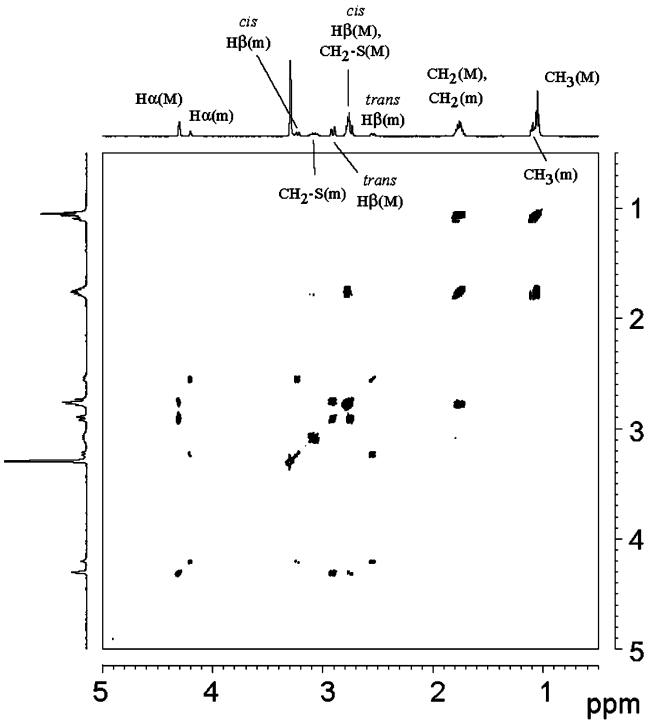

Figure 1. COSY spectrum of $Re(CO)_3$(PRCYS) (**3**) recorded at −8 °C in CD_3OD (M = major species; m = minor species). Cis and trans are referred to Hα.

ration. The X-ray crystal structure of **3** reveals the presence of both diastereoisomers (see X-ray structure discussion below).

A COSY experiment performed on $Re(CO)_3$(PRCYS) (**3**) in CD_3OD at −8 °C (Figure 1) revealed an intense set and a weak set of signals. The relative intensity of the two sets is 2.5:1. NH NMR signals are not present due to exchange with solvent deuterium atoms (occurring within 30 min). For the intense set, the propyl triplet at 1.05 ppm (methyl) correlates with the multiplet at 1.75 ppm (central methylene), which in turn correlates with the signal at 2.76 ppm (*S*-methylene). Because the NH's had exchanged, we assigned Hα by analogy to compound **2** (see below). Both the Hβ signals correlate with the broad signal at 4.31 ppm, which is therefore assigned to the Hα for the major diastereoisomer. The signal at 2.90 ppm is assigned to the Hβ trans to Hα from the doublet of doublets [Hβ coupling with the geminal Hβ ($J = 14$ Hz) and to the Hα itself ($J = 4$ Hz)]. The signal at 2.77 ppm (almost overlapped with the *S*-methylene signal) is assigned to the Hβ cis to Hα.

Assignment of the propyl signals of the minor diastereoisomer was performed in an analogous fashion by analyzing the correlations between signals at 1.09 ppm (methyl), 1.77 ppm (central methylene), and 3.08 ppm (*S*-methylene). The doublet at 3.22 ppm is assigned to Hβ cis to Hα, because of the cross-peak with the broad Hα signal at 4.20 ppm and with the poorly resolved doublet of doublets at 2.54 ppm, which is assigned to the Hβ trans to Hα.

$Re(CO)_3$(MECYS) (**2**) has ^{1}H NMR characteristics similar to those of **3**: broad peaks at room temperature; sharp peaks at low temperature; and the presence of two sets of signals (in a 4:1 ratio). In a COSY experiment performed on **2** in CD_3OD at −10 °C (Figure 2), the more intense singlet at 2.45 ppm (*S*-methyl group) correlates with the doublet at 2.69 ppm (assigned to the Hβ cis to Hα, $J_{gem} = 12$ Hz) and with the doublet of doublets at 2.94 ppm (assigned to the Hβ trans to Hα, $J_{gem} = 12$ Hz; $J_{vic} = 3$ Hz). The singlet at 2.45 ppm also shows a long-range correlation with the broad signal at 4.31 ppm, assigned to the Hα of the major species. The same Hα signal also correlates with the two doublets at 4.95 and 6.18 ppm, assigned to the two nonequivalent NH protons ($J_{gem} = 9$ Hz), the first cross-peak being smaller than the second. Finally, we observed a cross-peak between the two NH proton signals and a long-range correlation between the most downfield NH signal (6.18 ppm) and the doublet at 2.69 ppm for the Hβ cis to Hα.

By analogy with these assignments for the major diastereoisomer, the signals of the minor diastereoisomer were

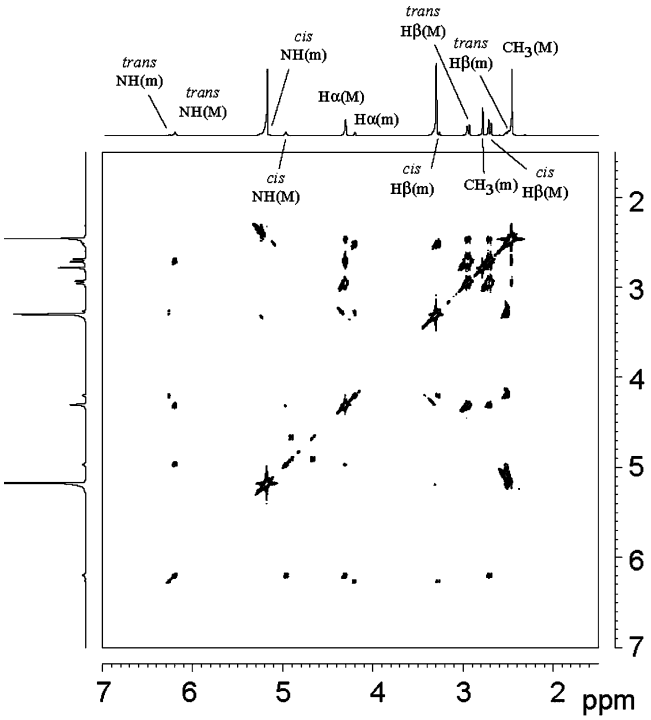

Figure 2. COSY spectrum of $Re(CO)_3$(MECYS) (**2**) recorded at −10 °C in CD_3OD (M = major species; m = minor species). Cis and trans are referred to Hα.

assigned. Because of the relatively low intensity of the minor diastereoisomer, we observed a correlation of the *S*-methyl singlet (2.78 ppm) only to the Hβ trans to Hα signal (doublet of doublets at 2.52 ppm; J_{gem} = 14 Hz; J_{vic} = 5 Hz) and not to the Hβ cis to Hα doublet (3.26 ppm). On the other hand, the two Hβ signals both correlate with the broad signal at 4.20 ppm, assigned to the Hα. We also observed a very weak cross-peak between the two NH signals (doublets at 5.15 and 6.26 ppm, J_{gem} = 9 Hz). Only the most downfield of the two NH signals correlates with the Hα signal. Finally, we observed a long-range correlation between the most downfield-shifted NH signal and the Hβ cis to Hα) doublet.

The ^{1}H NMR spectrum of compound **4** is not very informative because the signals are quite broad. Even at −10 °C, the signals of **4** are still relatively broad and broader than those of compounds **2** and **3** (−10 °C). However, the broad peak for S−CH_3 (2.70 ppm) observed at room temperature is clearly split into two singlets at −10 °C (2.77 and 2.68 ppm) in an approximate 1:1 ratio. Six broad aliphatic signals integrating to five protons vs the three methyl protons are also present. Two broad, poorly resolved signals (3.78, 3.82 ppm) integrating for a total of one proton are assigned to Hα.

The molecular structure of $Re(CO)_3$(PRCYS) (**3**) shows little difference in the chelate ring conformation between the diastereoisomers; on the other hand, the inversion at the sulfur atom causes a deshielding/shielding magnetic effect, more evident in the cysteine Hβ (CH_2) ^{1}H NMR signals. The different chemical shifts can be attributed to differential van der Waals interactions with the lone pair of electrons on the S.[74] Moreover, it is interesting to note that the NH_2 signals of **2** (both species) are sharp, show geminal coupling, and do not exchange with deuterium atoms. In contrast, the NH_2 group of **3**, freshly prepared in CD_3OD, gave initially only a low intensity peak, which completely exchanged in 30 min. When dissolved in CD_3OD containing DCl, **3** has a ^{1}H NMR spectrum with one NH signal (6.10 ppm, integrating for one proton), while, in dry DMSO-d_6, three broad NH signals (6.12 ppm, integrating for one proton, and 5.03 (minor) and 4.87 ppm (major), together integrating for one proton) are observed, consistent with the presence of two isomers.

Reaction, Synthesis, and Characterization of Isomers of $Re(CO)_3$(CCMH). Superior renal agents require the presence of a dangling carboxyl group.[16] *S*-(carboxymethyl)-L-cysteine ($CCMH_2$) provides a set of donors for effective coordination to the $\{Re(CO)_3\}^+$ moiety and an extra carboxylate acid group for the renal receptor. A solution of **1** and $CCMH_2$ at pH 5−6 was heated at reflux for 1 h, and crystals formed upon cooling.

HPLC analysis showed one peak (**5B**) for the crystals and two peaks (**5A** and **5B**) for the mother liquor. HPLC analysis of the product (dissolving crystals of **5B** in MeOH and combining with the mother liquor) indicates that the synthetic procedure gives a **5B**:**5A** ratio of roughly 4:1. The ^{1}H NMR spectrum of **5B** in DMSO-d_6 exhibits resonances assignable to the cysteine NH and CH protons (Table 3), as well as to the S−CH_2CO_2 group (3.60 and 3.43 ppm; the presence of these two signals (doublets) confirms the diastereotopic character of the methylene protons, consistent with this group being within the chelate ring). The S−CH_2CO_2 methylene signals of **5B** in D_2O disappeared immediately after a small drop of NaOD was added, revealing the acidic nature of these protons. Three strong bands between 1875 and 2029 cm^{-1} in the IR spectrum of **5B** are consistent with the presence of the *fac*-$\{Re(CO)_3\}^+$ moiety.

When attempts to isolate pure **5A** from the mother liquor failed, we suspected that **5A** converted to **5B**. We repeated the reaction under mild conditions and monitored the reaction by HPLC. Indeed, at relatively short times and before the reaction was completed, we observed the formation of **5A** as a major product and **5B** as a minor product. With time the amount of **5A** decreased while that of **5B** increased. Another experiment, at 5 °C, yielded cocrystals of **5A** and **5B**. NMR (see below) and HPLC analysis of the crystals showed essentially equal amounts of **5A** and **5B**. X-crystallography revealed that **5A** and **5B** are diastereoisomers, with CCMH coordinated through the thioether group, the amino group, and the carboxymethyl carboxylate group instead of the α-carboxylate group (see below).

5B is slightly soluble in water, and HPLC analysis revealed that it remained unchanged in solution for up to 6 h at room temperature. However, after the solution was heated at reflux for 1 h, **5A** was present, and the ratio of **5B** and **5A** was 4:1, as observed for the synthetic reaction. **5B** is thermodynamically preferred, whereas **5A** is kinetically preferred.

The ^{1}H NMR spectrum in DMSO-d_6 of **5A** (from the cocrystals of **5A** and **5B**) reveals a similar set of cysteine

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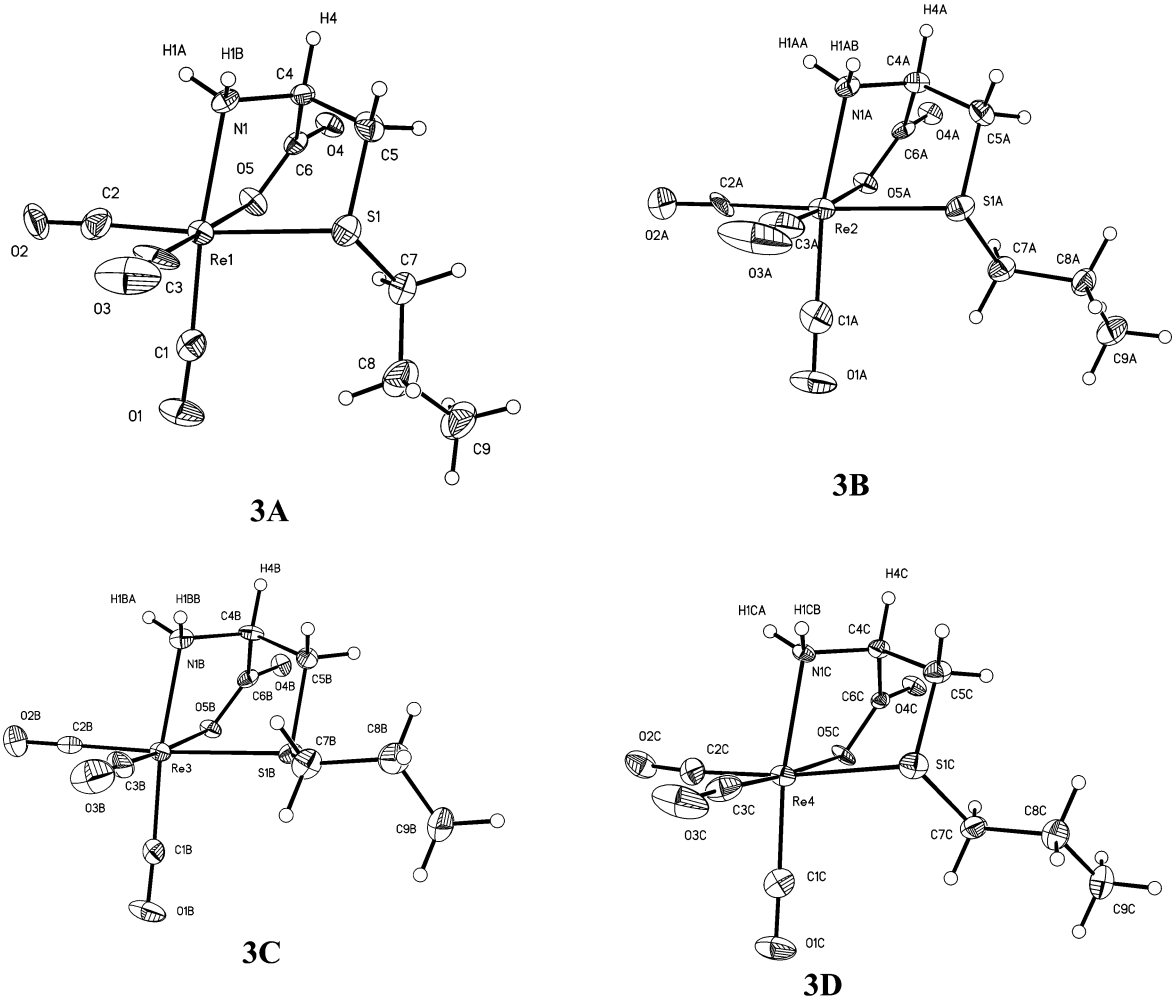

Figure 3. Perspective drawings of four independent molecules of $Re(CO)_3$(PRCYS) (**3**) with 50% probability for the atomic displacement parameters (ADP's). **3A**, **3B**, and **3D** have the same chirality at sulfur, and **3C** has different chirality at sulfur.

NH, CH, and $S-CH_2CO_2$ methylene signals as found for **5B** (see Table 3). The differences in chemical shifts for the two NH signals and the two Hβ signals are greater for **5A** compared to these differences in **5B**. This is particularly true for the NH signals (6.21 and 3.98 ppm for **5A**; 5.71 and 5.08 ppm for **5B**). We attribute this behavior to the fact that the relationship of the protons to the remainder of the complex interchanges between the isomers. The NH cis to Hα (downfield NH signal of each isomer) experiences a deshielding environment in **5A** but a shielding environment in **5B**. The opposite holds true for the NH trans to Hα (upfield signal).

It is important to note that the amino acid Hα signals of complexes **2**−**4** are significantly downfield shifted with respect to the free amino acid. On the other hand, the Hα signals in complexes **5A** or **5B** are shifted little from the free ligand value. Because the amino acid utilizes only the amine N and the thioether S (but not an α carboxyl O) to bind in complexes **5A** or **5B**, whereas all three amino acid donor groups participate in complexes **2**−**4**, the relative shift of the Hα signal may possibly be a useful indication of the presence or absence of α-carboxyl group coordination.

Crystallographic Studies of 3, 4, 5A, and 5B. Structure of $Re(CO)_3$(PRCYS) (3). Remarkably, the asymmetric unit of complex **3** contains four molecules with four independent structures (Figure 3). Structural differences lie mainly in the configuration of the sulfur center and in the orientation of the propyl group. **3A**, **3B**, and **3D** have the same chirality at sulfur, where the lone pair of electrons is *endo* to the carbonyl (trans to Re−OCO). In **3A** the propyl plane defined by three carbon atoms is approximately equatorial to the octahedral plane defined by Re−S, Re−OCO, and two Re−C bonds, while it has axial orientation in **3B** or **3D**. **3B** and **3D** are almost identical. **3C** has different chirality at sulfur, where the lone pair is *exo* to the carbonyl (trans to Re−OCO). The molecules with the *endo* configuration are most abundant, a result consistent with previous experiments as well as theoretical calculations for related $Re(CO)_3$ complexes with a substituent on a nitrogen center.[75]

All four molecules have very similar Re−S bond distances of ~2.50 Å, a value within the range for reported rhenium thioether tricarbonyl complexes (2.45−2.52 Å).[42,45,76−79] All four molecules have very similar bond angles: cis and trans

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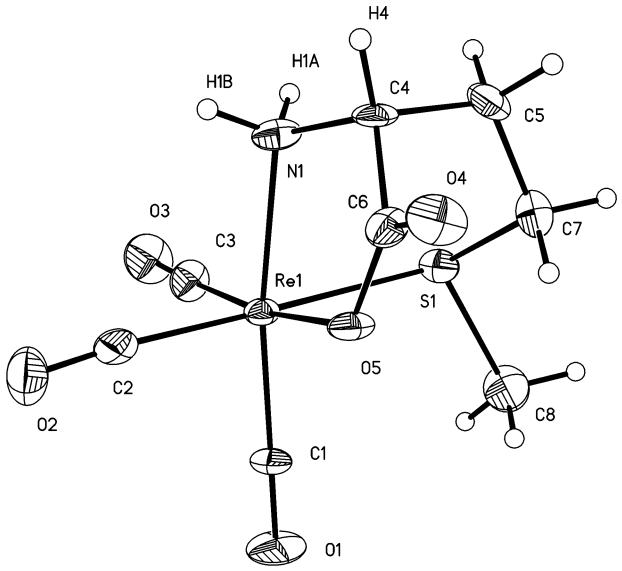


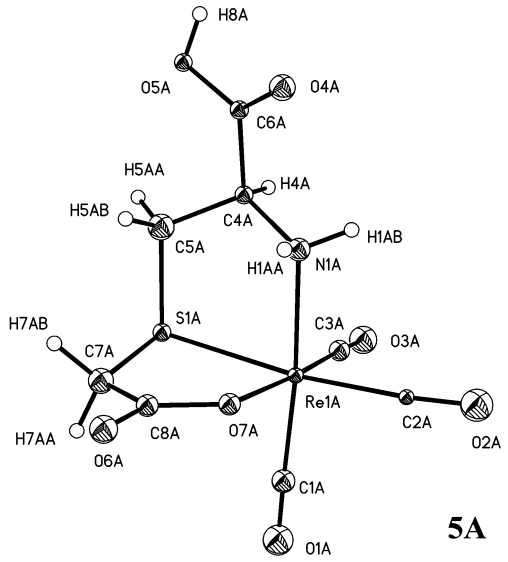
Figure 4. Perspective drawing of $Re(CO)_3$(D-MET) (**4**) with the MET^- ligand having a D absolute configuration with 50% probability for the ADP's.

bond angles are in the ranges 73.8−102.4 and 172.4−174.6°, respectively. The cis bond angle values indicate a higher distortion from the idealized octahedral geometry in **3** than in **5A** or **5B** (see below).

Of particular interest is the fact that intermolecular hydrogen bonds formed between the nonbonded carboxyl oxygen and an amino proton occur between the same kind of molecules (**3A**−**3A**, **3B**−**3B**, **3C**−**3C**, **3D**−**3D**; not e.g. **3A**−**3B**). This hydrogen bonding creates four well-organized one-dimensional infinite strands.

Structure of $Re(CO)_3$(MET) (4). Attempts to obtain X-ray-quality $Re(CO)_3$(L-MET) crystals failed, but the D,L-methionine product formed suitable crystals and Figure 4 shows the geometry of the enantiomer of **4** with D-methionine. Although the thioether is prochiral, only one chirality is found in the crystal [S lone pair *endo* to the carbonyl (trans to Re−OCO)]. The MET^- coordinates tridentately, forming five-membered, six-membered, and seven-membered chelate rings. Reported structures show methionine acting chiefly as a bidentate ligand, through N, S (e.g. Pt) or N, O (e.g. Cu).[62−67] To our knowledge, this is the first crystal structure of a metal carbonyl complex with methionine acting as a tridentate ligand. The Re−S bond distance of **4** is the same as that of **3**, at the longer end of the Re−S(thioether) bond distance range for rhenium tricarbonyl complexes.[42,45,76−79]

Intermolecular hydrogen bonds are formed between the nonbonded carboxyl oxygen and the amino proton. Again, it is interesting to note that the hydrogen bonds occur between the identical types of molecules, i.e., only between $Re(CO)_3$(D-MET) or between $Re(CO)_3$(L-MET). Hydrogen bonds make two infinite strands and a six-membered cavity between them, as shown in the Supporting Information.



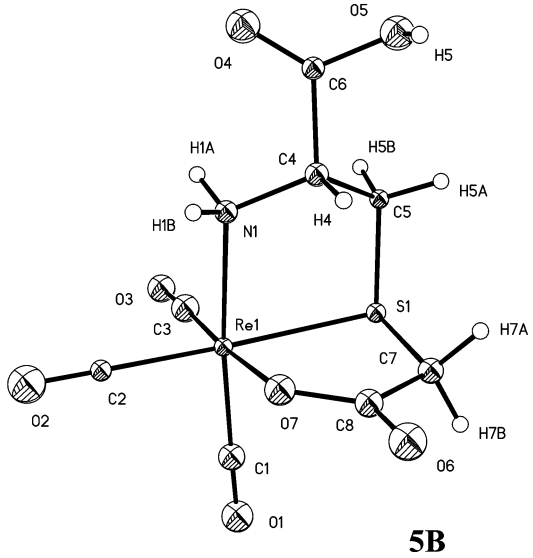


Figure 5. Perspective drawing of $Re(CO)_3$(CCMH) (**5A**) and $Re(CO)_3$(CCMH) (**5B**) from the cocrystals of **5A** and **5B** with 50% probability for the ADP's. The water molecule is omitted for clarity.

Structures of $Re(CO)_3$(CCMH) (5A and 5B). The asymmetric unit of the cocrystals contains **5A** and **5B** and one water of crystallization. The molecular structures of the **5B** and **5A** diastereomers are shown in Figure 5. The molecular structure of **5B** from the cocrystal is chemically identical with that of **5B** obtained from the crystal of pure **5B**, for which HPLC shows only one peak. The latter crystals formed as extremely small needles, and long exposure times were required for each frame to achieve the intensity necessary to obtain a satisfactory structure of **5B**.

The formation of diastereomers is a consequence of the prochiral sulfur and the asymmetric carbon of the $CCMH_2$ ligand. Because the chelate rings define coordination sphere chirality and because they are linked by a sulfur with opposite chiralities, **5A** and **5B** have different chiralities around the metal. Exchanging the position of the dangling carboxyl and the hydrogen in the α- position (L-cysteine becomes D-cysteine) in **5A** would give the enantiomer of **5B**. Likewise,

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this L to D conversion in **5B** would give the enantiomer of **5A**. In both **5A** and **5B**, the dangling carboxylic group is axial (perpendicular) to the coordination plane defined by Re−S, Re−OCO, and two Re−C bonds. This position of the uncoordinated carboxyl group defines the orientation of the Hα proton to be *exo* to the carbonyl (trans to Re−OCO) in **5B** and *endo* in **5A**. This is the major difference between the two hypothetical pairs of enantiomers.

In **5A** and **5B**, the Re−S (thioether) bond distances of ∼2.45 Å are within the previously reported range (2.45−2.52 Å) for rhenium tricarbonyl complexes.[42,45,76−79] The Re−S bonds in **5A** and **5B** are 2.455(3) and 2.454(3) Å, shorter than those in **3** (e.g., 2.500(2) Å) and **4** (2.499(2) Å), consistent with the involvement of S in two chelate rings in **5A** and **5B** but only one ring in **3** and **4**. The cis and trans bond angles within the octahedron are in the ranges 80.9−97.3 and 171.9−176.2° for **5B** and 79.8−98.7 and 172.4−175.5° for **5A**, respectively. The values of the cis bond angles are considerably closer to the octahedral values than these values for **3** and **4**.

We attribute this lower distortion of the Re bond angles in **5A** and **5B** to the presence in **5A** and **5B** of only two (five-membered) chelate rings, producing less coordination strain than produced by the three chelate rings in **3** and **4**. Likewise, the bond angles in **4** are closer to those for an octahedron because one of the three chelate rings formed by the bound MET^- ligand is six membered.

It should be pointed out that MET^- ligand displays similar coordinating and solution behavior in the $ReOX_2(MET)$ complex,[51] as we discussed above. In this complex, MET^- is a tridentate S, N, and O ligand. Two isomers coexist in equilibrium in acetone. Exchange between these two isomers is fast above room temperature, but the rate is slower below 0 °C.

Summary. The new, reliable, and straightforward synthesis of *fac*-$[Re(CO)_3(H_2O)_3]^+$ aqueous solutions described here should permit convenient and more widespread synthesis and characterization of water−soluble Re tricarbonyl complexes. The resulting information should facilitate design and development of ^{99m}Tc tricarbonyl radiopharmaceuticals containing the radionuclide which is widely used throughout the world and which is utilized in the large majority of diagnostic nuclear medicine procedures. Not only will parallel studies of Re and ^{99m}Tc agents facilitate ^{99m}Tc tracer design but the chemistry will spur the development of therapeutic β-emitting ^{186}Re- and ^{188}Re-based radiopharmaceuticals.[80,81] Most of the current ^{99m}Tc agents utilize th e $\{^{99m}Tc^{V}O\}^{3+}$ core, but the numerous synthetic advantages of the $^{99m}Tc^{I}$ precursor $[^{99m}Tc(CO)_3(H_2O)_3]^+$ have shifted the focus of radiopharmaceutical development to tricarbonyl agents;[6,18,19,21] a desire to apply this approach to renal imaging agents has led us to evaluate in animal models new ^{99m}Tc tricarbonyl agents containing ethylenediamine-*N*,*N*′-diacetic acid and thioether-bearing amino acids.[22,82] Our early work preparing Re analogues was hindered by the lack of a reliable source of *fac*-$[Re(CO)_3(H_2O)_3]^+$, but the methods described herein eliminate this impediment.

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Supporting Information Available: X-ray crystallographic data for structure determinations of compounds **3**, **4**, and **5B** and the cocrystal of **5A** and **5B** in CIF format, a one-dimensional hydrogen-bonded strand formed by $Re(CO)_3$(D-MET) within crystals of **4** viewed along the *b* axis and along the *c* axis, and a table of selected bond angles of **3**, **4**, and **5A** and **5B**. This material is available free of charge via the Internet at http://pubs.acs.org.

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