The Synthesis, NMR Spectroscopy, and X-ray Structure of a New Rhenium N_2S_2 Chelate Complex

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A new chelate, mercaptoacetyl-L-histidinyl-*S*-benzyl-L-cysteine methyl ester was synthesized by standard peptide coupling techniques and reacted with $ReOCl_3(PPh_3)_2$ to give two diastereomers, **7a** and **7b**. The two isomers were separated by reversed-phase HPLC and characterized by NMR spectroscopy and electrospray mass spectrometry. An X-ray structure of one isomer, **7a**, confirmed that the chelated complex was analogous to other $Re-N_2S_2$ compounds in that it formed a square pyramidal complex where the four donor atoms were the base of the pyramid and the oxygen attached to the rhenium was at the apex. The *S*-benzyl group, as expected, was cleaved during the formation of **7**, and the resulting complex was a zwitterion where the rhenium was formally −1 and the counterion was the protonated imidazole ring.

Introduction

An approach to the development of site specific radioimaging/radiotherapeutic agents is to derivatize a chelate, which binds a particular radionuclide, with a biomolecule whose purpose is to concentrate the radionuclide at a specific site. A radionuclide of particular interest for the treatment of tumors is ^{186}Re ($t_{1/2}$ = 90 h, β^- = 1.07 MeV) because it can be used in concert with ^{99m}Tc, the most commonly used isotope in diagnostic imaging;[1] ^{99m}Tc and ^{189}Re can be considered a matched pair for imaging and therapy.[2] Technetium and rhenium complexes of chelates which contain two nitrogen and two sulfur donor atoms (N_2S_2) have been shown to have sufficient in vivo stability to function as effective radioimaging/therapy agents.[3] Three examples of N_2S_2 chelates (Figure 1) are the diamide dithiol (DADS)[4] ligand, which forms an anionic complex with technetium and rhenium, and the bis(aminoethanethiol) (BAT) ligand[5] and the monoamine monoamide (MAMA) ligand,[6] both of which form neutral technetium and rhenium complexes.

While testing some cardiac imaging agents which contained the DADS chelant, we encountered solubility problems. Compounds were either too hydrophobic to perform accurate binding assays *in vitro* or insufficiently lipophilic to gain access to the site of interest *in vivo*. We therefore decided to develop a new N_2S_2 chelating system in which the solubility of a complex could be "tuned" to a desired lipophilicity. It was postulated that this goal could best be accomplished by using amino acids as the chelate's synthon units.

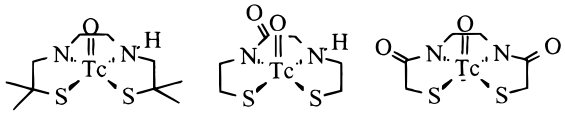

Figure 1. N_2S_2 chelates.

A chelate composed of mercaptoacetic acid (Mer), an amino acid, and cysteine (i.e., Mer-X-Cys) would have a structure analogous to the DADS chelate. The solubility (and potentially the coordination chemistry) of the chelate could be altered by simply changing the central amino acid. This type of flexibility is not possible for the DADS, BAT, or MAMA types of technetium chelates. Extensive synthesis would be required to provide as many different derivatives for these chelates as could be easily and economically prepared by the use of amino acids as synthons. As an initial study of the proposed Mer-X-Cys chelating system, this paper reports the synthesis of a rhenium chelate complex which contains histidine (His) as the central amino acid.

Experimental Section

Materials and Methods. Analytical TLC was performed on silica gel 60-F_{254} (Merck) plates with detection by long-wavelength ultraviolet light unless specified otherwise. Silica gel chromatography was performed with the use of either a chromatotron (Harrison Research model 7924T) that used a 4 mm plate (EM Science silica gel 60 PF_{254} containing gypsum) or silica gel column chromatography (200−400 mesh). All commercial reagents were used as supplied. Solvents were distilled, under nitrogen, from calcium hydride. All reactions were protected from light and carried out under a slow flow of nitrogen unless stated otherwise. Solvents were evaporated with a rotary evaporator (20 mmHg) at moderate temperatures (30−50 °C). Melting points were recorded on a Gallenkamp capillary tube melting point apparatus.

Selected NMR spectra were recorded on either a Bruker Avance DRX-500 spectrometer or a Bruker AC-200 spectrometer. Chemical ionization (CI) mass spectra, with ammonia as the reagent gas, and electron impact (EI) mass spectra were recorded on a VG Analytical ZAB-E double-focusing mass spectrometer. Electrospray ionization mass spectrometry (ESMS) was performed with 50/50 CH_3CN/H_2O as the mobile phase at a flow rate of 15 mL/min, with the use of a

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Brownlee Microgradient syringe pump. Solid samples were dissolved in 50/50 CH_3CN/H_2O immediately before analysis. Full-scan ESMS experiments were performed with a Fisons Platform quadrapole instrument. X-ray crystallographic data was collected from a single-crystal sample, which was mounted on a glass fiber. Data were collected using a P4 Siemens diffractometer, equipped with a Siemens SMART[7] 1K charge-coupled device (CCD) area detector (using the program SMART) and a rotating anode using graphite-monochromated Mo Kα radiation ($\lambda = 0.710\ 73$ Å). The crystal-to-detector distance was 3.991 cm, and the data collection was carried out in a 512 × 512 pixel node, utilizing 2 × 2 pixel binning. The initial unit cell parameters were determined by a least-squares fit of the angular settings of strong reflections, collected by a 4.5° scan in 15 frames over three different parts of reciprocal space (45 frames total). One complete hemisphere of data was collected, to better than 0.8 Å resolution. Upon completion of the data collection, the first 45 frames were re-collected in order to improve the decay corrections analysis (if required). Processing was carried out by the use of the program SAINT,[8] which applied Lorentz and polarization corrections to three dimensionally integrated diffraction spots. The program SADABS was utilized for the scaling of diffraction data, the application of a decay correction, and an empirical absorption correction based on redundant reflections. The structure was solved using the direct methods procedure in the Siemens SHELXTL[9] program library, and it was refined by full-matrix least-squares methods with anisotropic thermal parameters for all non-hydrogen atoms.

Reversed-phase HPLC analyses were performed at 40 °C using a Hewlett-Packard model 1090 liquid chromatograph equipped with a diode array detector. For analytical injections a Vydac 201TP54 column (4.6 mm × 250 mm) was used with a 20 mL injection loop at a flow rate of 1.0 mL/min. For preparative injections a Vydac 201HS1010 semipreparative column (9.4 × 250 mm) was used with a 100 mL injection loop at a flow rate of 2.5 mL/min. The following linear gradient elution program was used: initial, 10% acetonitrile (AN), 90% H_2O; 25 min, 35% AN, 65% H_2O; 28 min, 35% AN, 65% H_2O; 30 min, 10% AN, 90% H_2O. Chromatograms were monitored and averaged over two wavelength ranges: 333−337 and 230−370 nm. In the case of semipreparative chromatography, the crude reaction mixture in methanol was filtered and injected in 100 mL aliquots, and two peaks were collected between 16.1 and 16.9 min and between 17.3 and 18.4 min.

Synthetic Preparations. *S*-Bn-L-Cys-OMe-*p*-TsOH (1). *S*-Benzyl-L-cysteine (5.0 g, 23.7 mmol) was dissolved in methanol (150 mL), and *p*-toluenesulfonic acid was added (18 g, 104 mmol). The mixture was heated to reflux for 48 h, whereupon the solution was evaporated to dryness and the product isolated by recrystallization of the resulting solid from diethyl ether. Compound **1**: colorless solid (9.3 g, 98%); mp 78−79 °C; ^{1}H NMR (CD_3OD) [200 MHz]: δ 7.688, 7.245 (m, 9H, H aryl), 5.176 (s, 2H, SCH_2Ph), 4.149 (m, 1H, C*H*CH_2), 3.779 (s, 3H, OCH_3), 2.926 (m, 2H, CHC*H*$_2$), 2.353 (s, 3H, $PhCH_3$); ^{13}C NMR ($CDCl_3$) [50 MHz] δ 169.37 (ester C(O)), 142.78, 141.86, 138.43, 129.99, 129.79, 129.54, 128.31, 126.82, 53.80 ($CHCH_2$), 53.15 (OCH_3), 36.78 (SCH_2Ph), 31.94 (CH*C*H$_2$), 21.35 ($PhCH_3$).

***N*-*t*-Boc-L-His-*S*-Bn-L-Cys-OMe (3).** Compound **1** (7.07 g, 17.8 mmol) was suspended in CH_2Cl_2 (65 mL) and extracted with 10% Na_2CO_3 (50 mL). The organic layer was separated, dried over sodium sulfate, and evaporated to dryness. The oily residue was dissolved in CH_2Cl_2 (40 mL), and *N*-*t*-Boc-L-histidine (5.0 g, 19.6 mmol) was added followed by EDC (1-ethyl-3-(3-(dimethylamino)propyl)carbodiimide) (3.76 g, 19.58 mmol) and diisopropylethylamine (1.5 mL). The reaction mixture was stirred under a slow flow of nitrogen and protected from light. After 48 h the solution was extracted with 0.1 M HCl (2 × 20 mL), 1 M $NaHCO_3$ (2 × 20 mL), and distilled water (2 × 10 mL). The organic layer was concentrated to dryness and the residue dissolved in CH_2Cl_2 (2 mL). The title compound, a colorless crystalline solid (6.0 g, 72%), was isolated by radial chromatography ($MeOH/CH_2Cl_2$): mp 58−60 °C; TLC $R_f = 0.52$ (10% $MeOH/CH_2Cl_2$); ^{1}H NMR ($CDCl_3$) [200 MHz] δ 8.230 (m, 1H, amide NH), 7.480 (d, J = 5.3, 1H, NHC*H*N), 7.270 (m, H aryl), 6.78 (d, CC*H*N), 6.047 (t, J = 7.5, 1H, Boc-NH), 4.680 (m, 1H, Cys-αCH), 4.436 (m, 1H, His-αCH), 3.652 (m, overlap, OCH_3, SCH_2Ph), 3.069 (m, 2H, His-CH_2), 2.771 (m, 2H, CH_2SBn), 1.401 (s, 9H, $C(CH_3)_3$); ^{13}C NMR ($CDCl_3$) [50 MHz] δ 172.02 (ester C(O)), 170.95 (amide C(O)), 155.52 (carbamate C(O)), 137.44, 137.26, 135.07, 128.75, 128.38, 127.05 (C aryl), 80.04 (*C*$(CH_3)_3$), 54.18 (His-CH), 52.42 (OCH_3), 51.75 (Cys-CH), 36.19 (S*C*H_2Ph), 32.81 (*C*H_2SBn), 29.15 (CH_2-imidazole), 28.12 (*C*$(CH_3)_3$); MS (HRSDEI) calcd 439.2283, obsd 439.2267.

L-His-*S*-Bn-L-Cys-OMe Ditrifluoroacetate Salt (4). Compound **3** (1.0 g, 2.28 mmol) was dissolved in trifluoroacetic acid (5 mL) with rapid stirring. Triethylsilane was added dropwise until the color of the solution discharged. The solution was stirred for an additional 1 h before the trifluoroacetic acid was removed in vacuo. The product was used without further purification.

Tr-*S*-Mer-L-His-*S*-Bn-L-Cys-OMe (5). To compound **4** (2.28 mmol) in CH_2Cl_2 (30 mL) were added 2-(triphenylmethylthio)ethanoic acid *N*-hydroxysuccinimido ester (1.1 g, 2.5 mmol) and triethylamine (2.5 mL). The solution was stirred for 36 h before extraction with brine (3 × 15 mL). The organic layer was concentrated to 2 mL and the product isolated by radial chromatography ($CHCl_3$/MeOH). The product was a crystalline solid (1.0 g, 65%): mp 56−59 °C; ^{1}H NMR (CD_3OD) [200 MHz] δ 7.513 (s, 1H, NC*H*NH), 7.292 (m, H-aryl), 6.809 (s, 1H, CC*H*N), 4.584 (m, 1H, His-αCH), 4.473 (m, 1H, Cys-αCH), 3.716 (s, 2H, SCH_2Ph), 3.689 (s, 3H, OCH_3), 2.954 (s, $TrSCH_2$), 2.804 (m, 4H, CHC*H*$_2$); ^{13}C NMR ($CDCl_3$) [50 MHz] δ 172.93, 172.29 (amide C(O)), 170.777 (ester C(O)), 145.51 (Tr-ipso), 135.55 (NH*C*N), 130.70 (Tr-ortho), 130.08 (HC-imidazole), 129.49 (CH_2C), 129.04 (Tr-meta), 127.99 (Tr-ortho), 68.37 (Ph_3C), 54.68 (His-αCH), 53.39 (OCH_3), 52.93 (Cys-αCH), 37.11 (SCH_2Ph), 36.90 ($TrSCH_2$), 33.41-($CHCH_2$).

Re-Mer-L-His-L-Cys-OMe (7a, 7b). Compound **5** (103 mg, 0.152 mmol) was dissolved in trifluoroacetic acid (5 mL) with rapid stirring while triethylsilane was added dropwise until the color discharged. The solvent was removed in vacuo and the residue dissolved in MeOH (20 mL) and evaporated to dryness. The residue was dissolved in a 1/1 THF/MeOH solution (10 mL) and freshly prepared 1 M sodium acetate added (1.5 mL) followed by $ReOCl_3(PPh_3)_2$ (139 mg, 0.167 mmol). The reaction mixture was heated to reflux for 12 h, whereupon it was cooled, filtered, and evaporated to dryness. The residue was dissolved in acetonitrile (500 mL) and filtered through a plug of glass wool. The dark red homogeneous solution was concentrated to approximately half its volume and the product isolated by reversed phase HPLC. Fraction 1, **7a**, was obtained as an orange semisolid: MS (ES) *m*/*z* (relative intensity) 543.1/545.1 (23/39) [M]; ^{1}H NMR (CD_3OD) [500 MHz] δ 8.567 (s, 1H, imidazole-CH), 7.156 (s, 1H, imidazole-CH), 5.093 (t, J = 5.2 Hz, 1H, His-αCH), 4.812 (d, J = 7.3 Hz, 1H, Cys-αCH), 3.935 (d, J = 12.0 Hz, 1H, Cys-βCH (A)), 3.827 (AB, J = 8.2 Hz, 1H, TrSCH(A)), 3.752 (AB, 1H, TrSCH(B)), 3.519 (s, 3H, OCH_3), 3.376 (m, 2H, His-βCH_2), 3.243 (m, 1H, Cys-βCH (B)); ^{13}C NMR (CD_3OD) [125.77 MHz] δ 200.001, 194.75 (amide C(O)), 171.88 (ester C(O)), 133.13 (imidazole-CH), 119.6 (imidazole-C), 117.15 (imidazole-CH), 67.45 (Cys-αCH), 67.12 (His-αCH), 51.20 (OCH_3), 47.06 (Cys-βCH_2), 40.05 ($TrSCH_2$), 26.95 (His-βCH_2). Fraction 2, **7b**, was obtained as an orange semisolid: ^{1}H NMR (CD_3OD) [500 MHz]: δ 8.558 (s, 1H, imidazole-CH), 7.301 (s, 1H, imidazole-CH), 4.914 (dd, 1H, J = 5.1 and 3.76 Hz, His-αCH), 4.317 (dd, J = 10.1 and 7.15 Hz, 1H, Cys-αCH), 3.792 (AB, J = 17.0 Hz, 1H, TrSCH(A)), 3.752 (AB, 1H, TrSCH(B)), 3.712 (s, 3H, OCH_3), 3.680 (m, 1H, Cys-βCH (A)), 3.362 (m, 2H, His-βCH_2), 3.004 (m, 1H, Cys-βCH (B)); ^{13}C NMR (CD_3OD) [125.77 MHz] δ 193.95 (amide C(O)), 191.03 (His amide C(O)), 173.75 (ester C(O)), 133.94 (imidazole-CH), 128.16 (imidazole-C), 118.11 (imidazole-CH), 68.36 (Cys-αCH), 66.37 (His-αCH), 51.26 (OCH_3), 46.18 (Cys-βCH_2), 39.45 ($TrSCH_2$), 27.00 (His-βCH_2).

Results and Discussion

Synthesis of Tr-*S*-Mer-L-His-*S*-Bn-L-Cys-OMe (5). The first disconnection in the retrosynthesis of chelates for use in

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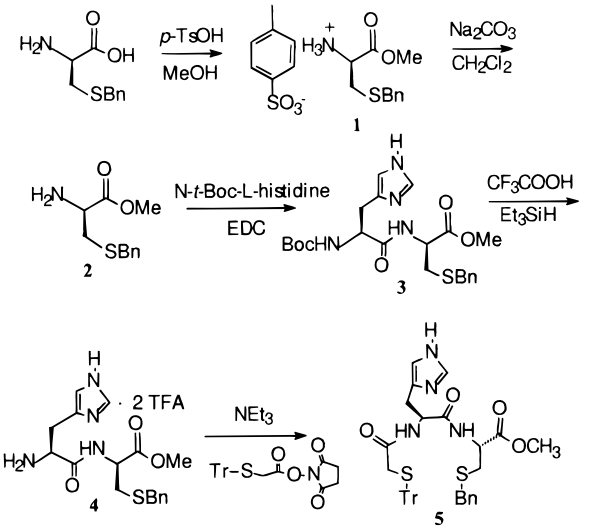
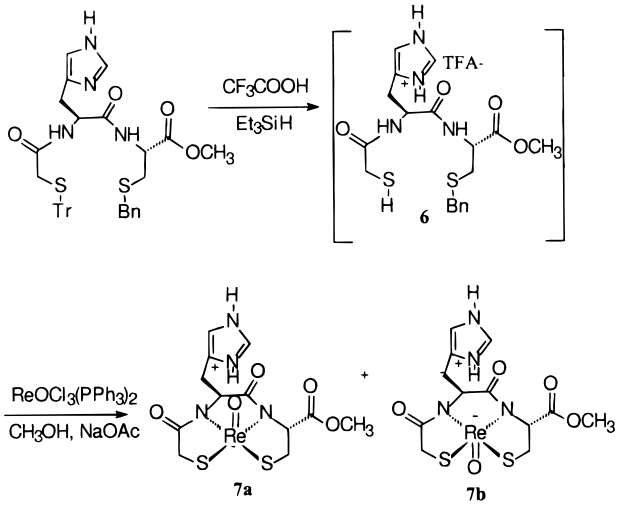
Scheme 1



Scheme 2



radioimaging or therapy is the step in which the metal is incorporated into the chelate. In the case of the Mer-X-Cys chelates, we proposed that a partially deprotected form of the chelate, such as **6**, in which the sulfur species were present as one free thiol and one *S*-benzyl thioether, would readily incorporate rhenium or technetium. It was proposed that, upon reaction with rhenium or technetium, the four donor atoms of the chelate would bind to the metal and that cleavage of the *S*-benzyl group would occur to produce a DADS-like coordination complex.

S-Benzyl-L-cysteine methyl ester *p*-toluenesulfonic acid salt **1** (Scheme 1), which was prepared by Fisher esterification of commercially available *S*-benzyl-L-cysteine, was deprotonated prior to coupling to *N-tert*-butoxycarbonyl-L-histidine; the resulting dipeptide **3** was isolated in good yield (72%). Conversion of the Boc carbamate **3** to the amine **4** was accomplished by the use of trifluoroacetic acid and triethylsilane.[10] Because the deprotection was performed in TFA, which is an excellent solvent for acid-stable amino acids, the product of the deprotection was the bis(trifluoroacetate) salt. An excess of triethylamine or diisopropylethylamine was used to liberate the amine during the coupling of **4** to the *N*-hydroxysuccinimido ester of trityl-protected mercaptoacetic acid.[11]

Synthesis of Re-Mer-L-His-L-Cys-OMe. Compound **5** was deprotected (TFA, Et_3SiH)[4] to give the thiol **6**, which was reacted with $ReOCl_3(PPh_3)_2$,[12] a common starting material for the synthesis of rhenium(V) complexes (Scheme 2). Sodium acetate was included as a buffer in the preparative reaction because the metal displaces two amide protons during formation of the complex.

Silica thin-layer chromatography (TLC) of the methanol/tetrahydrofuran soluble fraction of the reaction mixture indicated the presence of a polar colored compound which moved on the plate in 10% methanol in dichloromethane. Electrospray mass spectrometry (ESMS) indicated the presence of a high-mass compound which contained an isotope ratio pattern similar to that for rhenium. Attempts at purification of this apparent rhenium compound by silica gel chromatography or silica preparative plate chromatography were unsuccessful as the products were always contaminated with various impurities including residual triphenylphosphine and/or triphenylphosphine oxide. Semipreparative reversed-phase high-performance liquid chromatography (HPLC) was, however, successful in isolating two major peaks (fractions 1 and 2). For both fractions, the negative ion electrospray mass spectra indicated the presence of an anion (m/z = 543/545), which confirmed that the *S*-benzyl protecting group had been cleaved. Thin-layer chromatography of each of the HPLC-purified fractions indicated that both products coeluted on silica gel (10% CH_3OH/CH_2Cl_2) when UV was used as the detector.

The ^{1}H NMR spectrum of the first fraction to elute from the HPLC exhibited two downfield multiplets at 5.09 and 4.81 ppm which were assigned to the α protons of the histidine and cysteine, respectively. In a COSY experiment, the multiplet at 5.09 exhibited a correlation to the multiplet at 3.38 ppm. Because the AB part of this ABX type spin system did not exhibit an unusual chemical shift change, which is usually observed for protons within the chelate ring upon complexation of rhenium, the resonance at 3.38 ppm was assigned to the β protons of histidine. Because the Cys β protons were in the ring of the chelate, they were affected by the magnetic anisotropy induced by the rhenium. This explains why the two β protons of cysteine differed in chemical shift by approximately 0.8 ppm. The splitting pattern of the Cys spin system indicated that one of the β protons must be at nearly right angles to the Cys α proton thereby giving a coupling constant value of 0 (i.e., it appeared as a doublet).

The splitting pattern of the cysteine α proton in a ^{1}H spectrum of fraction 2 was a doublet of doublets (δ = 4.32 ppm, J = 10.1 and 7.2 Hz). Because the coupling constants between the α and both β protons were nonzero, the torsion angle between the α and β protons must be different from those in fraction 1. The corresponding Cys β protons were at 3.68 and 3.00 ppm. The His α proton in fraction 2 was also a doublet of doublets (δ = 4.91 ppm, J = 5.1 and 3.8 Hz), and its corresponding β protons exhibited a spin pattern very similar to that of fraction 1.

The most distinguishing feature of the ^{13}C NMR spectra of both fractions was the change in the chemical shift of the carbon atoms of the amide groups. The significant downfield shift stems from the fact that, upon coordination to rhenium, the electron density on the nitrogen of the amide bond is less available to participate in resonance delocalization with the carbonyl group.

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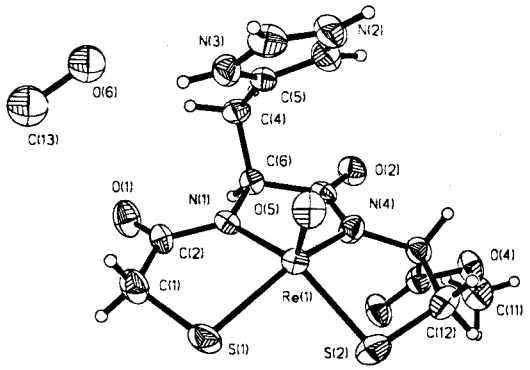

Figure 2. ORTEP diagram of **7a** and a methanol of crystallization showing 50% thermal probability ellipsoids.

The data from the NMR, HPLC, and ESMS suggested that the two fractions were diastereomers. In compounds **7a** and **7b**, the metal is a stereogenic center and its associated oxygen atom can be on the same side as the α protons of the Cys and His amino acids or on the opposite side. From the peak heights in the HPLC chromatogram there were approximately equal amounts of each isomer, suggesting that they must be roughly equal in ground state energy. Reinjection of fraction 1 on an analytical reversed-phase column showed that after 24 h in solution there was only one peak present; that is, there was no indication that the isomers began to equilibrate under these conditions.

Single crystals, from the first fraction to elute from the HPLC of compound **7**, were obtained by slow evaporation of a saturated methanol solution, and these proved suitable for X-ray crystallographic analysis. A summary of the crystallographic data is presented in Table 2. The structure (Figure 2), a typical square pyramidyl arrangement, contained the imidazole ring on the same side as the rhenium oxygen (the syn isomer). The complex was a zwitterion with the metal having a charge of −1 and the counterion being the protonated imidazole ring. The Re−O, Re−N, and Re−S distances (Table 1) were all within expected values. The torsion angles between the α and β protons of cysteine were 24.6° for $HC_\alpha C_\beta H_A$ and −93.1° $HC_\alpha C_\beta H_B$ (A indicates the hydrogen on the same side of the ring as the rhenium oxygen, while B indicates the hydrogen on the opposite side) and were entirely consistent with the coupling constants observed in the ^{1}H NMR for structure **7a**. HPLC fraction 1 was thus structure **7a**, and we postulate that, from NMR and mass spectral data, fraction 2 can be assigned to structure **7b**.

Table 1. Selected Bond Distances (Å) and Angles (deg) for **7a**

Re(1)−O(5)	1.684(5)	Re(1)−S(2)	2.292(2)
Re(1)−N(1)	2.003(5)	Re(1)−S(1)	2.310(2)
Re(1)−N(4)	2.015(5)		
O(5)−Re(1)-N(1)	112.1(2)	N(4)−Re(1)-S(2)	81.5(2)
O(5)−Re(1)-N(4)	110.0(3)	O(5)−Re(1)-S(1)	108.7(2)
N(1)−Re(1)-N(4)	78.0(2)	N(1)−Re(1)-S(1)	82.53(14)
O(5)−Re(1)-S(2)	110.7(2)	N(4)−Re(1)-S(1)	140.9(2)
N(1)−Re(1)-S(2)	136.7(2)	S(2)−Re(1)-S(1)	90.25(7)

Table 2. Summary of Crystal, Intensity, Collection, and Refinement Data

empirical formula	$C_{26}H_{30}N_8O_{12}Re_2S_4$
fw	1147.22
a, Å	10.980(3)
b, Å	8.160(2)
c, Å	11.101(3)
β, deg	106.07(10)
V, Å^3	955.71(4)
Z	1
d_{calcd}, g cm^{-3}	1.993
wavelength, Å	0.710 73
cryst syst	monoclinic
space group	*P*2(1)
abs coeff, mm^{-1}	6.612
F(000)	552
Θ range, deg for data collection	1.91−26.34
reflns collected	7724
indep reflns	3278 [*R*(int) = 0.0223]
data/restraints/params	3278/1/225
goodness-of-fit on F^2	0.756
R indices	R1 = 0.0292, wR2 = 0.0781
R indices (all data)	R1 = 0.0300, wR2 = 0.0801

Conclusions

The chelate Mer-L-His-*S*-Bn-L-Cys-OMe binds rhenium to form two diastereomers in approximately a 1/1 ratio. The two isomers were separated by HPLC, and one, the syn isomer, was characterized by X-ray crystallography. Incorporation of this chelate into biologically active oligopeptides for use in developing site-selective radiopharmaceuticals remains a goal for future research.

Acknowledgment. Financial support from the Natural Science and Engineering Research Council of Canada is gratefully acknowledged as is the award of a Postgraduate scholarship to J.F.V.

Supporting Information Available: Tables listing crystal data, atomic coordinates, isotropic and anisotropic displacement parameters, and bond lengths and bond angles for **7a** (9 pages). Ordering information is given on any current masthead page.

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