Synthesis and Characterization of Neutral $M^{V}O$ (M = Tc, Re) Amine–Thiol Complexes Containing a Pendant Phenylpiperidine Group

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The reaction of the racemic bis(amino thio)–phenylpiperidine compound BAT-PPP with $^{99}TcO_4^-$ and stannous tartrate or $Tc^{V}O$(ethylene glycol)$_2$, resulted in two neutral isomeric complexes. In both complexes, the Tc is coordinated to an amide nitrogen atom, an amine nitrogen atom and both thiolate sulfur atoms in a square pyramidal coordination environment with oxygen in an apical position. The isomer with the pendant group syn to the Tc=O bond appears to display longer retention time in reverse phase HPLC than the anti isomer. Both isomers were characterized in the solid state and in detailed NMR studies. The TcO(BAT-PPP) syn isomer ($TcOC_{22}H_{36}S_2N_3O$) crystallizes in the monoclinic space group $P2_1/n$, with $Z = 4$; the cell constants are $a = 12.390(2)$ Å, $b = 11.470(2)$ Å, $c = 18.320(3)$ Å, $\beta = 103.09(1)°$, and $V = 2534.92(69)$ Å^3. The TcO(BAT-PPP) anti isomer ($TcC_{22}H_{36}S_2N_3O$) crystallizes in the orthorhombic space group $Pna2_1$, with $Z = 8$; the cell constants are $a = 19.823(2)$ Å, $b = 11.530(2)$ Å, $c = 22.373(4)$ Å, and $V = 5114.17(15)$ Å^3. The corresponding rhenium analogs were prepared by ligand exchange reactions. The ReO(BAT-PPP) syn isomer ($ReC_{22}H_{36}S_2N_3O$) crystallizes in the monoclinic space group $P2_1/c$ with $Z = 8$, $a = 17.681(2)$ Å, $b = 13.425(2)$ Å, $c = 21.301(4)$ Å, $\beta = 99.81(1)°$, and $V = 4982.3(9)$ Å^3. The solution NMR data, taken in $CDCl_3$, are consistent with the structures determined by X-ray diffraction experiments. The effects of the constrained ligand system and the M=O group are clearly seen in the patterns for the syn and anti MO(BAT-PPP) (M = Tc, Re) isomers in proton and ^{13}C NMR spectroscopy. The proton and ^{13}C chemical shifts do not change significantly going from Tc to Re. Biodistribution differences between Tc isomers of BAT-PPP and isomers of a BAT ligand with a pendant biphenylylpiperizine (BPA) group may be rationalized in terms of the flexibility of the latter pendant group compared to the relative rigidity of the phenylpiperizine pendant group.

Introduction

The development of ^{99m}Tc based cerebral perfusion agents has been a major focus of nuclear medicine for the last decade.[1] The criteria for an ideal brain imaging agent include (1) blood brain barrier penetrability, which in many cases is dependent on parameters such as lipophilicity, charge, molecular weight, and protein binding capabilities; (2) prolonged retention; and (3) fixed regional distribution in the brain, which is often dependent on mechanisms such as enzymatic hydrolysis of the molecule[2] or *in vivo* decomposition.[3,4]

The bis(amino thiol) (BAT) ligand system has been shown to form stable neutral $Tc^{V}O$ complexes which penetrate the blood brain barrier.[5-7] Simple alkyl-substituted ^{99m}TcO(BAT) complexes demonstrated blood brain barrier penetrability, but showed poor brain retention, presumably due to lack of a brain trapping mechanism.[8] Recently, we prepared Tc complexes of the BAT derivative containing an *N'*-benzylpiperazinyl (BPA) side chain.[9] Due to the presence of a chiral center, a mixture of diastereomers (syn and anti) were obtained following chelation with ^{99m}Tc and ^{99}Tc (Scheme I). The syn isomer displayed a higher *in vivo* brain uptake in rats (2.77 and 0.57% dose/organ at 2 min, respectively) and longer brain retention than the corresponding anti isomer (1.08 and 0.27% dose at 15 min, respectively). We extended the study of the BAT framework to include a number of monoamine (piperidinyl) derivatives. As in the case of the BPA derivatives, these ligands also included a chiral center on the BAT framework as well as a chiral center on the C-4 carbon of the piperidinyl moiety. For each ligand, a mixture of two diastereomers was obtained upon chelation with ^{99m}Tc. In a similar biodistribution study in rats, the diastereomers exhibited widely different brain uptake values which diminished as the steric bulk of the substituent at the C-4 position of the piperidinyl ring increased.[10] In the case of ^{99m}Tc-BAT-PPP (Scheme I), the brain uptake in rats at 2 min post injection was 1.19 and 1.46% dose/organ for syn and anti isomers, respectively; at 15 min, the brain uptake was 0.54 and 0.64% dose/organ, respectively. The disparity in brain uptake for ^{99m}Tc-BAT-PPP between syn and anti isomers was contrary

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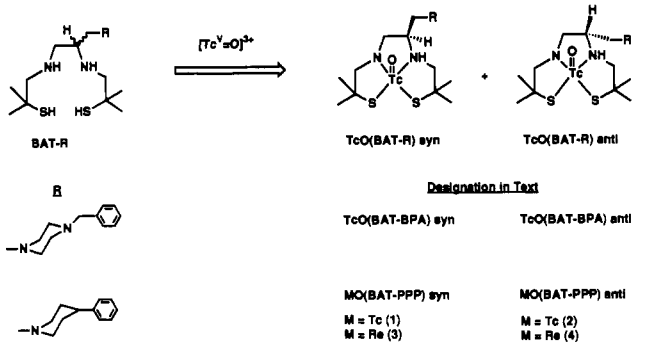
Scheme I



to that observed for BAT-BPA. We undertook the present study to determine if any structural features were responsible for the disparity in brain uptake and retention of the phenylpiperidinyl derivatives. Structural determination of Tc complexes of 4-phenylpiperidinyl–BAT in solid state as well as in solution are reported (Scheme I).

Due to the interest in correlating Tc and Re chemistry, the study was extended to include the Re analogs. The radioisotopes ^{186}Re (β^- = 1.07 MeV, $t_{1/2}$ = 90 h) and ^{188}Re (β^- = 2.12 MeV; $t_{1/2}$ = 17 h) are potentially useful isotopes for radiotherapeutic applications.[11a-d] A few studies comparing properties of Tc and Re analogs have recently been published.[12-15]

Experimental Section

General Comments. ^{99}Tc is a weak β emitter (energy 292 KeV) with a half-life of 2.21×10^5 years. The handling of milligram quantities of this material does not pose a serious health hazard since common laboratory materials provide adequate shielding. Normal radiation safety procedures must be used to prevent contamination.

All common laboratory chemicals were reagent grade, purchased from commercial sources and used without further purification. Silica gel (60–140 mesh) and silica gel TLC plates (Kieselgel 60 F_{254}) were purchased from Baker and EM Science, respectively. The ligand BAT-PPP·3HCl was prepared by the published procedure.[10] ^{99}Tc, as $NH_4{}^{99}TcO_4$ was obtained from Oak Ridge National Laboratory, Oak Ridge, TN. (30% H_2O_2 was added to an aqueous solution of NH_4TcO_4 to oxidize any TcO_2 present.) The ammonium pertechnetate solution was standardized prior to use as previously described.[16] Saline solutions of $Na[^{99m}TcO_4]$ were obtained from a $^{99m}Tc/^{99}Mo$ generator (NEN/DuPont, North Billerica, MA). The ^{99m}Tc glucoheptonate complex was prepared from a Glucoscan kit (stannous glucoheptonate, NEN/DuPont). UV–visible spectra were recorded in acetonitrile on a Beckman DU-7 spectrophotometer at ambient temperatures. Infrared spectra were recorded on a Mattson-Polaris instrument as KBr pellets. Elemental analysis was carried out by Atlantic Microlabs Inc., Norcross, GA. High-performance liquid chromatography (HPLC) measurements were made on a PRP-1 column (25 cm) (Hamilton) at a flow rate of 1 mL/min; the mobile phase consisted of acetonitrile–5 mM 3,3-dimethylglutaric acid, pH = 7 (80:20). The positive ion fast atom bombardment mass spectra (FABMS) were measured on a MAT 731 high-resolution mass spectrometer equipped with an Ion Tech B11N FAB gun with xenon used as the neutral gas. The samples were dissolved in methylene chloride and the matrix was *m*-nitrobenzyl alcohol.

The metal reagents, $[Tc^{V}O(eg)_2]Na$ and $Re^{V}OCl_3(PPh_3)_2$, were prepared as described previously.[17,18] The $Re^{V}O$(citrate) stock solution[19] was prepared by treating a 15-mL solution of $K[ReO_4]$ (1.7 mmol) and sodium citrate (20 mmol) at pH = 6 with a suspension of stannous tartrate (0.7 g) in 10 mL of water. The resulting blue solution (0.67 M in Re) was used in situ for the preparation of the ReO(BAT-PPP) isomeric complexes.

Collection of NMR Data. All NMR spectra were obtained on a Bruker AM-500 spectrometer at T = 300 K in quadrature detection mode. Proton spectra were obtained at a frequency of 500.13 MHz in $CDCl_3$ solution with TMS as an internal reference. The 2D homonuclear Correlated Spectroscopy experiments (COSY) were run using a 90°–t_1–45° pulse sequence (COSY-45). Acquisition parameters were as follows: SW = 3311.258 Hz; 1K data points; 256 FIDs of eight scans and two dummy scans each. The initial t_1 time was 3 μs and a 1-s relaxation delay was used after each acquisition. The data were processed in the magnitude mode. Nonshifted sinebell functions were applied in each dimension before Fourier transformation.

Proton-decoupled carbon spectra were obtained at 125.77 MHz using composite pulse decoupling (CPD) in the WALTZ-15 mode. Multiplicities were obtained from DEPT spectra where the last decoupler pulse has a value of 135°. In this case, methyne and methyl carbons have opposite phases from methylene carbons. Assignments of carbon resonances were based on the results of 2D proton carbon correlated experiments (HC CORR). Experimental conditions were as follows: SW = 17241.4 MHz; 2K data points; 552 scans and two dummy scans; initial t_1 = 3 μs; 1-s relaxation rate after acquisition. The delays D3 preceding the last 90° pulse and D4 following the 90° pulse were 3.7 and 1.85 ms, respectively. For the proton dimension, SW was 3649.6 Hz, and 349 experiments were performed. After zero filling, the final size was 2K × 1K. Before processing, FID's in both dimensions were multiplied by nonshifted sinebell functions. Data were processed in the magnitude mode.

Preparation of $Tc^{V}O$(BAT-PPP) Syn (1) and Anti (2) Isomers. Method 1. From $[Tc^{V}O(eg)_2]Na$. $[Tc^{V}O(eg)_2]Na$ (50 mg, 0.2 mmoL) and 115 mg of BAT-PPP·3HCl (0.22 mmoL) were added to 30 mL of $CHCl_3$. To this suspension was added 10 mL of 0.2 M NaOH, and the reaction was stirred vigorously for 1 h and then heated at 45 °C. The reaction consisted of an orange yellow $CHCl_3$ solution and a clear, colorless water solution. The layers were separated and the aqueous layer was washed once with 20 mL of $CHCl_3$. The $CHCl_3$ layers were combined, dried with Na_2SO_4, and evaporated to a filmy solid. The solid was dissolved in CH_2Cl_2 and loaded on a 20 × 1 cm Kieselgel column prepared in CH_2Cl_2. Elution with CH_2Cl_2 resulted in one yellow brown peak, compound **1**. The column was washed with increasing percentages of $CHCl_3$ and a brown diffuse peak was eluted with $CHCl_3$ (compound **2**). Ethanol was added to both fractions, and crystals were grown by slow evaporation. Yield: compound **1** (syn isomer), 15 mg (14% based on Tc); compound **2** (anti isomer), 19 mg (18% based on Tc). Analytical data for both isomers are given in Table I. NMR data for proton, comparison of proton and ^{13}C chemical shifts for the syn and anti isomers are given in Tables II–IV, respectively.

Method 2. From $NH_4[TcO_4]$. To a solution of the ligand BAT-PPP·3HCl (106 mg, 0.205 mmoL) in 30 mL of ethanol/H_2O (60/30) were added an aqueous solution of NH_4TcO_4 (0.65 mL, 0.306 M, 0.20 mmol) and an additional 10 mL of ethanol. The solution was heated and stirred for ca. 10 min to form a light yellow solution. A slurry of stannous tartrate (55 mg, 0.205 mmol) in water was added to the heated solution (60 °C) followed by 5 mL of 1 M $NaHCO_3$ and then 30 mL of ethanol. The suspension was heated and stirred at 60 °C for ca. 1 h. The resulting dark brown solution was evaporated under reduced pressure to a yellow-brown solid. The solid was dissolved in 1.5 mL of CH_2Cl_2. The solution was loaded onto a silica gel column (25 × 1 cm) prepared in CH_2Cl_2 and eluted with CH_2Cl_2. One yellow band eluted with CH_2Cl_2. Upon elution with $CHCl_3$, a second, brown band eluted. To these fractions, ethanol was added to crystallize both products. Yield: compound **1** (syn isomer), 12 mg (12% yield based on Tc); compound **2** (anti isomer), 15 mg (15% yield based on Tc). These isomers are identical to those prepared by method 1 as determined by TLC, HPLC, and NMR data.

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Table I. Analytical Data for *syn*- and *anti*-MO(BAT-PPP) (M = Tc, Re) Isomers

	anal.							
	% element	calcd	obsd	UV/vis[a] λ, nm (ε, M^{-1}, cm^{-1} L)	MS $(M + H)^+$, *m/e*	IR[b] M=O, cm^{-1}	TLC, R_f ($CHCl_3$)	HPLC[c] R_t, min
syn-TcO(BAT-PPP)	C	50.67	50.89	265 (7800)	522	919	0.34	19.5
	H	6.95	7.02	336 (sh)				
	N	8.05	8.01	414 (2000)				
anti-TcO(BAT-PPP)	C	50.67	50.57	266 (11 000)	522	900	0.19	14.1
	H	6.95	7.09	330 (sh)				
	N	8.05	8.00	424 (3900)				
syn-ReO(BAT-PPP)	C	43.35	43.41	236 (9000)	610	935	0.37	16.2
	H	5.91	5.98	260 (sh)				
	N	6.90	6.84	348 (3000)				
				507 (44)				
				540 (40)				
anti-ReO(BAT-PPP)	C	43.35	43.38	237 (7700)	610	929	0.17	12.3
	H	5.91	5.89	260 (sh)				
	N	6.90	6.93	352 (2500)				
				530 (60)				

[a] In CH_3CN. [b] KBr pellet. [c] Column: 25 cm PRP-1 (Hamilton) 80/20 CH_3CN/5 mM DMGA; pH = 7; 1 mL/min.

Preparation of $Re^{V}O(BAT\text{-}PPP)$ Syn (3) and Anti (4) Isomers. Method 1. From $Re^{V}OCl_3(PPh_3)_2$. A 185-mg sample of BAT PPP·3HCl ($C_{22}H_{39}N_3S_2$·3HCl, 0.358 mmol) was dissolved in ca. 20 mL of methanol to give a clear solution. $Re^{V}OCl_3(PPh_3)_2$ (255 mg, 0.35 mmol) was dissolved in 80 mL of CH_2Cl_2 to give a yellow solution. The Re solution was added to the ligand solution. Immediately, a clear brown rust-colored solution resulted. A methanolic solution of NaOAc (2.5 mL of 0.75 M NaOAc in methanol) was added dropwise. The reaction turned rose-colored and deposited a white solid. The mixture was heated gently, ca. 40 °C, and stirred for ca. 2 h; then the suspension was cooled and filtered. (The filtrate was still slightly cloudy.) The solution was evaporated to dryness to give an oily rose-colored solid, redissolved in CH_2Cl_2, and loaded onto a silica gel column, prepared in CH_2Cl_2. The column was eluted with CH_2Cl_2. One band (rose-colored) eluted (compound **3**). The solvent system was changed to 50% CH_2Cl_2/50% $CHCl_3$ to elute a purple band (compound **4**). Ethanol was added to these fractions and crystals were obtained upon slow evaporation. The first band resulted in the syn isomer, compound **3**. The second band resulted in the anti isomer, compound **4**. Yield: complex **3** (syn isomer), 30 mg, 14% based on Re; complex **4** (anti isomer), 30 mg, 14% based on Re. Analytical data for both isomers are given in Table I. Tables II–IV show proton NMR data and a chemical shift comparison for proton and ^{13}C spectra of the isomers, respectively.

Method 2. From ReO(citrate). BAT-PPP·3HCl (200 mg, 0.385 mmol) was dissolved in 20 mL of water. A stock solution of rhenium citrate (10.4 mL, 0.35 mmol) was added. The resulting suspension was blue. NaOH (5 mL, 1 N) was added to pH = 9–10. The resulting suspension was greenish-brown. The suspension was stirred for 30 min, followed by the addition of $CHCl_3$ to form two layers: a top brown-green layer and a bottom rose-colored layer. The layers were separated. The organic layer was dried with Na_2SO_3, filtered, and evaporated to give a rose-colored film. This film was dissolved in CH_2Cl_2 and chromatographed on silica gel as described for method 1. Yield: complex **3** (syn isomer), 25 mg, 11% based on Re; complex **4** (anti isomer), 28 mg, 13% based on Re. The isomers prepared by this method show identical TLC, HPLC, and NMR behavior to those prepared by method 1.

Preparation of $^{99m}Tc^{V}O(BAT\text{-}PPP)$ Isomers. The $^{99m}Tc^{V}O(BAT\text{-}PPP)$ isomers were prepared by the ligand exchange procedure described earlier[14] as well as a direct reduction of $^{99m}TcO_4^-$ by stannous tartrate in the presence of ligand. For the ligand exchange method, BAT-PPP·3HCl was reacted with a ^{99m}Tc–glucoheptonate radiopharmaceutical kit in water at pH = 7.4. The complexes were extracted into $CHCl_3$. Alternatively, the complexes could be obtained by loading the aqueous reaction solution on a reverse phase Sep-pak cartridge, washing with water and 50/50 (v/v) ethanol/water, and eluting the radioactive band with 100% ethanol. For the direct reduction method, 0.5 mg of ligand was dissolved in 200 μL of water; 0.2 mL of $Na[^{99m}TcO_4]$ generator eluate was added, followed by 25 μL of a saturated stannous tartrate solution. The solution was incubated for 15 min at room temperature; the pH of the solution prepared in this fashion was 3.3. Another sample was buffered using 0.5 mL of 1 M $NaHCO_3$ at pH = 9.5 before incubation. Both samples were worked up following the extraction method described above. For each sample prepared at the three different pH values by either the ligand exchange method (pH = 7.4) or the direct reduction method (pH = 3.3 or 9.5), two peaks of approximately equal intensity were obtained on reverse phase HPLC. These peaks were assigned to the syn and anti isomers (the longest retained was assigned to the syn isomer, the least retained assigned to the anti isomer). The ^{99m}Tc isomers eluted with the ^{99}Tc complexes when co-injected. The ^{99m}Tc isomers could be separated by collecting the appropriate peaks as they eluted from the reverse phase column.

Ligand Exchange Experiments with $^{99m}Tc^{V}O(BAT\text{-}PPP)$ Isomers. The isomers were purified and isolated as described above. The fractions were evaporated to dryness and redissolved in ethanol, and racemic ligand (150 mM) was added to each solution. The solutions were heated at 70 °C for a period of 3 h. Samples were analyzed at various time intervals by HPLC.[20]

Collection and Reduction of X-ray Data. Crystal and data collection parameters are summarized in Table V. Data were collected on a Nicolet R3m diffractometer using Mo Kα radiation (λ = 0.710 73 Å). Cell constants were determined by a least-squares fitting of the setting angles of 25 accurately centered reflections. The ω–2θ scan technique was used for data collection; the intensities of three standard reflections, measured every 197 reflections, showed no significant decay. Data were corrected for background, attenuators, and Lorentz and polarization effects in the usual fashion. Atomic scattering factors were taken from Cromer and Mann.[21] The structures were solved by standard heavy-atom Patterson and Fourier techniques. Refinement was by the full-matrix least-squares method to minimize $\sum w(|F_o| - |F_c|)^2$ where $w = 1/\sigma^2(F_o) + 0.005(F_o)$.

Results

(A) Synthesis of Complexes. The bis(aminoethanethiol) complexes of Tc(V) were prepared by two methods: by the direct reduction of pertechnetate with stannous ion, under basic conditions, in the presence of ligand; by ligand exchange from $Na[Tc^{V}O(eg)_2]$. Using both methods, the neutral, lipophilic complexes could be extracted into chloroform, purified, and isolated by column chromatography. Complex **1** elutes with methylene chloride; changing the eluant to chloroform results in elution of complex **2**.

The corresponding rhenium complexes cannot conveniently be prepared by reduction of perrhenate by Sn^{2+} similar to the Tc analogs. Perrhenate, ReO_4^-, is more difficult to reduce than TcO_4^-.[22] The rhenium complexes were, therefore, prepared by exchange reactions of intermediate $Re^{V}O$ complexes such as $Re^{V}OCl_3(PPh_3)_2$ or $Re^{V}O$(citrate) with the BAT-PPP ligand. The citrate intermediate was not isolated and characterized but was

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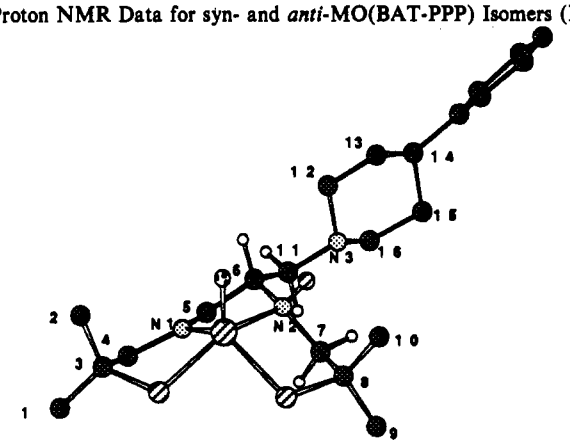
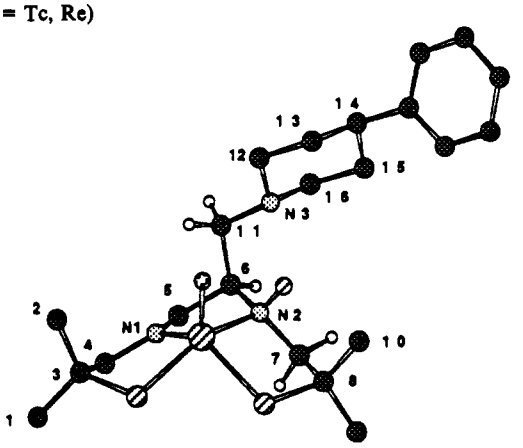
Table II. Proton NMR Data for syn- and *anti*-MO(BAT-PPP) Isomers (M = Tc, Re)





complex	chem shift, δ ppm	integration	multiplicity	assignment	$J_{(H-H)}$, Hz
TcO(BAT-PPP)	7.88	1 [H]	d	N–H	J_{NH-H7} = 11 (anti); J_{NH-H} = 2 (syn)
syn isomer	7.89–7.17	5 [H]	m	aromatic	
	3.64	1 [H]	d	H4	J_{H4-H4} = 11.2
	3.56	1 [H]	d	H4	
	3.45	1 [H]	dd	H11	$J_{H11-H11}$ = 12.4, J_{H11-H6} = 5.3
	3.35–3.26	3 [H]	m	H5, H11, H6	J_{H5-H6} = 4.5
	3.17	2 [H]	m	H12, H16	
	2.88	1 [H]	d	H7	J_{H7-H7} = 10.5
	2.68	1 [H]	dd	H5	J_{H5-H5} = 12.6
	2.62–2.56	2 [H]	m	H12, H14	
	2.34	1 [H]	t	H16	
	2.06–1.63	5 [H]	m	H7, H13, H15, H13, H15	
	1.76	3 [H]	s	methyl	
	1.72	3 [H]	s	methyl	
	1.54	3 [H]	s	methyl	
	1.51	3 [H]	s	methyl	
TcO(BAT-PPP)	7.32–7.18	5 [H]	m	aromatic	
anti isomer	6.25	1 [H]	d	N–H	J_{NH-H7} = 12.7 (anti); J_{NH-H} = 3.5 (syn)
	4.44	1 [H]	m	H6	
	3.71	1 [H]	d	H4	J_{H4-H4} = 11
	3.62	1 [H]	d	H4	
	3.58	1 [H]	dd	H5	J_{H5-H6} = 12.1 Hz, J_{H5-H6} = 11.3 Hz
	3.29	1 [H]	d	H16	
	3.03	1 [H]	t	H5	J_{H5-H6} = 5.3
	2.96	1 [H]	dd	H7	J_{H7-H7} = 10.41
	2.90	1 [H]	d	H12	
	2.64	1 [H]	dd	H11	$J_{H11-H11}$ = 13.5
	2.50	2 [H]	m	H11, H14	J_{H11-H6} = 11.3
	2.34	1 [H]	t	H12	
	2.07	1 [H]	t	H16	
	1.95–1.85	2 [H]	m	H13, H15	
	1.68–1.57	3 [H]	m	H13, H15, H7	
	1.78	3 [H]	s	methyl	
	1.67	3 [H]	s	methyl	
	1.51	3 [H]	s	methyl	
	1.45	3 [H]	s	methyl	
ReO(BAT-PPP)	8.10	1 [H]	s	N–H	
syn isomer	7.35–7.12	5 [H]	m	aromatic	
	3.61	1 [H]	d	H4	J_{H4-H4} = 10.9
	3.48–3.39	3 [H]	m	H11, H11, H4	J_{H11-H6} = 4; $J_{H11-H11}$ = 12.3
	3.28	2 [H]	m	H6, H5	J_{H5-H6} = 6
	3.16	2 [H]	m	H16, H12	
	2.74–2.69	2 [H]	m	H7, H5	J_{H7-H7} = 10.7
	2.62–2.55	2 [H]	m	H12, H14	
	2.35	1 [H]	t	H16	
	1.97–1.96	2 [H]	m	H7, H15	
	1.87	1 [H]	–	H13	
	1.77	1 [H]	dt	H13	
	1.65	1 [H]	–	H15	
	1.84	3 [H]	s	methyl	
	1.66	6 [H]	s	methyl	
	1.47	3 [H]	s	methyl	
ReO(BAT-PPP)	7.17–7.32	5 [H]	aromatic		
anti isomer	6.73	1 [H]	m	N–H	J_{NH-H7} = 12.8 (anti); J_{NH-H7} = 3.7 (syn)
	4.42	1 [H]	m	H6	J_{H5-H6} = 5.8; J_{H5-H6} = 11 Hz
	3.78	1 [H]	m	H5	J_{H5-H5} = 12.2
	3.69	1 [H]	d	H4	J_{H4-H4} = 10.9

Table II (Continued)

complex	chem shift, δ ppm	integration	multiplicity	assignment	$J_{(H-H)}$, Hz
ReO(BAT-PPP)	3.42	1 [H]	d	H4	
anti isomer	3.34	1 [H]	d	H16	
	2.97	1 [H]	t	H5	
	2.91	1 [H]	m	H12	
	2.83	1 [H]	m	H7	J_{H7-H7} = 10.3
	2.66, 2.65	2 [H]	m	H11, H11	J_{H11-H6} = 7.3
	2.52	1 [H]	m	H14	
	2.31	1 [H]	t	H12	
	2.03	1 [H]	t	H16	
	1.95–1.80	3 [H]	m	H15, H13, H15	
	1.65	1 [H]	m	H13	
	1.54	1 [H]	m	H7	
	1.85	3 [H]	s	methyl, H3	
	1.61	3 [H]	s	methyl, H8	
	1.59	3 [H]	s	methyl, H8	
	1.42	3 [H]	s	methyl, H3	

Table III. Proton Chemical Shifts, δ (ppm), and Δδ for Tc and Re Isomers

	chem shift			chem shift		
proton	*syn*-TcO(BAT-PPP)	*anti*-TcO(BAT-PPP)	Δδ(syn–anti)	*syn*-ReO(BAT-PPP)	*anti*-ReO(BAT-PPP)	Δδ(syn–anti)
N–H	7.88	6.25	+1.63	8.10	6.73	1.37
H4	3.64	3.62	–0.07	3.61	3.69	–0.08
H4	3.56	3.62	–0.06	3.39	3.42	–0.03
H5	3.33	3.58	–0.25	3.28	3.78	–0.50
H5	2.68	3.03	–0.35	2.69	2.97	–0.28
H6	3.32	4.48	–1.2	3.27	4.42	–1.15
H7	2.88	2.96	–0.08	2.74	2.83	–0.09
H7	2.06	1.62	0.44	1.97	1.54	0.43
H11	3.45	2.64	+0.81	3.48	2.66	+0.82
H11	3.31	2.57	0.74	3.42	2.65	+0.77
H12	3.17	2.90	0.27	3.16	2.91	0.25
H12	2.58	2.34	0.34	2.62	2.31	0.31
H13	1.87	1.94	–0.07	1.87	1.90	–0.03
H13	1.82	1.75	0.07	1.77	1.65	0.12
H14	2.58	2.55	0.03	2.55	2.52	0.03
H15	1.98	1.92	0.06	1.96	1.95	0.11
H15	1.70	1.72	0.02	1.65	1.80	–0.15
H16	3.17	3.29	–0.12	3.16	3.34	–0.18
H16	2.34	2.07	0.27	2.35	2.03	0.33

Table IV. Carbon-13 Chemicakl Shifts, δ (ppm), and Δδ for Tc and Re Isomers

	chem shift				chem shift		
carbon	*syn*-TcO(BAT-PPP)	*anti*-TcO(BAT-PPP)	Δδ(syn–anti)	carbon	*syn*-ReO(BAT-PPP)	*anti*-ReO(BAT-PPP)	Δδ(syn–anti)
C3	55.44	56.10	–0.66	C3	61.47	62.34	–0.87
C4	81.62	82.28	–0.66	C4	81.77	82.47	–0.70
C5	58.85	65.04	–6.19	C5	59.07	67.19	–8.12
C6	57.95	60.44	–2.49	C6	61.32	63.74	–2.42
C7	67.12	58.98	+8.14	C7	68.81	60.25	+8.56
C8	51.22	52.25	–1.03	C8	56.43	58.09	–1.60
C11	65.09	55.92	+9.87	C11	67.31	55.18	+12.13
C12	56.24	56.36	–0.12	C12	56.09	56.39	+0.30
C13	33.86	34.21	–0.35	C13	33.79	34.33	–0.54
C14	42.21	42.28	–0.07	C14	42.20	42.29	–0.09
C15	34.06	33.20	+0.86	C15	34.07	33.18	0.89
C16	52.37	53.64	–1.27	C16	52.42	53.74	–1.32

used when formed *in situ* by the reduction of ReO_4^- by Sn^{2+} in citric acid. This method is commonly used to prepare tracer ^{186}Re complexes.[12] The neutral, lipophilic Re analogs can be purified and isolated in a method similar to that of the Tc complexes.

The isomeric sets of the ^{99}Tc and Re complexes were formed in approximately equal amounts regardless of the preparation method. This is consistent with the tracer ^{99m}Tc isomers prepared by exchange from ^{99m}Tc–glucoheptonate reported previously with this ligand system[10] and with the BPA ligand system.[9] When the complexes are prepared by reduction of $^{99m}TcO_4^-$ with $SnC_4H_4O_6$ at pH = 3–10, an isomer ratio of approximately 50/50 anti:syn is observed by HPLC. The tracer ^{99m}Tc complexes elute with the ^{99}Tc complexes when co-injected (Figure 1), indicating that the chemical species are similar under the HPLC conditions. Aqueous solutions of the ^{99m}Tc isomers were stable for a period of hours.[10] The $M^{v}O$(BAT-PPP) (M = ^{99}Tc, Re) isomers were very stable in the solid state (for months) and in organic solution and in mixtures of organic aqueous solution (for a period of weeks), as shown by NMR and HPLC. The conversion of one isomer to another was not observed under these conditions. On the tracer (^{99m}Tc) level however, in the presence of excess ligand in the free thiol form, the anti isomer was found to convert approximately 5–10% to the syn isomer after heating for 3 h. The conversion of the syn isomer to the anti isomer under identical conditions was not observed. This is consistent with results obtained by us for other isomeric pairs[20] and suggests that the syn isomer is more thermodynamically stable than the anti isomer.

The R_f values on silica gel TLC and retention times on reverse phase HPLC (Table I) are consistent with the high lipophilicity

Table V. Crystal Data and Data Collection Parameters

	syn-TcO(BAT-PPP)	*anti*-TcO(BAT-PPP)	*syn*-ReO(BAT-PPP)
formula	$TcC_{22}H_{36}S_2N_3O$	$TcC_{22}H_{36}S_2N_3O$	$ReC_{22}H_{36}S_2N_3O$
fw	522	522	610
cryst class	monoclinic	orthorhombic	monoclinic
space group	$P2_1/n$; $Z = 4$	$Pna2_1$; $Z = 8$	$P2_1/c$; $Z = 8$
cell consts			
a, Å	12.390(2)	19.823(2)	17.681(2)
b, Å	11.470(2)	11.530(2)	13.425(2)
c, Å	18.320(3)	22.373(4)	21.301(4)
β, deg	103.09(1)		99.81(1)
V, Å^3	2534.92(69)	5114.17(1.5)	4982.3(9)
D_{calc}, gcm^{-3}	1.36	1.352	1.62
μ, mm^{-1}	0.72	0.73	0.51
scan range	$0.0° < 2\theta < 50°$	$0.0° < 2\theta < 50°$	$0.0° < 2\theta < 50°$
no. of reflcns used in refinenemt	3484 [$F_o \geq 6\sigma(F_o)$]	2853 [$F_o \geq 6\sigma(F_o)$]	5188 [$F_o \geq 6\sigma(F_o)$]
R	0.029	0.048	0.033
R_w	0.033	0.052	0.036
goodness of fit	1.09	1.44	1.13

of these complexes.[10] The M^{v}O(BAT-PPP) syn isomers, **1** and **3**, have longer retention times in reverse phase chromatography than the anti isomers, **2** and **4**, and have higher R_f values on silica gel. Complexes which are lipophilic will have greater mobility (higher R_f) on silica gel as well as longer retention time in reverse phase chromatography. The rhenium isomers show a longer retention time in reverse phase chromatography than the corresponding technetium analogs.

(B) Spectroscopy. The molecules exhibit strong M=O stretching frequencies at 900–919 and 929–935 cm^{-1} for the Tc and Re isomeric pairs respectively, as shown in Table I. These are at the low end of the ranges generally observed for monooxo M^{v}O (M = Tc, Re)(900–1000 cm^{-1} for Tc; 930–1000 cm^{-1} for Re),[23] consistent with the strong σ- and π-donating properties of the dithiolate sulfurs and the amide nitrogen of the ligand. The Re=O stretching frequencies were found ca. 15–25 cm^{-1} higher than the corresponding Tc complexes. This difference in the stretching frequencies between analogous Tc and Re complexes has been previously observed.[12-14] Furthermore, the syn isomers exhibited stretching frequencies of slightly higher energy than the anti isomers.

The UV-visible spectroscopic data are presented in Table I. The Tc molecules exhibit UV–visible absorptions in the 400–425-nm region, giving rise to the gold-brown color as well as a strong band around 260–270 nm. This presumably arises from a ligand-to-metal charge transfer from the π orbitals of the sulfur atoms to the empty d_{xz} and d_{yz} orbitals of the Tc(V) atom. The rhenium analogs show strong bands at ca 350 and 235 nm and weak bands at 500–540 nm; presumably, the latter are due to weak d→d transitions, resulting in the faint rose color of the Re complexes.

Each molecule shows a molecular ion, $(M + H)^+$ in the positive ion FAB mass spectrum. Also observed in the mass spectra of the Tc^{v}O(BAT-PPP) isomers were ions at M_2H^+. These are presumably due to association of a cation, MH^+, and a neutral species, M, and not to dimeric impurities in the samples. This phenomenon has been observed previously for neutral chelate complexes.[24,25] The Re^{v}O(BAT-PPP) anti isomer displayed a cluster at m/z = 1219, consistent with the M_2H^+ species.

Using the results of 1D ^{1}H and ^{13}C spectra, DEPT spectra, double irradiation experiments, and 2D COSY and HC-CORR experiments, complete assignments of the ^{1}H and ^{13}C resonances of the M^{v}O(BAT-PPP) (M = Tc, Re) isomers can be made. The

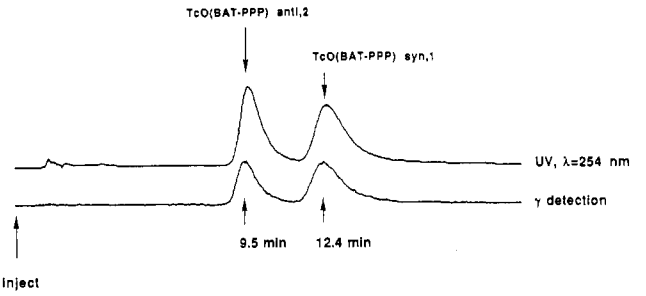


Figure 1. HPLC profile of the ^{99}Tc/^{99m}TcO(BAT-PPP) isomers. Conditions: 25 mm Hamilton PRP-1 column; mobile phase, 85% CH_3CN/15% 5 mM DMGA; pH = 7; 1 mL/min. Top trace: ^{99}Tc complexes using UV detection, λ = 254 nm. Bottom trace: the ^{99m}Tc complexes using γ detection.

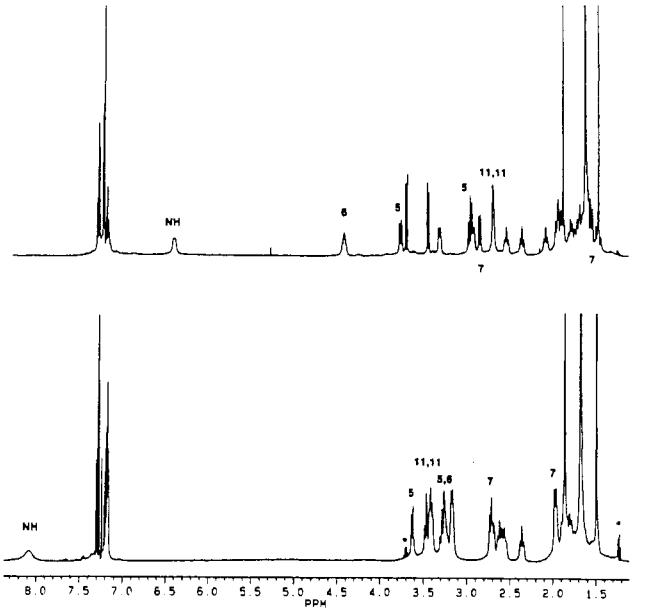


Figure 2. Proton NMR spectra ($CDCl_3$, 27 °C) for ReO(BAT-PPP) syn (**3**) (bottom) and anti (**4**) (top) isomers.

proton NMR data (chemical shifts, integration, multiplicity, assignments, and the values of some coupling constants) for the Tc and Re isomers are shown in Table II. Table III shows the chemical shift comparisons for the corresponding proton resonances of the syn and anti Tc and Re isomers. The ^{13}C chemical shift comparisons between the two sets of isomers are displayed in Table IV. Figure 2 shows the 1D proton spectra for the Re^{v}O(BAT-PPP) isomers. Figure 3 shows the 1D carbon-13 spectra for the Re^{v}O(BAT-PPP) isomers. As an example, the COSY and ^{1}H–^{13}C correlation spectra for the Re^{v}O(BAT-PPP) anti isomer only are shown in Figures 4 and 5, respectively.

Comparison of the proton spectra of the syn and anti isomers reveals salient chemical shift differences (2–10 ppm) for N–H, the proton on the chiral carbon, C6, and the carbons adjacent to it: C7, C5, and C11. Coupling is observed (determined from the COSY experiment, Figure 3, and double irradiation experiments) between the amine proton and the protons on C2 for all of the isomer sets. By double irradiation experiments, coupling constants could be determined for some of the protons as indicated in Table II. In some cases, from these proton coupling constant data the stereochemistry of the protons on C5, C7, and C11 could be assigned; these are indicated in Table II. The complexity of the spectra precludes assignment of all of the coupling constants.

The amine hydrogen of the Tc and Re syn isomers is found at ca. 8 ppm compared to ca. 6.5 ppm for amine hydrogen resonance for the Tc and Re anti isomers. This pattern of chemical shifts has been observed in preliminary experiments for the syn and anti isomers of Tc and Re N2S2 ligands containing a pendant

(23) Bandoli, G.; Mazzi, U.; Roncari, E.; Deutsch, E. *Coord. Chem. Rev.* **1982**, *44*, 191.
(24) Finnegan, M. M.; Lutz, T. G.; Nelson, W. O.; Smith, A.; Orvig, C. *Inorg. Chem.* **1987**, *26*, 2171.
(25) Bryson, N. Ph.D. Thesis, MIT, 1988.

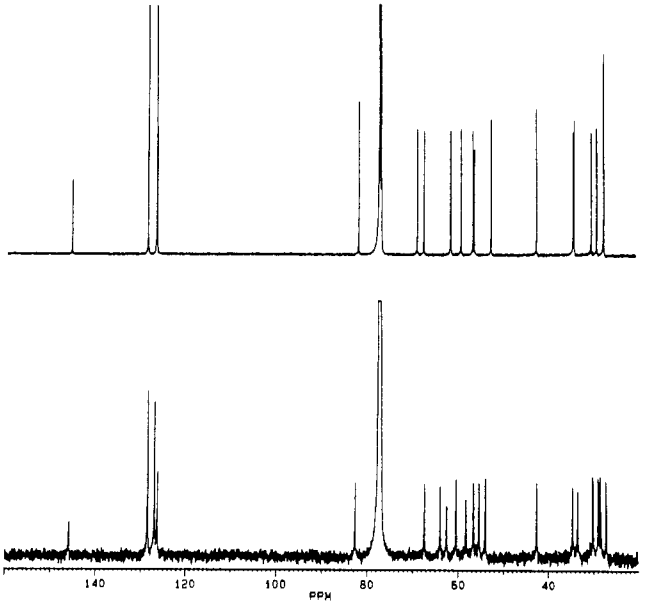


Figure 3. Carbon-13 spectra ($CDCl_3$, 27 °C) for ReO(BAT-PPP) syn (**3**) (bottom) and anti (**4**) (top) isomers.

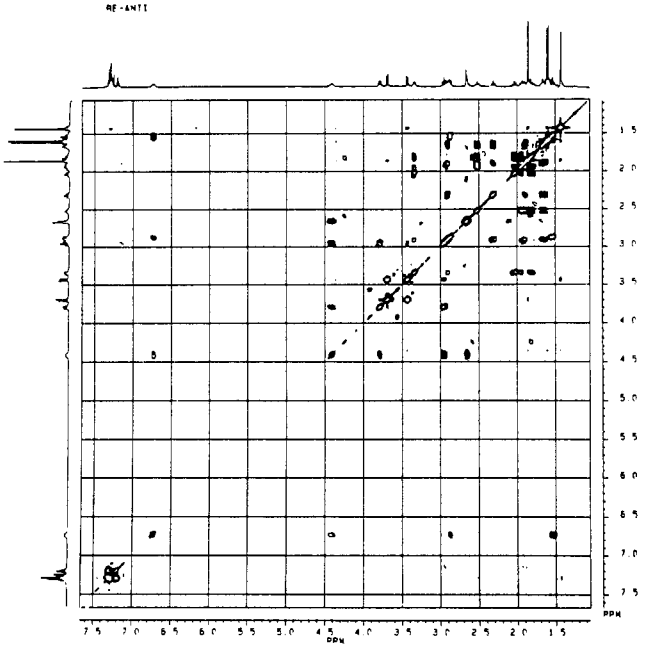


Figure 4. Proton homonuclear COSY spectra for the ReO(BAT-PPP) anti isomer (**4**).

benzylpiperizine (BPA) group.[26] The downfield chemical shifts in the syn isomers may be due to the effects of weak hydrogen bonding interactions between the basic N3 of the piperidine ring and the amine hydrogen (vide infra).[27] There are no intramolecular H-bonding interactions in the anti isomer.[27]

The proton on C7 which is anti to the amine proton is found at a chemical shift of ca. 1.64 ppm for all Re and Tc isomers (cf. Tables II and III). As a consequence of the syn position of the amine proton relative to the oxygen, the methylene proton on the carbon (C7) adjacent to the amine, which is anti to the amine proton, is very shielded (δ = 1.64 ppm) relative to methylene protons. This shielding probably results from a strong magnetic anisotropy of the Tc=O bond. This phenomenon has been observed previously in $Tc^{v}O$(BAT-TE), a neutral $Tc^{v}O$(N2S2) complex which has the same basic 5–5–5 Tc–chelate ring structure as these isomers, without the pendant group.[28]

(26) Francesconi, L. C.; Kung, H. F. Unpublished data.
(27) Supplementary material.

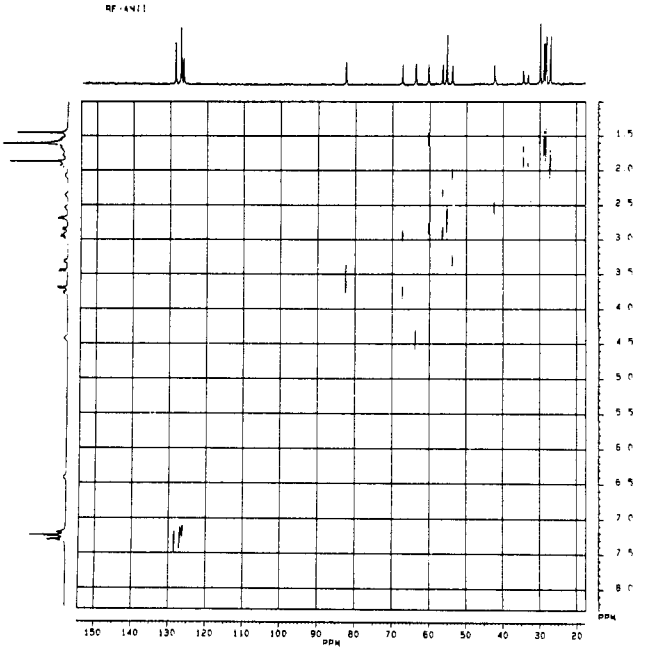


Figure 5. ^{1}H–^{13}C correlation spectrum for the ReO(BAT-PPP) anti isomer (**4**).

Table VI. Selected Bond Distances (Å) and Angles (deg) for the MO(BAT-PPP) (M = Tc, Re) Isomers

		anti-TcO(BAT-PPP)		*syn*-ReO(BAT-PPP)	
	syn-TcO(BAT-PPP)	molecule 1	molecule 2	molecule 1	molecule 2
M1–O	1.681(2)	1.691(8)		1.697(6)	
M2–O			1.670(8)		1.701(6)
M–N2	2.138(2)	2.157(2)		2.121(6)	
M–N5			2.142(12)		2.147(6)
M–N1	1.925(2)	1.941(12)		1.913(6)	
M–N4			1.920(12)		1.927(6)
M–S2	2.290(1)	2.308(5)		2.298(2)	
M–S4			2.303(5)		2.279(3)
M–S1	2.283(1)	2.278(7)		2.277(2)	
M–S3			2.292(6)		2.283(2)
O–M–N2	99.5(1)	101.8(4)		100.4(3)	
O–M–N5			100.6(5)		98.5(2)
O–M–N1	116.9(1)	116.1(5)		117.0(2)	
O–M–N4			116.9(5)		118.9(3)
O–M–S2	117.3(1)	116.9(4)		115.8(2)	
O–M–S4			116.2(5)		116.0(2)
O–M–S1	110.0(1)	109.6(4)		109.6(2)	
O–M–S3			109.0(4)		109.1(2)
N2–M–N1	79.7(1)	79.8(5)		79.3(3)	
N5–M–N4			79.1(5)		78.5(3)
S2–M–N2	82.9(1)	82.7(3)		82.0(2)	
S4–M–N5			83.0(3)		83.3(2)
N1–M–S1	83.1(1)	82.5(4)		82.3(2)	
N4–M–S3			83.2(4)		83.3(2)
S1–M–S2	87.3(1)	87.0(2)		89.6(1)	
S3–M–S4			88.3(2)		89.4(1)

(C) X-ray Crystallography. The $Tc^{v}O$(BAT-PPP) isomers and the syn $Re^{v}O$(BAT-PPP) isomer were crystallized by slow evaporation of CH_2Cl_2/ethanol solutions. Selected bond distances and angles are given in Table VI. Atomic positional parameters are given in Tables VII–IX for *syn*-$Tc^{v}O$(BAT-PPP) (**1**), *anti*-$Tc^{v}O$(BAT-PPP) (**2**), and *syn*-$Re^{v}O$(BAT-PPP) (**3**), respectively. The asymmetric unit cell of *syn*-$Tc^{v}O$(BAT-PPP) contains one metal complex, while the asymmetric cells for *anti*-$Tc^{v}O$(BAT-PPP) and *syn*-$Re^{v}O$(BAT-PPP) each contain two crystallographically independent molecules of complex. Figures 6–8 contain ORTEP representations for the $Tc^{v}O$(BAT-PPP) syn and anti isomers, and of one crystallographically independent

(28) John, C.; Francesconi, L. C.; Wehrli, S.; Graczyk, G.; Carroll, P.; Kung, H. F. *Polyhedron* **1992**, *11*, 1145.

Table VII. Atomic Coordinates ($\times 10^4$) and Equivalent Isotropic Displacement Parameters ($Å^2 \times 10^3$) for *syn*-TcO(BAT-PPP) (**1**)

	x	*y*	*z*	*U*(eq)[a]
Tc	2458(1)	1470(1)	1039(1)	40(1)
S(1)	1251(1)	2839(1)	422(1)	57(1)
S(2)	1457(1)	1485(1)	1947(1)	57(1)
O(1)	3747(2)	2024(2)	1266(1)	58(1)
N(1)	2043(2)	652(2)	100(1)	45(1)
N(2)	2804(2)	-284(2)	1414(1)	40(1)
N(3)	4931(2)	-855(2)	1479(2)	45(1)
C(1)	289(3)	2980(3)	-1080(2)	74(2)
C(2)	2365(3)	2900(3)	-730(2)	64(1)
C(3)	1309(3)	2452(3)	-546(2)	52(1)
C(4)	1269(3)	1129(3)	-560(2)	55(1)
C(5)	2176(3)	613(3)	70(2)	49(1)
C(6)	3000(3)	-1004(3)	774(2)	45(1)
C(7)	2030(3)	-769(3)	1836(2)	48(1)
C(8)	1865(3)	87(3)	2433(2)	51(1)
C(9)	906(4)	-313(3)	2772(2)	75(2)
C(10)	2923(4)	237(4)	3040(2)	77(2)
C(11)	4197(3)	-790(3)	729(2)	50(1)
C(12)	5191(3)	-2063(3)	1723(2)	55(1)
C(13)	5810(3)	-2100(3)	2533(2)	58(1)
C(14)	6882(3)	-1328(3)	2670(2)	50(1)
C(15)	6598(3)	-145(3)	2360(2)	59(1)
C(16)	5954(3)	-166(3)	1546(2)	55(1)
C(17)	7498(3)	-1349(3)	3484(2)	53(1)
C(18)	8640(3)	-1432(4)	3672(2)	75(2)
C(19)	9237(4)	-1338(4)	4400(3)	93(2)
C(20)	8691(5)	-1156(4)	4963(3)	96(2)
C(21)	7555(5)	-1083(4)	4797(2)	91(2)
C(22)	6960(4)	-1190(3)	4061(2)	68(2)

[a] Equivalent Isotropic *U* defined as one-third of the trace of the orthogonalized U_{ij} tensor.

molecule of the $Re^{V}O$(BAT-PPP) syn isomer, respectively. (Figure S1 of the supplementary material contains the second molecule.) For all molecules, three protons of the ligand (two thiolate protons and one amine proton) were ionized upon complexation to the $[Tc^{V}O]^{3+}$ unit, so that the overall charge of the Tc^{V}=O(N2S2) core is zero. Upon complexation of the racemic ligand with the MO^{3+} (M = Tc, Re) core, two isomers form: one in which the pendant group is syn to the M=O bond and one in which it is anti to the M=O bond. The $M–N_{amine}$ single bond distances and angles as well as the NMR data (vide infra) indicate that, in all molecules, the nitrogen (N2 for **1**; N2 and N5 for **2**; N2 and N4 for **3**) which retains its proton is adjacent to the chiral carbon, C6 or C36. The amine hydrogen was observed in the difference map for one of the crystallographically independent Re^{V}OBAT-PPP and was refined. This hydrogen was found to be syn to the -yl oxygen. The positions of the amine hydrogens of the other molecules can be calculated, and consistent with other Tc^{V}O(BAT) structures, these amine hydrogens are found to be syn to the -yl oxygen in all cases. The $M–N_{amide}$ (N1 for **1**; N1 and N4 for **2**; N1 and N5 for **3**) bond distances are shorter than the range generally found for Tc/Re–N single bonds, indicating multiple bonding $M–N_{amide}$ character.

The M(V) (M = Tc, Re) in all three molecules are in distorted square pyramidal coordination environments with oxygen in the apical position. The square planes defined by the nitrogen and sulfur atoms are distorted, with the two nitrogens lying above and below the plane and the two sulfur atoms lying above and below the plane by about 0.2 Å.[27] The Tc and Re atoms lie above the plane by ca. 0.74 Å.[27] This distortion results, in part, from the puckering of the chelate rings surrounding the metal center, which can be clearly demonstrated by examination of the torsion angles for the atoms of these five-membered chelate rings.[27] Comparison of the torsional angles between the syn and anti Tc isomers and the Re syn isomer shows minor differences in the corresponding five-membered chelate rings.

Also contributing to the distortion of the square pyramid are the influences of the two types of nitrogens (amine and amide)

Table VIII. Atomic Coordinates and Equivalent Isotropic Displacement Parameters ($Å^2 \times 10^3$) for *anti*-TcO(BAT-PPP) (**2**)

	x	*y*	*z*	*U*(eq)[a]
Tc(1)	7652(1)	5848(1)	1096(1)	51(1)
S(1)	7184(3)	7322(5)	1633(3)	69(2)
S(2)	7139(2)	6646(4)	266(2)	69(1)
O(1)	8502(4)	5938(8)	1132(6)	68(4)
N(1)	7220(6)	4904(11)	1704(5)	60(5)
N(2)	7511(5)	4256(10)	605(5)	47(4)
N(3)	7564(5)	1756(12)	254(6)	63(5)
C(1)	6649(11)	7160(19)	2758(10)	107(7)
C(2)	7857(9)	6546(17)	2647(8)	85(5)
C(3)	7168(9)	6566(15)	7377(8)	77(5)
C(4)	6909(8)	5338(13)	2233(7)	64(4)
C(5)	7050(8)	3717(13)	1574(7)	61(4)
C(6)	7469(7)	3304(12)	1053(8)	60(4)
C(7)	6961(8)	4797(14)	160(8)	66(5)
C(8)	7070(9)	5390(15)	-238(8)	72(5)
C(9)	6441(9)	5552(15)	-637(8)	81(5)
C(10)	7719(8)	5237(17)	-612(9)	75(5)
C(11)	7204(8)	2141(17)	777(8)	66(4)
C(12)	7233(9)	790(16)	15(8)	78(5)
C(13)	7593(8)	742(17)	-528(8)	74(5)
C(14)	8313(7)	-131(13)	-332(7)	61(4)
C(15)	8652(7)	967(13)	-118(7)	52(4)
C(16)	8760(7)	1437(14)	408(7)	65(4)
C(17)	8684(8)	719(15)	-828(8)	74(5)
C(18)	8554(13)	-1763(22)	-989(11)	127(8)
C(19)	8920(18)	-2444(32)	-1471(14)	185(15)
C(20)	9421(13)	-1893(23)	-1691(11)	111(7)
C(21)	9615(13)	-867(22)	-1514(12)	126(8)
C(22)	9257(11)	-233(21)	-1101(10)	111(7)
Tc(2)	-166(1)	4129(1)	320	50(1)
S(3)	269(3)	2622(4)	-225(3)	63(2)
S(4)	369(2)	3379(3)	1148(2)	61(1)
O(2)	-1007(4)	4040(8)	315(6)	68(4)
N(4)	244(6)	5054(11)	-294(6)	61(5)
N(5)	-29(5)	5739(10)	782(6)	50(4)
N(6)	-100(5)	8270(11)	1067(6)	61(5)
C(31)	739(9)	7655(14)	-1382(8)	75(5)
C(32)	-425(9)	3327(18)	-1232(8)	87(5)
C(33)	300(7)	3341(13)	-975(7)	65(4)
C(34)	553(9)	4504(14)	-847(8)	78(5(
C(35)	424(9)	6230(15)	-182(8)	75(5)
C(36)	8(6)	6691(11)	315(8)	56(3)
C(37)	540(7)	5687(12)	1221(7)	56(4)
C(38)	447(7)	4683(18)	1627(7)	57(4)
C(39)	-164(8)	4821(18)	2024(9)	75(6)
C(40)	1082(9)	4545(16)	2026(9)	85(5)
C(41)	281(8)	7824(16)	551(7)	63(4)
C(42)	249(8)	9358(14)	1778(8)	68(5)
C(43)	-101(9)	9863(21)	1822(9)	91(6)
C(44)	-851(8)	10142(15)	1680(8)	68(4)
C(45)	-1196(8)	8998(14)	1413(3)	70(5)
C(46)	-812(7)	8547(15)	914(7)	64(4)
C(47)	-1260(9)	10827(15)	2120(8)	79(5)
C(48)	-1104(10)	11979(18)	2215(8)	95(6)
C(49)	-1474(10)	12593(17)	2620(9)	97(6)
C(50)	-2041(10)	12199(17)	2896(9)	95(5)
C(51)	-2188(11)	11092(17)	2791(9)	101(6)
C(52)	-1812(10)	10393(20)	2406(9)	100(6)

[a] Equivalent isotropic *U* defined as one-third of the trace of the orthogonalized U_{ij} tensor.

of the ligand backbone. The M–N1 (M–N4) bond distances are short, ca. 1.91–1.94 Å compared to ca. 2.15 Å, typical of M–N single bonds[29–33] suggesting multiple bonding character. These bond lengths are within the range observed for $M–N_{amide}$ (M = Tc, Re) bonds in $M^{V}O$ five coordinate square pyramidal

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Table IX. Atomic Coordinates and Equivalent Isotropic Displacement Parameters ($Å^2 \times 10^3$) for *syn*-ReO(BAT-PPP) (**3**)

	x	y	z	U(eq)
Re(1)	3960(1)	41(1)	6463(1)	30(1)
Re(2)	9160(1)	2140(1)	1718(1)	32(1)
S(1)	2862(1)	4471(2)	816(1)	43(1)
S(2)	4658(1)	3962(2)	896(1)	40(1)
S(3)	275(1)	7801(2)	4072(1)	47(1)
S(4)	2014(1)	7530(2)	3855(1)	45(1)
O(1)	3936(3)	4592(4)	2222(3)	44(2)
O(2)	709(3)	7783(4)	2583(3)	45(2)
N(1)	3567(4)	6256(5)	1221(3)	38(2)
N(2)	4988(4)	5803(5)	1603(3)	34(2)
N(3)	5449(4)	6366(5)	2799(3)	40(2)
N(4)	-181(3)	6246(5)	3108(3)	35(2)
N(5)	1265(4)	5816(4)	3303(3)	42(3)
N(6)	-729(4)	5978(4)	1883(3)	42(3)
C(1)	1663(6)	5620(8)	207(5)	72(4)
C(2)	1900(5)	5659(7)	1400(5)	56(4)
C(3)	2270(5)	5611(6)	809(4)	39(3)
C(4)	2837(5)	6468(6)	808(4)	44(3)
C(5)	4065(5)	7146(6)	1321(5)	50(3)
C(6)	4816(5)	6873(5)	1737(5)	42(3)
C(7)	5503(5)	5643(6)	1136(4)	38(3)
C(8)	5626(5)	4522(6)	1079(4)	41(3)
C(9)	6051(5)	4314(7)	538(4)	51(3)
C(10)	6062(5)	4092(6)	1700(4)	49(3)
C(11)	4807(5)	6943(6)	2450(4)	44(3)
C(12)	6149(5)	6951(6)	2910(5)	57(4)
C(13)	6831(5)	6274(7)	3113(5)	54(4)
C(14)	6754(5)	5668(6)	3691(4)	46(3)
C(15)	5970(5)	5157(7)	3609(4)	49(3)
C(16)	5317(5)	5885(7)	3379(4)	49(3)
C(17)	7419(5)	4919(7)	3867(5)	49(3)
C(18)	7793(7)	4839(8)	4488(5)	66(4)
C(19)	8397(7)	4185(9)	4647(6)	82(5)
C(20)	8658(6)	3621(9)	4186(7)	77(5)
C(21)	8285(6)	3691(7)	3589(6)	65(4)
C(22)	7674(6)	4341(7)	3424(5)	55(4)
C(31)	-1035(7)	7228(9)	4507(6)	86(5)
C(32)	-1202(6)	7890(7)	3379(6)	68(4)
C(33)	-698(5)	7258(6)	3889(5)	48(3)
C(34)	-605(5)	6193(6)	3664(4)	45(3)
C(35)	3(5)	5258(5)	2845(4)	40(3)
C(36)	786(5)	4940(6)	3170(5)	48(3)
C(37)	2064(5)	5580(7)	3587(5)	59(4)
C(38)	2574(5)	6484(6)	3596(5)	51(4)
C(39)	2764(6)	6687(8)	2946(5)	75(5)
C(40)	3300(5)	6358(8)	4096(6)	75(5)
C(41)	-39(5)	5402(7)	2146(5)	50(3)
C(42)	-1396(5)	5342(7)	1710(5)	51(3)
C(43)	-2120(5)	5973(6)	1587(5)	52(3)
C(44)	-2087(5)	6745(6)	1063(4)	45(3)
C(45)	-1304(5)	7323(7)	1213(4)	49(3)
C(46)	-657(5)	6628(7)	1353(4)	52(4)
C(47)	-2791(5)	7425(6)	973(4)	42(3)
C(48)	-2966(6)	8012(6)	1460(5)	51(3)
C(49)	-3606(6)	8613(6)	1378(5)	53(4)
C(50)	-4098(6)	8645(7)	803(5)	57(4)
C(51)	-3920(6)	8058(7)	309(5)	55(4)
C(52)	-3288(6)	7457(7)	394(4)	55(4)

complexes.[7,12a,34-36] The amide nitrogens are sp^2 hybridized. The amide nitrogen is ca. 0.11–0.16 Å out of the plane formed by the metal and two carbon atoms adjacent to the amide nitrogen.[27] The angles about N_{amide} are on the order of 120° rather than 109° for sp^3 hybridization.[27] The amine nitrogens are sp^3 hybridized, and the $M-N_{amine}$ bond distances are in the range observed for M–amine nitrogen bonds. The metal–sulfur bond distances are in the range 2.277–2.308 Å, also consistent with other Tc- and Re–thiolate complexes.[36-47] The N1–M–N2 bond

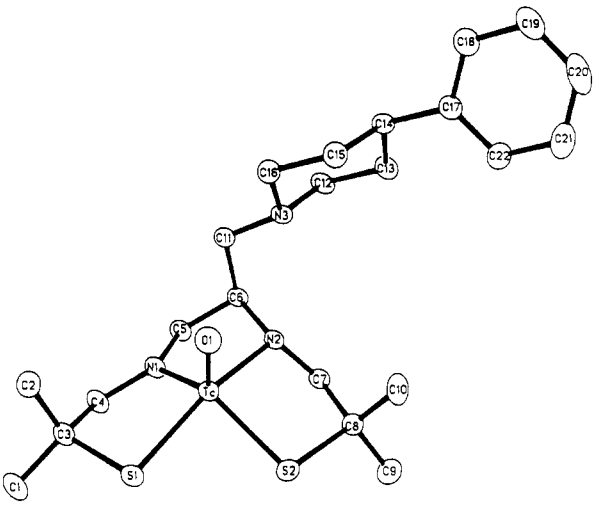

Figure 6. ORTEP representation of the TcO(BAT-PPP) syn isomer (**1**) showing the atom numbering scheme.

angles are all approximately 79° which is consistent with structures of molecules with a five-membered N–C–C–N–Tc chelate ring.[9,28,37,46]

The M=O (M = Tc, Re) bond distances range from 1.670(8) to 1.70 Å for the Tc and Re isomers. These bond distances are on the long side of the range generally found for square planar $M^{V}O$ complexes.[48] This is consistent with the low M=O stretching frequencies observed in the IR spectra.

A weak intramolecular hydrogen bonding interaction is observed between the amine hydrogen and the nitrogen of the piperidine ring in the $M^{V}O$(BAT-PPP) syn isomers.[27] The amine nitrogen–piperidine nitrogen distance and angles about the amine nitrogen for the Tc anti isomers preclude intramolecular hydrogen bonding interactions in these molecules.[27] However, examination of the unit cell of the anti isomer shows a weak intermolecular hydrogen bonding interaction between the oxygen of one molecule and the amine hydrogen of another.[27]

Discussion

We have noted that the $^{99m}Tc^{V}O$(BAT-BPA) syn isomer (Scheme I) (both the syn and anti ^{99}Tc complexes have been prepared and characterized by X-ray crystallography) have high extraction and retention into the brain relative to the anti isomer. On the basis of the HPLC behavior of the analogous BPA

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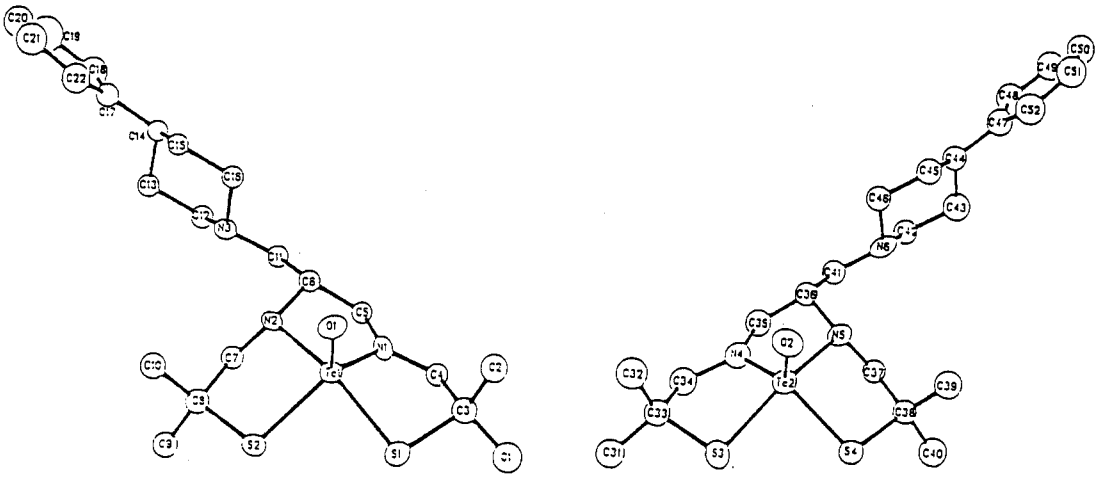

Figure 7. ORTEP representation of the two crystallographically independent molecules of the TcO(BAT-PPP) anti isomer (**2**), showing the atom numbering scheme.

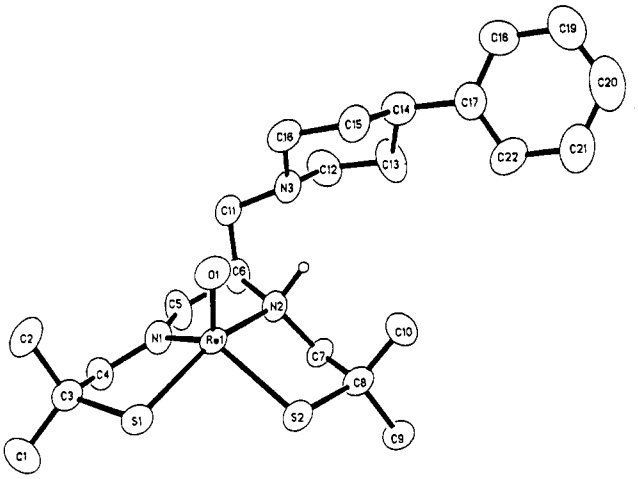

Figure 8. ORTEP representation of one of the crystallographically independent molecules of the ReO(BAT-PPP) syn isomer (**3**), showing the atom numbering scheme.

complexes, the Tc^{V}O(BAT-PPP) complex, which was highly retained on the reverse phase column, was assigned to the ^{99m}Tc^{V}O(BAT-PPP) syn isomer.[10] Yet in the biodistribution studies, the anti isomer showed slightly higher cerebral uptake than the syn isomer.[10] Partial impetus for this study was to examine any structural and/or chemical changes in the Tc^{V}O-(BAT-PPP) molecules which may be responsible for the disparity in biodistribution. Another motivation for the study was to provide information concerning the structure and chemistry of the analogous rhenium complexes, which may be prototypes for biologically significant complexes labeled with ^{186}Re or ^{188}Re.

X-ray data confirm the assignment of the syn and anti isomers of the M^{V}O(BAT-PPP) complexes (M = Tc, Re). The ^{99}Tc^{V}O(BAT-PPP) isomers coelute with the ^{99m}TcO(BAT-PPP) isomers (Figure 1), indicating that the chemical species are the same. The X-ray data further show that the Tc (and Re) N2S2 cores of the M^{V}O(BAT-PPP) syn and anti molecules and the TcO(BAT-BPA) syn and anti molecules[9] are similar in the solid state. The geometry about the Tc is, in all cases, distorted square pyramidal with oxygen in the apical positions. The metal–ligand bond distances are similar for all molecules. Furthermore, preliminary NMR data suggest that the syn and anti assignments for solution structures are similar for the Tc^{V}O(BAT-PPP) and Tc^{V}O(BAT-BPA) isomer pairs.[26]

The differences in biodistribution may be due to the flexibility of the pendant group. The tertiary amine and benzylic group of Tc^{V}O(BAT-BPA) derivatives imparts flexibility to the pendant arm. However, the phenylpiperidine moiety of the Tc^{V}O(BAT-PPP) derivatives is more rigid. The flexibility of the Tc^{V}O(BAT-BPA) analogs, particularly the syn isomer, in combination with intramolecular H-bonding possible between the proximal piperizine nitrogen and the amine hydrogen may allow the molecule to fold over and become more compact in solution. The rigid nature of the BAT-PPP ligand precludes this internal self-coiling and compacting in solution.

Another important factor in the biodistribution is the possibility for the complex to bind to proteins in the blood. A recent study of neutral tracer ^{99m}Tc complexes of BAT ligands monosubstituted on the amino thiol branch examined protein binding capabilities of a number of monosubstituted amine derivatives.[49] The PPP and BPA analogs displayed the highest protein binding compared to nonaromatic ring-containing analogs. Hydrogen bonding and aromatic–aromatic interactions are factors which may influence the protein binding properties of molecules. Both of these types of interactions are possible with the BPA and PPP pendant groups.

Examination of the unit cells for the TcO(BAT-PPP) anti and the TcO(BAT-BPA) anti isomers show *intermolecular* H bonds between the -yl oxygen of one molecule and the NH of an independent molecule. No intramolecular H bonding is observed for the anti isomers. On the other hand, intramolecular H bonding is possible for the syn TcO(BAT-PPP) and TcO(BAT-BPA) isomers between the amine H and the proximal piperizine or piperidine nitrogen atom.[27] Weakly polar aromatic–aromatic interactions have recently been noted in protein crystal structures.[50,51] Similar interactions between the phenyl ring of the BAT-PPP or BAT-BPA molecules may be operative in protein binding properties of these molecules.

The solution NMR data, taken in $CDCl_3$, are consistent with the structures determined from X-ray diffraction experiments. The constrained ligand system and the effect of the M=O group is clearly seen in the patterns for the *syn*- and *anti*-MO(BAT-PPP) isomers in both proton and ^{13}C NMR spectroscopy (Figures 2 and 3, respectively). For example, the methine proton H6 on the chiral carbon is located syn to the -yl oxygen in the MO-(BAT-PPP) anti isomer, and thus shifted downfield (to ca. 4.4 ppm) due to deshielding by the M=O group. In the MO(BAT-PPP) syn isomer, the resonance assigned to H6 is found at 3.2 ppm. Similar patterns are found in the spectra for the methylene protons on C11, C7, and C5. Another salient feature of the NMR is the difference in chemical shift values of the amine hydrogen in the syn and anti isomer. This proton is found at ca.

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8 ppm for the syn isomer; presumably, the downfield shift is due to weak H-bonding to N3 of the piperidine moiety. In the anti isomer, the amine proton resonates at ca. 6.5 ppm.

Table III shows that the carbon-13 spectra for the homologous Tc and Re complexes are very similar. Further, carbons 6, 7, 5, and 11, which are adjacent to the amines and in close proximity to the pendant group, show significant differences in the chemical shifts when syn and anti isomers are compared. These differences are likely due to the constraint of the N2S2 backbone, the deshielding effects of the M=O bond and the H-bonding effects.

As seen from Tables III and IV, the proton and ^{13}C chemical shifts do not change significantly on going from Tc to Re. In a study of homologous neutral six coordinate MO(N2S2)Cl and $[MO(N2S2)]_2O$ (M = Tc, Re), where the N2S2 ligand was an unsaturated schiff base, *N,N'*-ethylenebis(thioacetylacetonylideneamine) showed a chemical shift dependence on the metal ion, where $\delta(Tc) - \delta(Re)$ for the methine and methyl protons ranged from 0.30 to 0.57 ppm.[15] This effect was not observed in a study of homologous Tc(V) and Re(V) diamide dithiol chelate epimers[12b] or in this study.

Conclusion

The reaction of BAT-PPP with TcO_4^- or $[TcO(eg)_2]Na$ resulted in the formation of two isomers: one in which the pendant phenylpiperidine group is syn to the -yl oxygen and one in which the pendant phenylpiperidine group is anti to the -yl oxygen. The rhenium analogs were prepared by ligand exchange reactions from Re^VO starting materials. X-ray crystallography and NMR data show that the solid and solution structures of the Tc and Re isomers are the same. Slight differences in the pendant group (BPA) vs PPP) may result in very different biodistribution behavior; this may be due to the flexibility of the molecule and the possibilities for protein binding. The proton and ^{13}C NMR chemical shifts do not differ significantly in the corresponding Tc and Re analogs. This study provides information on the solution characterization of analogous rhenium chelates of the N2S2 ligand system, which should be useful in preparation and characterization of biologically significant molecules labeled with ^{186}Re or ^{188}Re.

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Supplementary Material Available: Figure S1 and tables of crystallographic data, least squares planes, torsion angles, and intermolecular hydrogen bonding parameters, anisotropic thermal parameters, bond distances, and bond angles, and hydrogen atom parameters (30 pages). Ordering information is given on any current masthead page.