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# Novel Rhenium Chelate System Derived from Dimercaptosuccinic Acid for the Selective Labeling of Biomolecules

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This work is part of an effort to develop chelating agents for stable binding and easy conjugation of Re-188 to biologically interesting structures. Starting from the well-known in vivo stability of $[^{188}ReO(DMSA)_2]^-$, we want to exploit this coordination system for the design of $^{188}ReO(V)$ chelates, which are stable toward reoxidation to perrhenate and toward ligand exchange under all conditions of radiopharmaceutical development. Therefore, a new type of tetradentate ligand has been synthesized by bridging two molecules of *N*,*N*′-diisobutyl-2,3-dimercaptosuccinamide with *N*-(3-aminopropyl)propane-1,3-diamine. The resulting stereoisomeric tetrathiolato $S_4$ ligand of composition $(^iBu)_2N(O)C–C(SH)–C(SH)–C(O)NH–(CH_2)_3–NH–(CH_2)_3–NHC(O)–C(SH)–C(SH)–C(O)N(^iBu)_2$ forms anionic five-coordinate oxorhenium(V) complexes by a ligand-exchange reaction of $NBu_4[ReOCl_4]$ in methanol. In the absence of a base, the compounds were isolated as "betaine", $[ReO(S_4)]$, with the protonated nitrogen of the bridge serving as an internal "counterion". Two representatives have been fully characterized in both the solid and solution states and found to adopt the expected square-pyramidal coordination geometry. The equatorial plane is formed by four thiolate sulfur atoms, whereas the oxygen occupies the apical position. The orientation of the metal oxo group is exo in relation to the carbamido groups in both isomers. Both complexes are stereoisomeric regarding the junction of the triamine chain.

## Introduction

As part of our ongoing studies on the binding characteristics of sulfur-ligated metal ions, we attempt to design chelators that demonstrate significant stability toward radioactive metals. In this focus are chelators for the $\beta$-emitting isotope $^{188}Re$ ($E_{max} = 2.12$ MeV), one of the most attractive radioisotopes for radiotherapy and radioimmunotherapy. Because this nuclide is easily obtained carrier-free as a perrhenate ($ReO_4^-$) ion in a saline solution from a $^{188}W/^{188}Re$ generator system[1,2] at reasonable costs, it gives a good basis for the routine preparation of a variety of radiopharmaceuticals for the treatment of cancer. Therefore, there is an ongoing interest in the development of $^{188}Re$ radiopharmaceuticals,[3] where $^{188}Re$-containing chelate units are attached to biomolecules such as peptides[4] or monoclonal antibodies.[5] Conceptually, the metallopharmaceutical can be assembled by three building blocks: a site-specific targeting domain (e.g., in the form of a small peptide or monoclonal antibody), a bifunctional chelating unit, and a connecting linker that may also serve as a pharmacological modifier.

The pharmacologically acceptable integration of the transition-metal rhenium, with its complicated coordination chemistry, into the molecular entity of a biomacromolecule is a fundamental challenge, and the chelate plays an important role within this approach. The usefulness of such chelates is dependent on a number of factors such as the stability of radionuclide binding within the chelate and the reactivity of the chelate with the desired biomolecule. The efficiency of radiolabeling of the chelating compound to produce the desired radionuclide metal chelate is also important.

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A variety of ligands for complexation of rhenium at oxidation states 5+, 3+, and 1+ have been described in the literature [i.e., diethylenetriaminepentaacetic acid,[6] diphosphonates,[7] dimercaptosuccinic acid (DMSA),[8] ethylenedicysteine,[9] nitrido heterocomplexes,[10] MAG-3,[11] "4 + 1" mixed-ligand complexes,[12] and rhenium triarbonyls[13]].

Among them, DMSA is a well-known ligand that forms isomeric complexes with technetium(V)[14] and rhenium(V).[15] The tumor-targeting agent $[MO(DMSA)_2]^-$ has found clinical application for imaging (M = $^{99m}$Tc)[16] and therapy (M = $^{186}$Re, $^{188}$Re).[8,17]

A new tool to exploit $^{99m}$Tc-DMSA as a potential radiopharmaceutical consists of functionalization of the DMSA ligand with ester groups. Seifert et al. showed[18] that the introduction of one or two nonhydrolyzable ester groups into the $^{99m}Tc^{V}$-DMSA molecule leads to a decrease of bone accumulation without deterioration of the tumor uptake.

An important step toward using DMSA for conjugating rhenium to biomolecules has recently been proposed by Blower et al.[19a] They describe the synthesis of $[ReO(DMSA\text{-anhydride})_2]^-$, which may form amide-linked $^{188}$Re conjugates with peptides.[19b]

The aim of investigations described in this paper is the development of a novel chelating system based on DMSA. The Re chelate system to be developed should be capable of complexing Re(V) under mild conditions and should be stable toward reoxidation to perrhenate and toward ligand exchange under all conditions of radiopharmaceutical design and development. Furthermore, the chelate system should allow the fine-tuning of properties such as charge and lipophilicity, and conjugation with a biomolecule should be easily performed.

The concept for the development of such a ligand is to bridge two separate DMSA molecules by a suitable chain. Introduction of an alkylenediamine spacer element will form a tetradentate ligand with preorganized $S_4$ arrangement that is believed to be optimal for rhenium complexation. In this way, a more rigid molecular encapsulation of Re(V) should be obtained, exploiting the high stability of the well-characterized Re-DMSA system. Furthermore, a bridging amine group introduced into the ligand framework could (i) enhance the stability of the derived complexes further, provided a hydrogen bond between nitrogen and oxo groups occurs, and (ii) make available a reactive position for coupling biomolecules to the chelate.

We herein report the synthesis of $S_4$ ligands by bridging two DMSA molecules with an alkylenediamine chain and the preparation of complexes with nonradioactive rhenium. Rhenium complexes were characterized by conventional methods and by the X-ray crystal structure determination for two representative complexes.

## Experimental Section

**Materials and Methods.** All reagents used for the synthesis of the ligands were purchased from commercial sources unless otherwise noted. The cyclic prochiral anhydride 2,2-dimethyldihydro-[1,3]dithiolo[4,5-*c*]furan-4,6-dione was prepared according to the literature starting from *meso*-2,3-dimercaptosuccinic acid.[20] The isopropylidene protective group was cleaved using a procedure described by Jones, Singh, and co-workers.[21,22] Compounds **1**, **2**, and **3g** were obtained from procedures that were analogous to those described by von Bliggensdorfer.[23] The synthesis of $[ReO(DMSA\text{-anhydride})_2]^-$ has been described by Blower et al.[19a]

For thin-layer chromatography (TLC) studies, silica gel strips (Kieselgel 60, Merck) were used. For analytical examinations, a Knauer high-performance liquid chromatography (HPLC) system with a binary pump K-1001, a DA-Detector K-2700, and a Agilent RP18 column (Zorbax 300 SB-C18, 5 $\mu$m, 4.6 × 250 mm) was used. The separation of complexes **Re5a** and **Re5b** was done with a Knauer HPLC system with a binary pump K-1001 and a UV-Detector K-2501 ($\lambda$ = 220 nm) by using a preparative Agilent RP18 column (Zorbax PrepHT 300 SB-C18, 7 $\mu$m, 21.2 × 250 mm).

Analytical method: Zorbax 300 SB-C18, 5 $\mu$m, 4.6 × 250 mm, 1 mL/min, room temperature, solvent A comprised of acetonitrile with 0.1% trifluoroacetic acid (TFA) and solvent B comprised of water with 0.1% TFA, gradient elution of 0−20 min at 45% A, 20−25 min at 45−90% A, and 25−31 min at 90% A.

Preparative method: Zorbax PrepHT 300 SB-C18, 7 $\mu$m, 21.2 × 250 mm, 20 mL/min, room temperature, solvent A comprised of acetonitrile with 0.1% TFA and solvent B comprised of water with 0.1% TFA, gradient elution of 0−20 min at 45% A, 20−25 min at 45−90% A, and 25−31 min at 90% A.

Mass spectrometric (MS) analyses were carried out on a Micromass tandem quadrupole mass spectrometer (Quattro LC) operating in the MS mode. Mass spectral data were recorded at the negative and positive electrospray ionization (ESI) mode using cone voltages of 20 and 100 V. Approximately 1 mg of the sample dissolved in 1.0 mL of methanol and diluted (1:100) was infused

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at a flow rate of 5 $\mu$L/min. Nuclear magnetic resonance (NMR) spectra were recorded on a 400-MHz Varian Inova 400 spectrometer. Chemical shifts are reported as $\delta$ in ppm relative to the residual solvent signal or tetramethylsilane. IR spectra were recorded on a FTIR spectrometer IR 2000 (Perkin-Elmer) using KBr pellets. UV/vis spectra were recorded in acetonitrile at 20 °C on a Specord S10 (Zeiss). Elemental analyses were performed on a LECO elemental analyzer CHNS-932.

**Synthesis of 5-[(Diisobutylamino)carbonyl]-2,2-dimethyl-1,3-dithiolane-4-carboxylic Acid (1).** To a suspension of 2,2-dimethyldihydro[1,3]dithiolo[4,5-*c*]furan-4,6-dione (500 mg, 2.45 mmol) in methylene chloride (12 mL) was added slowly a solution of diisobutylamine (475 mg, 3.7 mmol) also dissolved in methylene chloride (2 mL). The reaction mixture was stirred at 0 °C under nitrogen for 1 h. The mixture was allowed to warm to room temperature and to stir for an additional 2 h. The solvent was removed in vacuo to give a brown foam. This crude product was dissolved in a small amount of ethanol and acidified with aqueous hydrochloric acid (10% by weight) until the product began to precipitate. The flask was kept in the refrigerator. The precipitate was collected, washed with aqueous hydrochloric acid, and dried to provide 510 mg (70%) of **1** as pale-pink solid. Mp: 148−150 °C. MS: positive ESI, $[M + H]^+$, *m*/*z* 334.0, $[M + Na]^+$, *m*/*z* 355.9; negative ESI, $[M - H]^-$, *m*/*z* 331.8. Anal. Calcd for $C_{15}H_{27}NO_3S_2$ (exact mass calcd, 333.51): C, 54.02; H, 8.16; N, 4.20; S, 19.23. Found: C, 53.93; H, 8.01; N, 4.09; S, 19.01. $^1$H NMR ($CDCl_3$, 399.95 MHz): $\delta$ 0.83 (d, $^3J$ = 6.6 Hz, 3H, C$H_3$−CH−$CH_3$), 0.87 (d, $^3J$ = 6.6 Hz, 3H, C$H_3$−CH−$CH_3$), 0.93 (d, $^3J$ = 6.6 Hz, 6H, 2C$H_3$−CH−$CH_3$), 1.77 (s, 3H, C$H_3$), 1.84 (s, 3H, C$H_3$), 1.88−1.98 (m, 1H, $CH_3$−C*H*−$CH_3$), 1.99−2.10 (m, 1H, $CH_3$−C*H*−$CH_3$), 2.53−2.59 (m, 1H, $CH_3$−CH−C$H_2$), 2.88−2.93 (m, 1H, $CH_3$−CH−C$H_2$), 3.13−3.19 (m, 1H, $CH_3$−CH−C$H_2$), 3.81−3.87 (m, 1H, $CH_3$−CH−C$H_2$), 4.80 (d, $^3J$ = 5.6 Hz, 1H, C*H*−S), 4.82 (d, $^3J$ = 5.6 Hz, 1H, C*H*−S), 9.22 (s, 1H, COO*H*). $^{13}$C NMR ($CDCl_3$, 100.57 MHz): $\delta$ 20.0 (*C*$H_3$−CH), 20.1 (*C*$H_3$−CH), 20.5 (*C*$H_3$−CH), 20.7 (*C*$H_3$−CH), 26.3 ($CH_3$−*C*H), 27.8 ($CH_3$−*C*H), 31.9 (*C*$H_3$), 36.5 (*C*$H_3$), 53.5 (*C*$H_2$), 54.8 (*C*H−S), 56.1 (*C*$H_2$), 59.5 (*C*H−S), 60.6 (S−*C*−S), 170.6 (N−*C*═O), 171.1 (O−*C*═O).

**Synthesis of 4-Nitrophenyl 5-[(Diisobutylamino)carbonyl]-2,2-dimethyl-1,3-dithiolane-4-carboxylate (2).** A mixture of **1** (200 mg, 0.59 mmol), 4-nitrophenol (84 mg, 0.6 mmol), and *N*,*N*′-dicyclohexylcarbodiimide (DCC; 122 mg, 0.59 mmol) in ethyl acetate (10 mL) was stirred vigorously at room temperature for 2 h, which resulted in the formation of *N*,*N*′-dicyclohexylurea. The solid was collected by filtration and discarded. The mother liquor was concentrated in vacuo to yield a brown oil. This crude material was purified by column chromatography on silica gel (diethyl ether/*n*-hexane, 1:1) to give 199 mg (75%) of **2** as a white solid. Mp: 88−90 °C. MS: positive ESI, $[M + H]^+$, *m*/*z* 455.1, $[M + Na]^+$, *m*/*z* 477.1. Anal. Calcd for $C_{21}H_{30}N_2O_5S_2$ (exact mass calcd, 454.60): C, 55.48; H, 6.65; N, 6.16; S, 14.11. Found: C, 55.62; H, 6.61; N, 6.16; S, 14.34. $^1$H NMR ($CDCl_3$, 399.95 MHz): $\delta$ 0.84−0.93 (m, 12H, 4C$H_3$−CH), 1.85 (s, 3H, C$H_3$), 1.89 (s, 3H, C$H_3$), 1.90−1.98 (m, 1H, $CH_3$−C*H*−$CH_3$), 1.99−2.08 (m, 1H, $CH_3$−C*H*−$CH_3$), 2.60−2.65 (m, 1H, $CH_3$−CH−C$H_2$), 2.95−3.00 (m, 1H, $CH_3$−CH−C$H_2$), 3.20−3.26 (m, 1H, $CH_3$−CH−C$H_2$), 3.70−3.75 (m, 1H, $CH_3$−CH−C$H_2$), 4.89 (d, $^3J$ = 5.6 Hz, 1H, C*H*−S), 4.93 (d, $^3J$ = 5.6 Hz, 1H, C*H*−S), 7.33−7.37 (m, 2H, 2 aromatic C*H*), 8.21−8.25 (m, 2H, 2 aromatic C*H*). $^{13}$C NMR ($CDCl_3$, 100.57 MHz): $\delta$ 20.0 (*C*$H_3$−CH), 20.1 (*C*$H_3$−CH), 20.4 (*C*$H_3$−CH), 20.5 (*C*$H_3$−CH), 26.5 ($CH_3$−*C*H), 27.8 ($CH_3$−*C*H), 32.4 (*C*$H_3$), 36.5 (*C*$H_3$), 53.0 (*C*$H_2$), 55.8 (*C*H−S), 56.2 (*C*$H_2$), 58.5 (*C*H−S), 62.2 (S−*C*−S), 122.7 (2 aromatic *C*H−C−O), 125.4 (2 aromatic *C*H−C−$NO_2$), 145.8 (aromatic *C*−O), 155.8 (aromatic *C*−$NO_2$), 167.5 (N−*C*═O), 169.1 (O−*C*═O).

**Synthesis of $N^5$,$N^{5\prime}$-(Iminodipropane-3,1-diyl)bis(*N*,*N*-diisobutyl-2,2-dimethyl-1,3-dithiolane-4,5-dicarboxamide) (3g).** To a solution of **2** (134 mg, 0.29 mmol) in toluene (5 mL) was added slowly a solution of *N*-(3-aminopropyl)propane-1,3-diamine (38 mg, 0.29 mmol) also dissolved in toluene (1 mL). The reaction mixture was stirred at room temperature for 1 h, at which time a reaction byproduct began to precipitate. This byproduct was collected and discarded. The mother liquor was concentrated in vacuo to provide 112 mg (quant.) of **3g** as a pale-yellow viscous oil. This material was suitable for use without further purification. MS: positive ESI, $[M + H]^+$, *m*/*z* 762.62; negative ESI, $[M - H]^-$, *m*/*z* 760.49. Exact mass calcd for $C_{36}H_{67}N_5O_4S_4$: 761.41. $^1$H NMR ($CDCl_3$, 399.95 MHz): $\delta$ 0.83−0.86 (m, 12H, 4C$H_3$−CH), 0.90−0.93 (m, 12H, 4C$H_3$−CH), 1.60−1.68 (m, 4H, 2$CH_2$−C$H_2$−$CH_2$), 1.81 (s, 3H, C$H_3$), 1.85 (s, 3H, C$H_3$), 1.91−2.00 (m, 4H, 4$CH_3$−C*H*−$CH_3$), 2.61−2.66 (m, 4H, C$H_2$−NH−C$H_2$), 3.00−3.10 (m, 6H, 4$CH_3$−CH−C$H_2$, 2C$H_2$−NH−C═O), 3.21−3.31 (m, 6H, 4$CH_3$−CH−C$H_2$, 2C$H_2$−NH−C═O), 4.64 (d, $^3J$ = 5.6 Hz, 2H, 2C*H*−S), 4.88 (d, $^3J$ = 5.6 Hz, 2H, C*H*−S), 7.15−7.21 (m, 2H, 2N*H*−C═O), amine proton was not detected. $^{13}$C NMR ($CDCl_3$, 100.57 MHz): $\delta$ 20.3 (4*C*$H_3$−CH), 20.4 (2 *C*$H_3$−CH), 20.5 (2*C*$H_3$−CH), 26.7 (2$CH_3$−*C*H), 28.2 (2$CH_3$−*C*H), 29.2 ($CH_2$−*C*$H_2$−$CH_2$), 29.3 ($CH_2$−*C*$H_2$−$CH_2$), 32.7 (*C*$H_3$), 32.8 (*C*$H_3$), 36.2 (2*C*$H_3$), 38.8 (*C*$H_2$−CH), 38.9 (*C*$H_2$−CH), 48.0 (NH−*C*$H_2$), 48.1 (NH−*C*$H_2$), 53.9 (2*C*$H_2$−NH−C═O), 56.2 (2*C*$H_2$−CH), 56.5 (*C*H−S), 56.6 (*C*H−S), 60.6 (*C*H−S), 60.7 (*C*H−S), 62.1 (S−*C*−S), 62.2 (S−*C*−S), 168.5 (N−*C*═O), 168.7 (N−*C*═O).

**Synthesis of $N^2$,$N^{2\prime}$-(Iminodipropane-3,1-diyl)bis(*N*,$^4$*N*$^4$-diisobutyl-2,3-dimercaptosuccinamide) (4g).** To a solution of **3g** (503 mg, 0.66 mmol) in acetonitrile/water (3:1, 20 mL) was added slowly a solution of $HgCl_2$ (1790 mg, 6.6 mmol) also dissolved in acetonitrile/water (3:1, 20 mL), and the resulting mixture was stirred at room temperature. The resulting mercury complex precipitates. After stirring for 2 h at room temperature, the solvent mixture was evaporated to dryness. The white solid was washed with water, collected by filtration, and dried. The dry solid was suspended in methanol (50 mL), and hydrogen sulfide was bubbled into the stirring suspension. The mercury complex dissolved, and HgS precipitated. After 1 h, the gas stream was stopped, and the black precipitate was collected by filtration and disposed of. The mother liquor was concentrated in vacuo to yield 405 mg (90%) of **4g** as a pale-yellow oil. This crude product was purified by preparative HPLC. MS: positive ESI, $[M + H]^+$, *m*/*z* 682.6; negative ESI, $[M - H]^-$, *m*/*z* 680.3. Exact mass calcd for $C_{30}H_{59}N_5O_4S_4$: 682.08. $^1$H NMR ($CDCl_3$, 399.95 MHz): $\delta$ 0.84−0.98 (m, 24H, 4C$H_3$−CH), 1.95−2.11 (m, 8H, 2$CH_2$−C$H_2$−$CH_2$, 4$CH_3$−C*H*−$CH_3$), 2.42 (d, $^3J$ = 10.2 Hz, 2H, 2S*H*), 2.44 (d, $^3J$ = 10.2 Hz, 2H, 2S*H*), 3.01−3.62 (m, 16H, C$H_2$−NH−C$H_2$, 4$CH_3$−CH−C$H_2$, 2C$H_2$−NH−C═O), 3.86 (dd, $^3J$ = 10.2 and 9.8 Hz, 2H, 2 C*H*−S), 3.94 (dd, $^3J$ = 9.8 and 10.2 Hz, 2H, C*H*−S), 7.82 (t, $^3J$ = 6.0 Hz, 2H, 2N*H*−C═O), amine proton was not detected.

**Synthesis of Rhenium Complex $N^2$,$N^{2\prime}$-(Iminium dipropane-3,1-diyl)bis($N^4$,$N^4$-diisobutyl-2,3-dithiolatosuccinamide)-(*S*,*S*,*S*,*S*) Oxorhenate(V) (Re5).** To a solution of tetrabutylammonium tetrachlorooxorhenate(V) (10 mg, 0.02 mmol) in dry methanol (10 mL) was added slowly a solution of **4g** (11 mg, 0.02 mmol) also dissolved in dry methanol (10 mL), and the resulting mixture was stirred at room temperature under nitrogen. Over time, the green solution changed to orange. After stirring for 1 h, the solvent was removed in vacuo to give a brown oil. The crude product was purified and separated by preparative HPLC (or alternatively by

**Table 1.** Crystal Data and Structure Refinement for Complexes **Re5a** and **Re5b**

| | **Re5a** | **Re5b** |
|---|---|---|
| empirical formula | $C_{30}H_{56}N_5O_5ReS_4 \cdot CH_3OH$ | $C_{30}H_{56}N_5O_5ReS_4$ |
| fw | 881.27/32.01 | 881.27 |
| cryst size ($mm^3$) | $0.02 \times 0.015 \times 0.01$ | $0.47 \times 0.07 \times 0.03$ |
| temp (K) | 273(2) | 273(2) |
| wavelength (Å) | 0.710 73 | 0.710 73 |
| cryst syst | triclinic | orthorhombic |
| space group | $P\bar{1}$ | *Pbca* |
| *a* (Å) | 10.576(6) | 16.754(14) |
| *b* (Å) | 12.616(7) | 20.074(17) |
| *c* (Å) | 14.844(9) | 25.080(2) |
| α (deg) | 98.539(11) | 90 |
| *β* (deg) | 97.841(11) | 90 |
| *γ* (deg) | 108.967(10) | 90 |
| *V* ($Å^3$) | 2078(2) | 8434(12) |
| *Z* | 2 | 8 |
| $D_{calc}$ ($Mg/m^3$) | 1.458 | 1.388 |
| abs coeff ($mm^{-1}$) | 3.167 | 3.118 |
| *F*(000) | 934 | 3600 |
| *σ* range (deg) | 1.92−25.00 | 1.78−25.00 |
| reflns collected | 10496 | 40513 |
| indep reflns | 7245 | 7397 |
| abs correction | *ψ* scan | *ψ* scan |
| max and min transm | 0.504 and 0.350 | 0.367 and 0.148 |
| refinement method on $F^2$ | full-matrix least squares | full-matrix least squares |
| data/restraints/params | 7245/7/440 | 7397/0/406 |
| GOF on $F^2$ | 0.861 | 0.765 |
| final *R* indices [$I > 2\sigma(I)$] | R1 = 0.0406, wR2 = 0.0742 | R1 = 0.0702, wR2 = 0.1363 |
| *R* indices (all data) | R1 = 0.0644, wR2 = 0.0778 | R1 = 0.1902, wR2 = 0.1594 |
| largest diff peak and hole ($e Å^{-3}$) | +1.707 and −1.446 | +1.369 and −2.184 |

silica gel column chromatography) to yield 4 mg per isomer **Re5a** and **Re5b** (60%). After dissolution in methanol and slow evaporation, intense orange crystals were obtained.

**Re5a.** MS: positive ESI, $[M + H]^+$, *m*/*z* 882.5; negative ESI, $[M]^-$, *m*/*z* 880.3. Exact mass calcd for $C_{30}H_{56}N_5O_5ReS_4$: 881.26. $^1H$ NMR ($CDCl_3$, 399.95 MHz): *δ* 0.84−0.93 (m, 24H, 8C$H_3$−CH), 1.79−1.83 (m, 4H, 4$CH_3$−C*H*−$CH_3$), 1.87−2.03 (m, 8H, 4$CH_3$−CH−C$H_2$), 2.75−2.87 (m, 4H, 2$CH_2$−C$H_2$−$CH_2$), 3.06−3.14 (m, 4H, C$H_2$−NH−C$H_2$), 3.52−3.68 (m, 4H, 2C$H_2$−NH−C═O), 3.91−3.96 (m, 2H, 2C*H*−S), 4.45−4.49 (m, 2H, 2C*H*−S), amine and amide protons were not detected. IR ($cm^{-1}$): 973.8 (m, Re═O), 1634.0 (s, C═O), 2959.8 (s, C−H), 3435.5 (m, N−H).

**Re5b.** MS: positive ESI, $[M + H]^+$, *m*/*z* 882.3; negative ESI, $[M]^-$, *m*/*z* 880.2. Exact mass calcd for $C_{30}H_{56}N_5O_5ReS_4$: 881.26. $^1H$ NMR ($CDCl_3$, 399.95 MHz): *δ* 0.64−0.72 (m, 24H, 8C$H_3$−CH), 1.42−1.46 (m, 2H, 2$CH_3$−C*H*−$CH_3$), 1.63−1.69 (m, 2H, 2$CH_3$−C*H*−$CH_3$), 1.71−1.83 (m, 4H, 2$CH_3$−CH−C$H_2$), 2.55−2.63 (m, 4H, 2$CH_3$−CH−C$H_2$), 2.77−2.88 (m, 4H, 2$CH_2$−C$H_2$−$CH_2$), 2.95−3,04 (m, 2H, C$H_2$−NH−C═O), 3.07−3.15 (m, 4H, C$H_2$−NH−C$H_2$), 3.19−3.28 (m, 2H, C$H_2$−NH−C═O), 3.63−3.72 (m, 2H, 2C*H*−S), 4.17−4.26 (m, 2H, 2C*H*−S), amine and amide protons were not detected. IR ($cm^{-1}$): 971.6 (m, Re═O), 1626.2 (s, C═O), 2959.4 (s, C−H), 3435.8 (m, N−H).

**X-ray Data Collection and Processing.** The X-ray data were collected at room temperature (293 K) on a SMART-CCD diffractometer (SIEMENS), using graphite-monochromatized Mo Kα radiation ($\lambda = 0.710\ 73$ Å). A summary of the crystallographic data of **Re5a** and **Re5b** is given in Table 1. The positions of the non-hydrogen atoms were determined by the heavy-atom technique. With the exception of the bridging amine hydrogens, which were able to be determined, the hydrogen positions were calculated according to ideal geometries after anisotropic refinement of these positions. Empirical absorption corrections were made using Ψ scans. Most of the calculations were carried out in the SHELXTL system with some local modifications. Selected bond lengths and angles are reported in Table 4. CCDC 265519 (**Re5a**) and CCDC 265520 (**Re5b**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via http://www.ccdc.cam.ac.uk/data_request/cif, by e-mailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, U.K., fax +44 1223 336033.

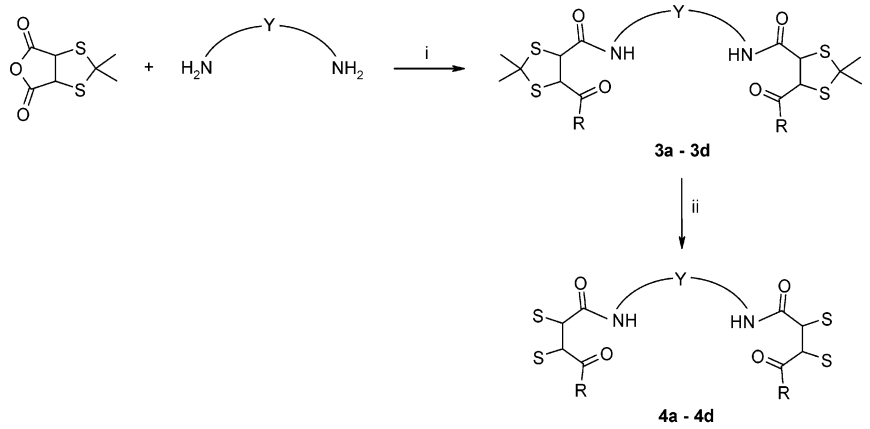
## Results and Discussion

**$S_4$ Ligand Chemistry.** Synthesis of the DMSA-based bridged $S_4$ ligands makes use of the cyclic anhydride published by Gerecke et al.[20] This synthon enables manifold functionalizations and is therefore a "key compound" in the present application.

The general route to prepare DMSA-based bridging $S_4$ ligands involves reaction of the prochiral cyclic anhydride with a diamine chain followed by cleavage of the protective isopropylidene group by $HgCl_2/H_2S$.[21,22] From this route, $S_4$ ligands with free carboxylic groups result (Scheme 1). Detailed information is available as Supporting Information.

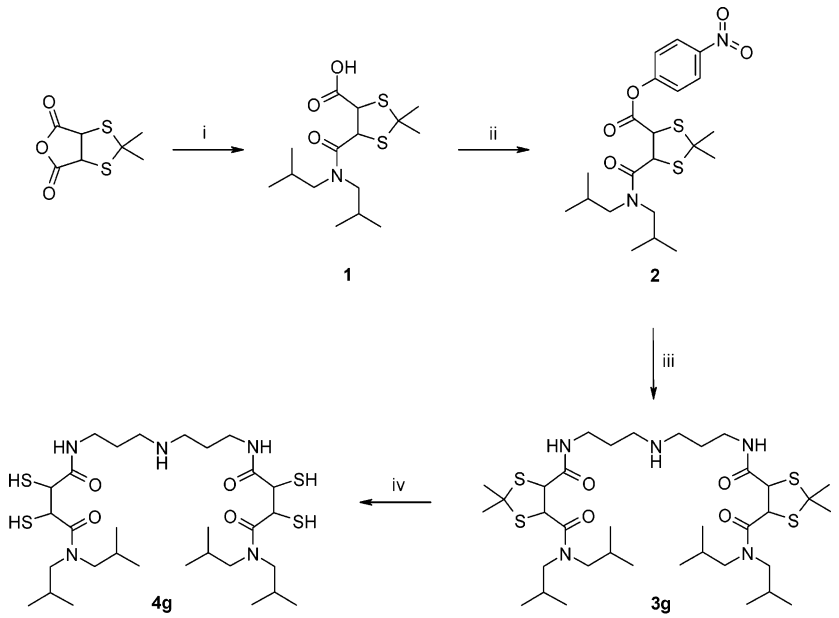
However, derivatization of the ligand is desirable not only for easier handling but also from the aspect of directing lipophilicity. This was accomplished by modification of the free carboxylic groups to amides (Scheme 2). The synthesis of such derivatives requires an alternative reaction procedure[23] that starts with the opening of the anhydride by a respective amine. The second carboxylic group in the resulting racemic compound **1** is transformed into the *p*-nitrophenyl ester **2**. Bridging of two molecules of **2** by *N*-(3-aminopropyl)propane-1,3-diamine gives **3g**, and subsequent removal of the protective group delivers the $S_4$ ligand **4g** in the form of its stereoisomers. The latter procedure is accompanied, as a rule, by a side reaction, from which an

**Scheme 1.** General Reaction Route to Aminoalkylene-Bridged $S_4$ Ligands[a]




[a] (i) Methylene chloride. (ii) $HgCl_2/H_2S$, acetonitrile/water. For experimental details, see the Supporting Information.

**Scheme 2.** Reaction Route to the Aminoalkylene-Bridged $S_4$ Ligand **4g**[a]




[a] For clarity only the meso ligand is shown (see Figure 1): (i) diisobutylamine, methylene chloride; (ii) DCC, 4-nitrophenol, ethyl acetate; (iii) *N*-(3-aminopropyl)propane-1,3-diamine, toluene; (iv) $HgCl_2/H_2S$, acetonitrile/water.

undefined product results and precipitates. A stoichiometric amount of the diamine reactant was insufficient, and an excess (1 equiv) is required for a complete reaction.

As a potential tool for coupling biomolecules to the ligand, an amine group was introduced into the alkylenediamine chain used for bridging. Furthermore, it is possible that interaction of the protonated amino group with the metal−oxo (hydrogen bond) might contribute to enhancement of the stability of the complex and may help to influence the distribution of isomers (see below).

As shown in Figure 1, the $S_4$ ligands exist as diastereomeric mixtures, a meso form, and two optically active forms. The meso form results from combining two different enantiomeric DMSA building blocks, either of the (2*S*,3*R*) and (2*R*,3*S*) enantiomeric form or of the (2*R*,3*S*) and (2*S*,3*R*) enantiomeric form. The racemate results from the combination of two similar enantiomeric DMSA building blocks. All preliminary studies for complexation refer, if not specially assigned, to this mixture.

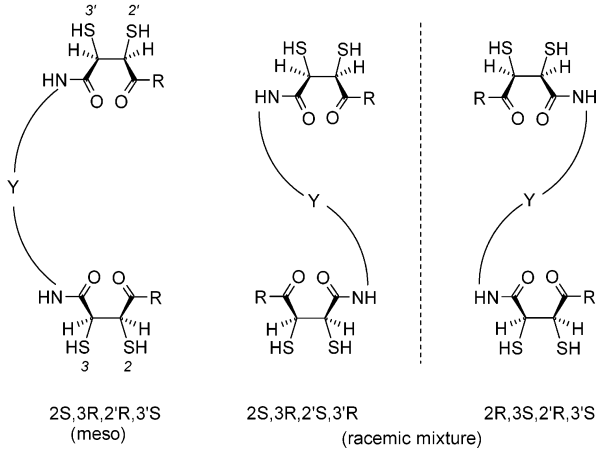



**Figure 1.** Stereoisomeric forms of the tetrathiolate $S_4$ ligands.

**Rhenium Complexes. (a) Determination of Chain-Length Conditions.** The ability of the preorganized ligand to bind with the rhenium−oxo core in the expected manner

**Table 2.** Formation of Oxorhenium(V) Complexes with Tetrathiolate $S_4$ Ligands of the Type R−(O)C−C(SH)−C(SH)−C(O)−Y−C(O)−C(SH)−C(SH)−C(O)−R (**4a**−**g**) with Dependence on the Length of the Linker

| ligand | R | linker (Y) | complex with **4** |
|---|---|---|---|
| **4a** | OH | HN−$(CH_2)_2$−NH−$(CH_2)_2$−NH | no |
| **4b** | OH | HN−$(CH_2)_7$−NH | yes (**Re1**) |
| **4c** | OH | HN−$(CH_2)_3$−NH−$(CH_2)_3$−NH | yes (**Re2**) |
| **4d** | OH | HN−$(CH_2)_8$−NH | no[a] |
| **4e** | N($^i$Bu)$_2$ | HN−$(CH_2)_5$−NH | yes (**Re4**) |
| **4f** | N($^i$Bu)$_2$ | HN−$(CH_2)_2$−NH−$(CH_2)_2$−NH | no |
| **4g** | N($^i$Bu)$_2$ | HN−$(CH_2)_3$−NH−$(CH_2)_3$−NH | yes (**Re5**) |

[a] Complex **Re3** can be obtained starting from a preorganized $ReOS_4$ precursor, as shown in Scheme 3.

will depend on the chain length of the bridge. To get a feeling for the requirement for the bridge length, we applied ligands where the alkylene chain varies in length from five to eight (number of methylene and amine groups), with and without insertion of an amino group. Table 2 represents a series of ligands that were synthesized by varying the linking group (Y). Experimental details have been compiled as Supporting Information.

The expectation based upon the chemistry of simple dithiole-ligand-derived Tc and Re complexes[24] was that the tetrathiolate ligands should form negatively charged (tetrathiolato)oxometal(V) complexes of the general formula $[MOS_4]^-$.

The synthesis route consists of ligand-exchange reactions with tetrabutylammonium tetrachlorooxorhenate(V) ($NBu_4$-$[ReOCl_4]$) as a reactive Re(V) precursor.

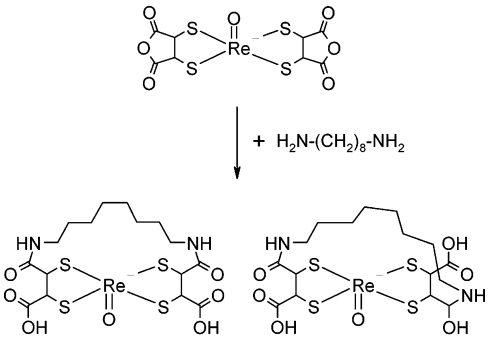
To determine the chain length necessary for complexation, the entire series of ligands was applied. Because complexation studies of ligands **4a**−**g** were done under the aspect of checking whether the expected $ReO(S_4)$ complexes are formed or not, the synthesis was done in microscopic scale and the yields were not optimized. The formation of mononuclear species was checked by ESI-MS of the crude reaction mixture. From this series of ligands, **4g** was chosen to study the rhenium chemistry and to clear the open questions in the stereochemistry of $ReO(S_4)$ complexes.

Table 2 shows that ligands **4b**, **4c**, **4e**, and **4g** react in the expected manner to form the related mononuclear rhenium complexes. Unlike these, there is no evidence for rhenium complexes with ligands **4a**, **4d**, and **4f**, showing that the chain length in these ligands is not suitable for complexation. In the case of a $C_5$ sequence, the resulting complex **Re4** was obtained. However, the $C_2NC_2$ sequence (**4a** and **4f**) is not adequate, presumably because of the disturbing influence of amine functionality (see below). $C_8$ (**4d**) is apparently too long for forming mononuclear complexes, potentially resulting in the formation of polymeric products.

Instead, we observed with both short ($C_2NC_2$) and long ($C_8$) bridged ligands the formation of brown precipitates that we consider as polymeric products. Indications for polymeric structures are that the precipitates are insoluble in common solvents with the exception of dimethyl sulfoxide, that they do not move in TLC, and that they show no MS signals in

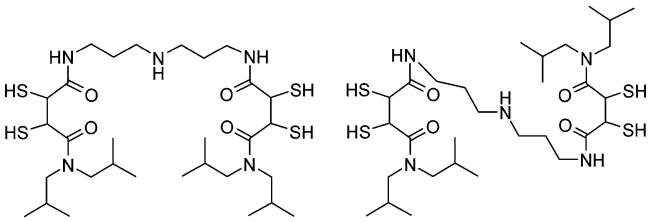
(24) Connor, K. A.; Walton, R. A. Rhenium. In *Comprehensive Coordination Chemistry*; Wilkinson, G., Gillard, R. D., McCleverty, J. A., Eds.; Elsevier: Oxford, U.K., 1985.

**Scheme 3.** Reaction of 1,8-Diaminooctane with [ReO(DMSA-anhydride)$_2$]− To Form Complex **Re3** as a Mixture of Isomers

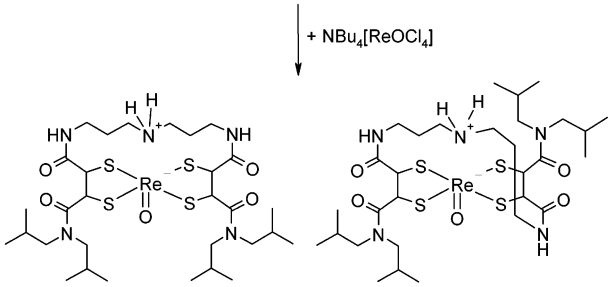



**Re3**
(mixture of isomers)

**Scheme 4.** Synthesis of Rhenium Complex **Re5**



**4g**
(mixture of isomers)




**Re5**
(mixture of isomers)

the expected kind and region. However, bands in the range of 960−970 $cm^{-1}$ in the infrared spectra reveal the presence of the Re═O core. The formation of polymers can be explained by the fact that both short ($C_2NC_2$) and long ($C_8$) chain lengths are insufficient to bring the donor atoms into a position required for forming mononuclear species, so that alternatively the dithiol units turn in a manner in which the competing reaction to form polymeric structures is favored.

In this respect, it is interesting to note that preorganization of the $ReOS_4$ coordination sphere enables access to complexes with nonoptimal ligands. The rhenium complex **Re3** (eight methylene groups in the bridge) is formed, definitely as an isomeric mixture, when 1,8-diaminoctane reacts with ReO(DMSA-anhydride)$_2$,[19a] checked by ESI-MS (Scheme 3).

**(b) Chemistry and Structure of Rhenium Complex Re5.** After having defined the chain length of five to seven atoms in the $S_4$ ligand as the preferred framework to form 1:1 complexes with oxorhenium(V), ligand **4g** was chosen as a prototype to study the formation of $ReS_4$ complexes (i.e., their structure and isomerism). Reaction of the ligand **4g** with tetrabutylammonium tetrachlorooxorhenate(V) resulted in

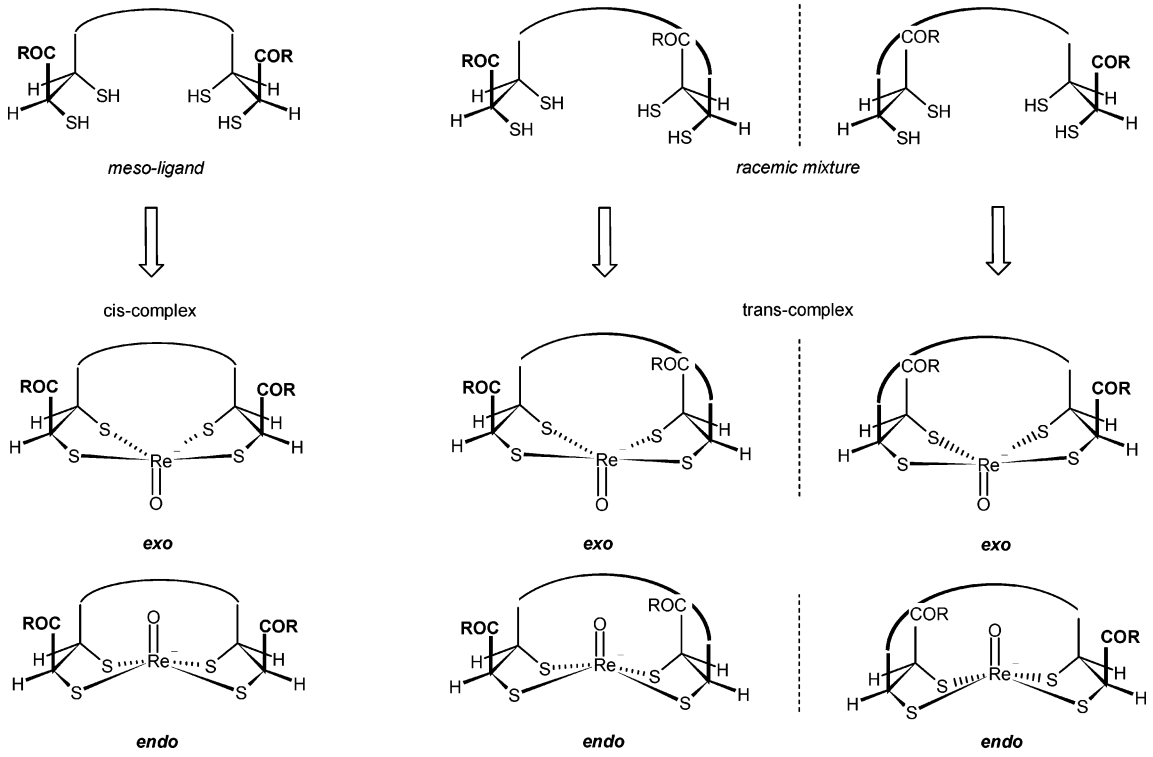



**Figure 2.** Stereochemistry of potential [ReO($S_4$)] complexes with tetrathiolate $S_4$ ligands.

**Table 3.** Analytical Data of Complexes **Re5a** and **Re5b**

| | **Re5a** | **Re5b** |
|---|---|---|
| IR | $\nu$(Re=O) = 974 cm$^{-1}$ | $\nu$(Re=O) = 972 cm$^{-1}$ |
| UV | $\lambda$ = 330 nm | $\lambda$ = 340 nm |
| $^1$H NMR | $\delta$ 3.91−3.96 (m, 2H, 2C*H*−S), 4.45−4.49 (m, 2H, 2C*H*−S) | $\delta$ 3.63−3.72 (m, 2H, 2C*H*−S), 4.17−4.26 (m, 2H, 2C*H*−S) |
| HPLC | $R_t$ = 14.7 min | $R_t$ = 8.7 min |

product spectrum of **Re5** as indicated by TLC and HPLC analysis (Scheme 4).

A possible explanation is that isomeric complexes are formed as a consequence of the ligand isomerism and, in view of previous experience with the DMSA chemistry of Tc and Re,[8] each stereochemically pure ligand gives rise to complexes with an arrangement of the M=O group in the exo or endo position relative to the bridging chain and the carbimido groups (Figure 2).

Workup of the reaction mixture by column chromatography on silica gel with a mixture of 2-propanol/chloroform/ammonia as the eluent resulted in the isolation of two crystalline species, **Re5a** and **Re5b**.

The MS spectrum indicated that the protonated form of the amino function was present (positive ESI, $[M + H]^+$, *m*/*z* 882.5; exact mass calcd for $C_{30}H_{56}N_5O_5ReS_4$, 881.26). $^1$H NMR showed no signals for the tetrabutylammonium ion, confirming that the complexes exist as the "betaine" with an internal counterion. $^1$H NMR, IR, UV, and HPLC confirmed the expected composition, regardless of significant differences in their analytical parameters (Table 3).

Final evidence for the proposed structures of the Re complexes **Re5a** and **Re5b** was obtained from X-ray crystal structure determination. Selected bond lengths and angles have been compiled in Table 4. As shown in Figures 3 and 4, the four sulfur atoms in both isomers coordinate to the oxorhenium core at equatorial positions, and oxygen is at the apex.

**Table 4.** Selected Bond Lengths (Å) and Angles (deg) of Complexes **Re5a** and **Re5b**

| selected bond lengths and angles | **Re5a** | **Re5b** |
|---|---|---|
| Re−O1 | 1.673(4) | 1.564(8) |
| Re−S2 | 2.311(2) | 2.301(4) |
| Re−S4 | 2.308(2) | 2.337(4) |
| Re−S1 | 2.323(2) | 2.297(4) |
| Re−S3 | 2.320(2) | 2.290(4) |
| O1−Re−S2 | 107.88(15) | 104.75(3) |
| O1−Re−S4 | 107.96(15) | 104.33(3) |
| O1−Re−S3 | 107.61(15) | 110.70(3) |
| O1−Re−S1 | 108.98(15) | 111.98(3) |
| S2−Re−S1 | 85.58(5) | 86.08(11) |
| S4−Re−S1 | 81.17(6) | 82.65(11) |
| S2−Re−S3 | 85.66(5) | 84.85(11) |
| S4−Re−S3 | 85.43(6) | 85.45(11) |
| S2−Re−S4 | 144.11(6) | 150.93(13) |
| S1−Re−S3 | 143.33(6) | 137.29(15) |

In both complexes, the oxorhenium group is in the exo position relative to the alkyl chain and the carbamido groups. To our knowledge, that is the first molecular structure of a DMSA-derived complex with the oxo group arranged in the exo position. For other known Re complexes with DMSA[15,28]

(25) Addison, A. W.; Rao, T. N.; Reedijk, J.; van Rijn, J.; Verschoor, G. C. *J. Chem. Soc., Dalton Trans.* **1984**, *7*, 1349.
(26) Blower, P. J.; Dilworth, J. R.; Hutchinson, J. P.; Nicholson, T.; Zubieta, J. *J. Chem. Soc., Dalton Trans.* **1986**, *9*, 1339.
(27) Clegg, W.; Boyde, S.; Garner, C. D. *Acta Crystallogr.* **1988**, *C44*, 172.
(28) Seifert, S.; Spies, H.; Leibnitz, P.; Reck, G. Forschungszentrum Rossendorf, Institut fuer Bioanorganische und Radiopharmazeutische Chemie. *Annu. Rep.* **1993**, FZR-32, 91−92.

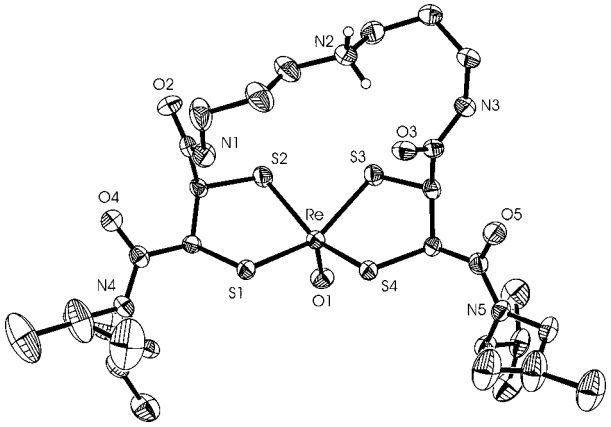



**Figure 3.** ORTEP diagram of complex **Re5a**. Atoms are drawn at 50% probability.

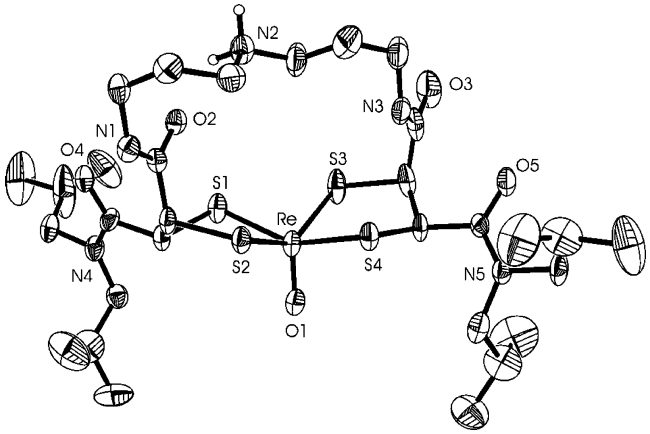



**Figure 4.** ORTEP diagram of complex **Re5b**. Atoms are drawn at 50% probability.

or DMSA-anhydride[19] ligands, endo arrangement was exclusively found in the crystal structure.

Both compounds are cis−trans isomers, with **Re5a** being exo−cis and **Re5b** being exo−trans.

There is some disparity between structures **Re5a** and **Re5b**. Therefore, it seems to be justified to discuss the factor $\tau$[25] when steric constraints caused by the alkyl bridge are to be considered. The $\tau$ factor is zero for a square-pyramidal arrangement and 1 for an ideal trigonal-prismatic arrangement. One could argue that $\tau = 0.23$, indicating a distortion to trigonal-bipyramidal, is indicative of higher steric restrictions for **Re5b** as compared to isomer **Re5a** ($\tau = 0.01$). In this respect, a comparison with the structure of a rhenium complex with ethylenedithiol (edt) as a ligand[26,27] is useful. As in Re-DMSA, the coordination sphere consists of four sulfur donors and an oxo group. However, there are by nature neither constraints by bridge nor by carboxylic groups. Interestingly, the $\tau$ value of $[ReO(edt)_2]^-$ (0.12) is between that of both isomers described herein. When $[ReO(edt)_2]^-$ is defined as the complex with lower steric requirements, the $\tau$ values of the complex isomers reflect distortions toward ideal square-pyramidal for **Re5a** and toward trigonal-bipyramidal for **Re5b**.

The Re═O bond length for **Re5a** (1.673 Å) is within the "normal" range found for rhenium bis(dithiolato) complexes. The value of the Re═O distance for **Re5b** is substantially lower (1.564 Å) than what might be expected, an effect that is ascribed, in part, to different space groups in the crystals.

Hydrogen bonding between one amide oxygen and the amine group in the bridge leads to formal shortening of the chain. This could explain the fact that no complexes result from amine group containing ligand **4a** as compared to ligand **4e**, which has a pure alkylene chain.

We want to mention that the structure and isomer distribution of **Re5a** and **Re5b** were computed using a new molecular mechanics force field for the design of oxotechnetium(V) and oxorhenium(V) radiopharmaceuticals. The calculated isomer distribution reveals that there is a clear trend for both isomers to adopt the exo conformation, irrespective of whether the ligand binds in the cis or trans configuration to the metal center. In both the cis and trans systems, there is a significant steric energy difference between the endo and exo forms, on the order of >10 kJ/mol. The results will be published in a separate paper.[29]

## Conclusions

Tetrathiolate $S_4$ ligands, obtained by bridging two DMSA molecules with an alkylenediamine chain, represent a new class of complexing agents for stable binding of oxorhenium(V). To prepare tetrathiolate $S_4$ ligands, each amine group of the alkylenediamine reacts with a carboxylic group of a DMSA molecule, thus connecting two DMSA molecules via amide bonds. Chain lengths (between the two nitrogen atoms of the amide groups) from five to seven seem to be preferred to form mononuclear rhenium complexes.

Ligand **4g** was chosen as a prototype from a series of ligands. **4g** has a seven-membered bridge ($C_3-N-C_3$); from this precursor, two rhenium complexes were isolated. The molecular structure of both species show exo orientation of the oxorhenium group relative to the bridge. It is likely, but remains to be proven, that prolongation of the bridge may favor the endo orientation because of the longer distance between the two carboxylic groups of two DMSA molecules in endo arrangement. However, preliminary results with ligand **4d** lower our expectation because the complex **Re3** was accessible only via a preorganized Re complex (see above). Investigations are ongoing to ascertain whether insertion of a group able to interact with the oxorhenium group into the chain favors the endo orientation. In summary, a new type of chelator is available as a building block for technetium- and rhenium-labeled biomolecules. Studies of labeling with radioactive rhenium and the stability of complexes with the new $S_4$ ligands as compared to similar systems are currently underway in order to determine the usefulness of the system as a radioactive label for biomolecules.

**Acknowledgment.** Financial support by Deutsche Forschungsgemeinschaft is gratefully acknowledged.

**Supporting Information Available:** Additional figures, schemes, and experimental and spectroscopic details (CIF and PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

IC051148S

(29) Comba, P.; Daubinet, A.; Martin, B.; Pietzsch, H.-J.; Stephan, H. *J. Organomet. Chem.* **2005**, submitted for publication.