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New Oxorhenium(V) Complexes from the Widely Used Diaminedithiol (DADT) Ligand System

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Synthesis of the 2,9-dimethyl-4,7-diaza-4-alkyl-2,9-decanedithiol (**1**, alkyl = morpholinylethyl in **a**, and alkyl = pyrrolidinylethyl in **b**), following a widely used synthetic scheme for diaminedithiol (DADT) ligands, led to the isolation of 1-alkyl-2-(1′-methyl-1′-sulfanylethyl)-3-(2″-methyl-2″-sulfanylpropyl)diazolidine (**3**) as the major product. Both ligands **1** and **2** gave complexes with the oxorhenium ReO(V) core. Ligand **1** gave the expected ReO[SNNS] complex (**2**) with the side chain on nitrogen in the *syn* configuration. Ligand **3** gave, in the presence of a monodentate aromatic thiol, complexes of the ReO[SNN][S][S] (**4**) and ReO[SNN][S] type (**5**), respectively, in which the diazolidine ring has rearranged to a thiazolidine ring. Crystallographic analysis showed that in **4** the coordination geometry about the metal is distorted octahedral where the equatorial plane is defined by the sulfur and one of the nitrogen atoms of the ligand and the two sulfurs of the aromatic thiols, while the axial positions are occupied by the oxygen of the ReO core and the second nitrogen of the ligand. Specifically, complex **4a** crystallizes in space group $P2_1/c$, a = 15.63(1) Å, b = 15.28(2) Å, c = 16.07(1) Å, β = 113.78(2)°, V = 3512(5) Å^3, Z = 4. Complex **4b** crystallizes in space group $P2_1/n$, a = 14.560(9) Å, b = 14.804(9) Å, c = 19.85(1) Å, β = 90.94(2)°, V = 4278(1) Å^3, Z = 4. In **5b**, the coordination geometry is distorted square pyramidal with the SNN donor atom of the ligand and the aromatic thiol defining the equatorial plane and the doubly bonded oxygen occupying the apex of the pyramid. Complex **5b** crystallizes in space group $P\bar{1}$, a = 9.387(5) Å, b = 11.306(5) Å, c = 14.040(6) Å, α = 84.51(1)°, β = 84.45(2)°, γ = 87.17(1)°, V = 1475(1) Å^3, Z = 2. All isolated complexes are neutral and lipophilic. Complete assignments of ^{1}H and ^{13}C NMR resonances are reported.

Introduction

In recent years, the β-emitting rhenium radionuclides ^{186}Re and ^{188}Re (E_{max} = 1.1 and 2.1 MeV, respectively) have become increasingly important in therapeutic nuclear medicine.[1] Rhenium-labeled receptor-based radiopharmaceuticals are being developed for radiotherapy applications aiming at the delivery of therapeutically significant radiation doses to malignant lesions.[2] A common approach to designing these radiopharmaceuticals involves linking a rhenium complex to a targeting molecule known to exhibit high-affinity binding for a specific receptor that is expressed at the malignant site. The rhenium complex is usually covalently attached to the targeting molecule through a hydrocarbon chain.[3]

In searching for ligands that would produce suitable rhenium complexes, one can benefit from the extensive library of technetium complexes because rhenium is technetium's third-row congener and displays many of the chemical properties of technetium. The chemistry of technetium has greatly developed over the two past decades because of the predominant use of ^{99m}Tc radiopharmaceuticals in diagnostic imaging.[4]

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(1) Duatti, A. In *Technetium, Rhenium and Other Metals in Chemistry and Nuclear Medicine 5*; Nicolini, M., Mazzi, U., Eds.; Servici Grafici Editoriali: Padova, Italy, 1999; p 3.
(2) Hashimoto, K.; Yoshihara, K. *Top. Curr. Chem.* **1996**, *176*, 275.
(3) Dilworth, J.; Parrot, S. *Chem. Soc. Rev.* **1998**, *27*, 43.
(4) (a) Schwochau, K. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 2258. (b) Johannsen, B.; Spies, H. *Top. Curr. Chem.* **1996**, *176*, 77. (c) Jurisson, S.; Lydon, J. *Chem. Rev.* **1999**, *99*, 2205. (d) Liu, S.; Edwards, S. *Chem. Rev.* **1999**, *99*, 2235.

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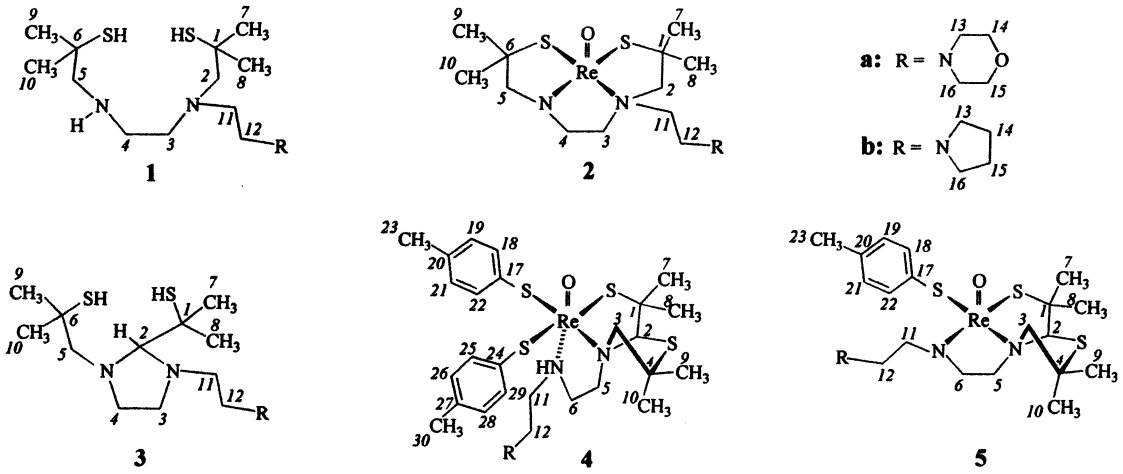

Figure 1. Structures of ligands **1** and **3** and complexes **2**, **4**, and **5**. The numbering of the atoms shown is the one used in the NMR assignments.

A well studied ligand for technetium complexes is the N_2S_2 diaminedithiol (DADT) ligand system $HSCH_2CH_2NHCH_2CH_2NHCH_2CH_2SH$. A great number of derivatives of this versatile chelate have been synthesized by carbon[5] and/or nitrogen[6] backbone substitution, and many of those gave oxotechnetium TcO[SNNS] complexes with interesting properties as potential brain radiopharmaceuticals. For example, the clinically used ^{99m}TcO(V)-ECD[7] for brain perfusion imaging is a DADT derivative. Furthermore, DADT complexes tethered to biologically active compounds have been designed for radiopharmaceutical applications aiming at specific receptor imaging[8] or scintigraphic bone imaging.[9] For one of the DADT conjugates, [^{99m}Tc]TRODAT-1,[8d,10] the phase I evaluation in humans as a dopamine transporter imaging agent has been completed. In addition, the DADT system has been shown to form stable complexes with gallium(III) and indium(III) which have important nuclear medicine applications.[11,12]

To further explore the chemistry of the versatile DADT ligand and to discern the nature of the ReODADT complexes for subsequent design of therapeutic radiopharmaceuticals, we proceeded to synthesize the N-substituted DADT ligand system **1** (Figure 1). In this type of ligand, the side chain on nitrogen (CH_2CH_2R) may be replaced by a wide range of target specific molecules enabling the corresponding oxorhenium complex to locate in problematic lesions. The presence of the geminal dimethyl groups on the ligand stabilizes the oxorhenium complex[13] by increasing the nucleophilicity of the thiols and by shielding the metal core from substitution reactions. Ligand **1** gave the expected ReO[SNNS] complex **2** which was characterized by mass spectrometry and NMR spectroscopy. Complexes of this general type with the oxorhenium core have been reported before.[14]

In the course of the synthesis of ligand **1**, cyclic ligand **3** was isolated for the first time and characterized. Ligand **3** was unable to function as a tetradentate ligand presumably because of the steric hindrance introduced by the presence

(5) (a) Kung, H. F.; Molnar, M.; Billings, J.; Wicks, R.; Blau, M. *J. Nucl. Med.* **1984**, *25*, 326. (b) Kung, H. F.; Guo, Y.-Z.; Yu, C.-C.; Billings, J.; Subramanyam, V.; Calabrese, J. C. *J. Med. Chem.* **1989**, *32*, 433. (c) John, C. S.; Francesconi, L. C.; Kung, H. F.; Wehrli, S.; Graczyk, G.; Carroll, P. *Polyhedron* **1992**, *11*, 1145. (d) Francesconi, L. C.; Graczyk, G.; Wehrli, S.; Shaikh, S. N.; McClinton, D.; Liu, S.; Zubieta, J.; Kung, H. F. *Inorg. Chem.* **1993**, *32*, 3114.

(6) (a) Lever, S. Z.; Burns, H. D.; Kervitsky, T. M.; Goldfarb, H. W.; Woo, D. V.; Wong, D. F.; Epps, L. A.; Kramer, A. V.; Wagner, H. N., Jr. *J. Nucl. Med.* **1985**, *26*, 1287. (b) Chiotellis, E.; Varvarigou, A. D.; Maina, Th.; Stassinopoulou, C. I. *Nucl. Med. Biol.* **1988**, *15*, 215. (c) Scheffel, U.; Goldfarb, H. W.; Lever, S. Z.; Gungon, R. L.; Burns, H. D.; Wagner, H. N. *J. Nucl. Med.* **1988**, *29*, 73. (d) Marchi, A.; Marvelli, L.; Rossi, R.; Magon, L.; Bertolasi, V.; Ferretti, V.; Gilli, P. *J. Chem. Soc., Dalton Trans.* **1992**, 1485. (e) Papadopoulos, M.; Stathaki, S.; Mastrostamatis, S.; Varvarigou, A.; Chiotellis, E. *Nucl. Med. Biol.* **1993**, *20*, 105. (f) Lever, S. Z.; Sun, S.-Y.; Scheffel, U. A.; Kaltovich, F. A.; Baidoo, K. E.; Goldfarb, H.; Wagner, H. N., Jr. *J. Pharm. Sci.* **1994**, *83*, 802.

(7) Leveille, J.; Demonceau, G.; De Roo, M.; Rigo, P.; Taillefer, R.; Morgan, R. A.; Kupranick, D.; Walovitch, R. C. *J. Nucl. Med.* **1989**, *30*, 1902.

(8) (a) DiZio, J. P.; Fiaschi, R.; Davison, A.; Jones, A. G.; Katzenellenbogen, J. A. *Bioconjugate Chem.* **1991**, *2*, 353. (b) DiZio, J. P.; Anderson, C. J.; Davison, A.; Ehrhardt, G. J.; Carlson, K. E.; Welch, M. J.; Katzenellenbogen, J. A. *J. Nucl. Med.* **1992**, *33*, 558. (c) Lever, S. Z.; Baidoo, K. E.; Mahmood, A.; Matsumura, K.; Scheffel, U.; Wagner, H. N., Jr. *Nucl. Med. Biol.* **1994**, *21*, 157. (d) Mozley, P. D.; Stubbs, J. B.; Plössl, K.; Dresel, S. H.; Barraclough, E. D.; Alavi, A.; Araujo, L. I.; Kung, H. F. *J. Nucl. Med.* **1998**, *39*, 2069. (e) Kung, H. F.; Meegalla, S.; Plössl, K.; Kung, M.-P.; Mu, M. In *Technetium, Rhenium and Other Metals in Chemistry and Nuclear Medicine 5*; Nicolini, M., Mazzi, U., Eds.; Servici Grafici Editoriali: Padova, Italy, 1999; p 373. (f) Baidoo, K. E.; Lin, K. S.; Zhan, Y.; Finley, P.; Scheffel, U.; Wagner, H. N., Jr. *Bioconjugate Chem.* **1998**, *9*, 218. (g) Chumpradit, S.; Kung, M.-P.; Mu, M.; Kung, H. F. In *Technetium, Rhenium and Other Metals in Chemistry and Nuclear Medicine 5*; Nicolini, M., Mazzi, U., Eds.; Servici Grafici Editoriali: Padova, Italy, 1999; p 497.

(9) Cleynhens, B.; Vanbilloen, H.; Bauwens, J.; Verbruggen, A. In *Technetium, Rhenium and Other Metals in Chemistry and Nuclear Medicine 5*; Nicolini, M., Mazzi, U., Eds.; Servici Grafici Editoriali: Padova, Italy, 1999; p 605.

(10) Kung, H. F. *Nucl. Med. Biol.* **2001**, *28*, 505.

(11) Liu, B. L.; Kung, H. F.; Jin, Y. T.; Zhu, L.; Meng, M. *J. Nucl. Med.* **1989**, *30*, 367.

(12) (a) Cotsyfakis, C.; Varvarigou, A. D.; Papadopoulos, M.; Stathaki, S.; Stassinopoulou, C. I.; Chiotellis, E. *Eur. J. Nucl. Med.* **1992**, *20*, 302. (b) Kung, H. F.; Liu, B. L.; Mankoff, D.; Kung, M. P.; Billings, J. J.; Francesconi, L.; Alavi, A. *J. Nucl. Med.* **1990**, *31*, 1635.

(13) Sun, Y.; Anderson, C. J.; Pajeau, T. S.; Reichert, D. E.; Hancock, R. D.; Motekaitis, R. J.; Martell, A. E.; Welch, M. J. *J. Med. Chem.* **1996**, *39*, 458.

(14) (a) Mahmood, A.; Baidoo, K. E.; Lever, S. Z. In *Technetium and Rhenium in Chemistry and Nuclear Medicine 3*; Nicolini, M., Bandoli, G., Mazzi, U., Eds.; Raven Press: New York, p 119. (b) Schultze, L. M.; Todaro, L. J.; Baldwin, R. M.; Byrne, E. F.; McBride, B. J. *Inorg. Chem.* **1994**, *33*, 5579.

of the diazolidine ring. However, in the presence of a monodentate thiol, it gave complexes **4** and **5** of the [SNN]-[S][S] and the [SNN][S] type, respectively. The unexpected finding was that in these complexes rearrangement of the diazolidine ring originally present in **3** had taken place with formation of a thiazolidine ring. Full crystallographic and spectroscopic characterization is reported here for these complexes.

The interesting chemistry exhibited by the widely applied DADT ligand system is the focus of this paper. Isolation of the cyclic ligand of the type of **3** has never been reported in the literature despite the broad use of the DADT ligand system. In addition, transformation of **3** during complex formation and isolation of rearranged complexes of the type of **4** and **5** has never been reported.

Experimental Section

Synthesis. All commercial reagents were of analytical grade and were used without further purification. Rhenium was supplied by Aldrich as potassium perrhenate(VII).

IR spectra were recorded in the range 4000−500 cm^{-1} on a Perkin-Elmer 1600 FT-IR spectrophotometer and were referenced to polystyrene. KBr pellets were used for solids, and NaCl windows, for the oily samples. Mass spectra were recorded on a ESI Navigator Finnigan spectrometer. UV spectra were aquired on a Hitachi 1500−20 spectrometer. Elemental analyses were performed on a Perkin-Elmer 2400/II automatic analyzer.

The precursors $ReOCl_3(PPh_3)_2$[15] and Re(V)gluconate[16] were synthesized according to literature procedures.

NMR data for ligands **1** and **3** as well as for complexes **2a**, **4a**,**b**, and **5a**,**b** are given in the NMR section.

2,2′-Dithiobis(2-methylpropanal) (6). This compound was prepared according to a reported method[5a] with modification. In a four-neck round-bottomed flask equipped with condenser and thermometer, a solution of isobutyraldehyde (144.2 g) in 420 mL of carbon tetrachloride was heated to 50 °C in a water bath with mechanical stirring under nitrogen. 98% S_2Cl_2 (137.8 g) was added dropwise at a speed that allowed the easy removal of the generated HCl. During addition, the temperature was kept constant with the help of ice. Upon completion of the addition, aqueous 5 N NaOH was slowly added with cooling until the pH of the medium reached 10. The organic layer was separated and washed with water and brine. The solution was subsequently dried with $MgSO_4$ and filtered. Volatiles were removed under reduced pressure. The residue was distilled under vacuum (bp 100−110 °C/0.5 mmHg) to give 172.0 g (83% yield) of colorless oil. ^{1}H NMR ($CDCl_3$, 25 °C): δ 1.40 (s, 12H, CH_3), 9.09 (s, 2H, CHO).

3,3,10,10-Tetramethyl-1,2-dithia-5,8-diazacyclodeca-4,8-diene (7). This compound was prepared according to a reported method[6a] with modification. To a stirred solution of **6** (48.6 g) in benzene (280 mL) is added *p*-toluenesulfonic acid (50 mg) followed by dropwise addition of ethylenediamine (14.2 g). The reaction mixture was refluxed with the azeotropic removal of water for 2 h. After the removal of the solvent, the residue was triturated with low boiling (40−60 °C) petroleum ether. The solution was concentrated until crystals began to form. The crystals were collected with filtration and washed with cold petroleum ether followed by ethanol to afford 44.0 g (81% yield) of product **7**: mp 166−169 °C. IR (KBr): 1651.8 cm^{-1} (C═N). ^{1}H NMR ($CDCl_3$, 25 °C): δ 6.64 (2H, CH), 4.13 (2H, CH_2), 3.22 (2H, CH_2), 1.42−1.34 (12H, $4CH_3$).

2,2,5,5-Tetramethyl-3,4-dithia-7,10-diazabicyclo[5.3.0]-decane (8). This compound was prepared according to a reported procedure[17] with slight modification. To a suspension of diimine **7** (10.0 g) in 50 mL of absolute ethanol was slowly added sodium borohydride (9.8 g). After 24 h of stirring at room temperature, acetone (100 mL) was added. The mixture was stirred for 20 min, and then, volatiles were removed under reduced pressure. To the residue, pentane (600 mL) was added, the resulting mixture was filtered, and the filtrate was evaporated to dryness. The solid white product was chromatographed on silica gel column with dichloromethane−ethanol 95:5 to yield 5.8 g of **8** (58% yield) as colorless oil. IR (cm^{-1}, NaCl window): 3285 (NH stretch). ^{1}H NMR ($CDCl_3$, 25 °C): δ 3.5 (s, 1H, CH), 2.71−3.30 (5H, CH_2), 2.61 (d, 1H, CH_2), 1.36−1.23 (12H, CH_3).

10-Chloroacetyl-2,2,5,5-tetramethyl-3,4-dithia-7,10-diazabicyclo-[5.3.0]decane (9). This compound was prepared according to a reported procedure[6a] with slight modification. A solution of chloroacetyl chloride (1.8 g) in ether (25 mL) was added dropwise over 20 min to a solution of **8** (5.4 g) in diethyl ether (100 mL). A white precipitate formed immediately, and after 1 h of stirring at room temperature, the reaction mixture was filtered. The collected precipitate was washed on the filter with warm ether, and the ethereal solution was concentrated until a white solid appeared (3.7 g, 75% yield): mp 98−100 °C. IR (KBr, cm^{-1}): 1658 (C═O stretch). ^{1}H NMR ($CDCl_3$, 25 °C): δ 4.73 (1H), 4.06 (2H), 2.58−3.79 (6H), 1.49−1.11 (12H).

10-(2′-Morpholinylacetyl)-2,2,5,5-tetramethyl-3,4-dithia-7,10-diazabicyclo[5.3.0]decane (10a). The compound was prepared according to a reported procedure[6a,b] with slight modifications. Morpholine (22.4 g) was added dropwise in a solution of **9** (10.7 g) in absolute ethanol. The mixture was heated under reflux for 2 h, and the progress of the reaction was monitored by TLC. Volatiles were removed under reduced pressure. Water was added in the residue, and the pH was adjusted to 11 with 0.1 N NaOH. The solution was extracted with diethyl ether, and the extract was dried with $MgSO_4$ and subsequently treated with decolorizing charcoal. The ethereal solution was filtered through silica gel over Celite. After the solution was concentrated, white crystals precipitated (10.0 g, 80% yield): mp 60 °C. IR (KBr, cm^{-1}): 1657 (C═O stretch). ^{1}H NMR ($CDCl_3$, 25 °C): δ 4.75 (1H), 3.92 (1H), 3.73 (4H), 3.45 (1H), 3.35 (1H), 3.20 (5H), 2.80 (3H), 2.59 (1H), 2.54 (4H), 1.35 (3H), 1.31 (3H), 1.27 (3H), 1.26 (3H).

10-(2′-Pyrrolidinylacetyl)-2,2,5,5-tetramethyl-3,4-dithia-7,10-diazabicyclo[5.3.0]decane (10b). The compound was prepared following the same procedure as the one described for **10a**. Yield 85%, mp 65 °C. IR (KBr, cm^{-1}): 1657 (C═O stretch). ^{1}H NMR ($CDCl_3$, 25 °C): δ 4.75 (1H), 3.92 (1H), 3.29 (5H), 2.79 (1H), 2.58 (5H), 1.79 (4H), 1.20−1.35 (12H).

Note. Crystals suitable for X-ray analysis were obtained for product **10** with R = piperidinyl which is not included in this publication. The crystallographic data are submitted as Supporting Information.

2,9-Dimethyl-4,7-diaza-4-morpholinylethyl-2,9-decanedithiol (1a) and 1-Morpholinylethyl-2-(1′-methyl-1′-sulfanylethyl)-3-(2″-methyl-2″-sulfanylpropyl)diazolidine (3a). Ligands **1a** and

(15) Chatt, J.; Rowe, G. A. *J. Chem. Soc.* **1962**, 4019.
(16) Noll, B.; Kniess, T.; Friebe, M.; Spies, H.; Johannsen, B. *Isot. Environ. Health Stud.* **1996**, *32*, 21.
(17) (a) Kung, H. F.; Molnar, M.; Billings, J.; Wicks, R.; Blau, M. *J. Nucl. Med.* **1984**, *25*, 326. (b) Kung, H. F.; Yu, C. C.; Billings, J.; Molnar, M.; Blau, M. *J. Med. Chem.* **1985**, *28*, 1280.

3a were products of the reduction of **10a** by $LiAlH_4$. The reduction was carried out following a literature procedure[6a,b] with modifications.

In a dry 250 mL round-bottom flask, **10a** (3.9 g) was dissolved in dry tetrahydrofuran (90 mL). Lithium aluminum hydride (0.9 g) was slowly added in the solution. After refluxing for 19 h, the reaction was quenched with saturated NH_4Cl while the mixture was kept cold with the help of an ice bath. The reaction mixture was filtered under vacuum, and the residue on the filter was extensively washed with ether and tetrahydrofuran. Volatiles were removed in the rotary evaporator under moderate heating at 40 °C. Water was added to the residue, and the pH was brought to 3.0 with concentrated HCl. It was subsequently adjusted to 5.3 by the addition of 1 M NaOH and extracted with diethyl ether (1 × 20 mL). The ether solution was discarded. The pH was then adjusted to 8.5 with 1 M NaOH and extracted again with ether (3 × 20 mL). The ether solutions were dried with $MgSO_4$ and filtered, and the filtrate was evaporated to dryness in the rotary evaporator. The oily colorless residue (2.0 g) was subjected to column chromatography on alumina. Elution with ether gave product **1a** (0.3 g, 8% yield) as a colorless oil. IR (NaCl, cm^{-1}): 2545 (SH). Further elution of the column with 5% methanol in ether gave product **3a** (1.3 g, 34%) as a colorless oil. IR (KBr, cm^{-1}): 2543 (SH).

2,9-Dimethyl-4,7-diaza-4-pyrrolidinylethyl-2,9-decanedithiol (1b) and 1-Pyrrolidinylethyl-2-(1′-methyl-1′-sulfanylethyl)-3-(2″-methyl-2″-sulfanylpropyl)diazolidine (3b). Ligands **1b** and **3b** were obtained in the same way as **1a** and **3a** and in corresponding yields.

(2,9-Dimethyl-4,7-diaza-4-ethylmorpholinyl-2,9-decanethiolato)oxorhenium(V) (2a). Ligand **1a** (139 mg) was added to a solution of precursor $ReOCl_3(P(C_6H_5)_3)_2$ (333 mg) in a 10 mL solution of 1 M NaOAc in MeOH. The reaction mixture was kept under reflux and magnetic stirring for 30 min. Dichloromethane was added to the reaction mixture, and the organic phase was washed with water. The organic layer was dried over $MgSO_4$ and filtered, and the volatiles were removed. The residue was chromatographed on an alumina column with 5% methanol in ether as eluent to yield complex **2a** as a violet solid (50% yield). IR (KBr, cm^{-1}): 941 (ReO). MS (ESI): m/z $(M + H)^+$ 548.3 and 550.3 (calcd for $C_{16}H_{32}N_3S_2O_2{}^{185}Re$ and $C_{16}H_{32}N_3S_2O_2{}^{187}Re$, 548.55 and 550.56, respectively). Anal. Calcd (%) for $C_{16}H_{32}N_3O_2ReS_2$ (549.15): C, 34.96; H, 5.87; N, 7.65; S, 11.64. Found: C, 35.31; H, 6.09; N, 7.93; S, 11.98.

{Bis-(*p*-methylphenolato)}{2-(1′-methyl-1′-sulfanylethyl)-3-(5″-morpholinyl-3″-azapentyl)-4,4-dimethylthiazolidinato}-oxorhenium(V) (4a) and {*p*-Methylphenolato}{2-(1′-methyl-1′-sulfanylethyl)-3-(5″-morpholinyl-3″-dehydroazapentyl)-4,4-dimethylthiazolidinato}oxorhenium(V) (5a). The complexes **4a** and **5a** were isolated from the same reaction mixture after gradual precipitation. Complex **5a** was isolated as the perrhenate salt.

a. $ReOCl_3(P(C_6H_5)_3)_2$ as Precursor. Ligand **3a** (139 mg), along with the monodentate ligand *p*-methylthiophenol (99 mg), was added to a solution of $ReOCl_3(P(C_6H_5)_3)_2$ precursor (333 mg) in 1 M NaOAc in CH_3OH (10 mL). The reaction mixture was boiled under reflux and magnetic stirring for 30 min. Dichloromethane was added to the reaction mixture, and the organic phase was washed with water. It was subsequently dried over $MgSO_4$ and filtered, and the volatiles were removed. The residue was dissolved in a mixture of chloroform and ethanol and was allowed to slowly evaporate. Complex **4a** crystallized first to give brown crystals in 20% yield. IR (KBr, cm^{-1}): 808 (CH aromatics), 945 (ReO). Anal. Calcd (%) for $C_{30}H_{46}N_3O_2ReS_4$ (795.20): C, 45.27; H, 5.83; N, 5.28; S, 16.08. Found: C, 45.52; H, 6.02; N, 5.31; S, 16.44.

Complex **5a** subsequently precipitated as a perrhenate salt from the above solution on standing in air. Yield 10%; IR (KBr, cm^{-1}): 904 (broad, ReO_4^-), 957 (ReO) 808 (CH aromatic); elemental analysis calcd (%) for $C_{23}H_{38}N_3O_2ReS_3 \cdot HReO_4$ (922.17): C 29.96, H 4.26, N 4.56, S 10.43; found C 30.10, H 4.40, N 4.63, S 10.65.

b. Re(V)gluconate as Precursor. In a 5 mL aqueous solution of 0.3 mmol of Re(V)gluconate adjusted to pH 5 with 0.1 M NaOH, a solution of ligand **3a (**0.3 mmol) in acetone (2 mL) was added along with the coligand *p*-methylthiophenol (0.6 mmol). The solution was magnetically stirred for 20 min and was then extracted with dichloromethane. The complexes **4a** and **5a** were isolated following the same procedure as described previously for the $ReOCl_3(P(C_6H_5)_3)_2$ precursor.

{Bis-(*p*-methylphenolato)}{2-(1′-methyl-1′-sulfanylethyl)-3-(5″-pyrrolidinyl-3″-azapentyl)-4,4-dimethylthiazolidinato}-oxorhenium(V) (4b) and {*p*-Methylphenolato}{2-(1′-methyl-1′-sulfanylethyl)-3-(5″-pyrrolidinyl-3″-dehydroazapentyl)-4,4-dimethylthiazolidinato}oxorhenium(V) (5b). Complexes **4b** and **5b** were isolated following the same procedure as that described for **4a** and **5a**.

4b. Yield 20%. IR (KBr, cm^{-1}): 946 (ReO stretch), 808 (CH aromatic). Anal. Calcd (%) for $C_{30}H_{46}N_3OReS_4 \cdot 2CHCl_3$ (1017.92): C, 37.76; H, 4.75; N, 4.13; S, 12.60. Found: C, 37.89; H, 4.55; N, 4.24; S, 12.65.

5b. Yield 10%. IR (KBr, cm^{-1}): 904 (broad, ReO_4^-), 958 (ReO), 810 (CH aromatic). Anal. Calcd (%) for $C_{23}H_{38}N_3OReS_3 \cdot HReO_4$ (906.17): C, 30.49; H, 4.34; N, 4.64; S, 10.61. Found: C, 30.36; H, 4.40; N, 4.90; S, 10.83.

Determination of SH Groups of 3 with the *N*-Ethylmaleimide Assay.[18] The assay is based on the fact that, when present in excess, *N*-ethylmaleimide reacts stoichiometrically with sulfydryl compounds. The reaction is monitored at 300 nm. The difference in absorption between the reacted and unreacted *N*-ethylmaleimide is divided by the molar extinction coeffiecient of this compound at 300 nm, and the quotient is equal to the molar sulfhydryl concentration of the sample. The molar extinction coefficient of *N*-ethylmaleimide was determined to be 628 at 300 nm. The concentration of *N*-ethylmaleimide in the aqueous medium was 0.001 M, and the concentration of ligand **3** was 0.0004 M. The recorded change in absorption was 0.60 corresponding to 2 free sulfydryl groups.

X-ray Crystal Structure Determination of Compounds 4a, 4b, and 5b. A red needlelike crystal of **4a** (0.08 × 0.15 × 0.40 mm^3), a red prismatic crystal of **4b** (0.20 × 0.40 × 0.60 mm^3), and a red prismatic crystal of **5b** (0.10 × 0.30 × 0.60 mm^3) were mounted on glass fibers. Diffraction measurements were performed on a four circle Crystal Logic dual goniometer diffractometer with graphite monochromated Mo Kα radiation ($\lambda = 0.710730$ Å). Unit cell dimensions were determined and refined by using the angular settings of 25 automatically centered reflections (Table 1). Intensity data were recorded using a $\theta-2\theta$ scan. Three standard reflections monitored every 97 reflections showed less than 3% variation and no decay. Lorentz, polarization, and ψ-scan absorption corrections were applied using Crystal Logic software; no extinction corrections were necessary. Further crystallographic details for **4a:** $2\theta_{max} = 38°$, scan speed 1.3° min^{-1}, scan range 2.0° + $\alpha_1\alpha_2$ separation, reflections collected/unique/used = 2881/2755 ($R_{int} = 0.0456$)/2755, 361 parameters refined, R1/wR2 (for all data) = 0.0613/0.1278, $\Delta\rho_{min}/\Delta\rho_{max} = 1.470/-1.258$ e $Å^{-3}$, $\Delta\sigma = 0.001$. For **4b:** $2\theta_{max} = 50°$, scan speed 3.0° min^{-1}, scan range 2.5° + $\alpha_1\alpha_2$ separation, reflections collected/unique/used = 7768/7538 ($R_{int} = 0.0234$)/7538,

(18) Alexander, N. *Anal. Chem.* **1958**, *30*, 1292.

Table 1. Summary of Crystal Data for Complexes **4a**, **4b**, and **5b**

	4a	**4b**·2$CHCl_3$	**5b**
formula	$C_{30}H_{46}N_3O_2ReS_4$	$C_{32}H_{48}Cl_6N_3OReS_4$	$C_{23}H_{39}N_3O_5Re_2S_3$
fw	795.17	1017.93	906.17
temp (K)	298	298	298
wavelength, λ (Å)	(Mo Kα) 0.710730	(Mo Kα) 0.710730	(Mo Kα) 0.710730
space group	$P2_1/c$	$P2_1/n$	$P\bar{1}$
a (Å)	15.63(1)	14.560(9)	9.387(5)
b (Å)	15.28(2)	14.803(9)	11.306(5)
c (Å)	16.07(1)	19.85(1)	14.040(6)
α (deg)			84.51(1)
β (deg)	113.78(2)	90.94(2)	84.45(2)
γ (deg)			87.17(1)
V (Å^3)	3512(5)	4278(1)	1475(1)
Z	4	4	2
ρ_{calcd} (g cm^{-3})	1.502	1.581	2.040
μ (cm^{-1})	0.3727	0.344	0.8447
octants collected	$\pm h, k, l$	$\pm h, -k, l$	$h, \pm k, \pm l$
GOF on F^2	1.105	1.012	1.061
R^a	0.0452[b]	0.0383[c]	0.0311[d]
$R_w{}^a$	0.1154[b]	0.0935[c]	0.0796[d]

[a] R values are based on F values, and R_w values are based on F^2; $R = \sum||F_o| - |F_c||/\sum(|F_o|)$, and $R_w = [\sum[w(F_o^2 - F_c^2)^2]/\sum[w(F_o^2)^2]]^{1/2}$. [b] For 2191 reflections with $I > 2\sigma(I)$. [c] For 5451 reflections with $I > 2\sigma(I)$. [d] For 4664 reflections with $I > 2\sigma(I)$.

580 parameters refined, R1/wR2 (for all data) = 0.0627/0.1080, $\Delta\rho_{min}/\Delta\rho_{max}$ = 0.974/−0.739 e Å^{-3}, $\Delta\sigma$ = 0.204. For **5b:** $2\theta_{max}$ = 50°, scan speed 3.5° min^{-1}, scan range 2.4° + $\alpha_1\alpha_2$ separation, reflections collected/unique/used = 5540/5191 (R_{int} = 0.0088)/5191, 457 parameters refined, R1/wR2 (for all data) = 0.0350/0.0834, $\Delta\rho_{min}/\Delta\rho_{max}$ = 0.716/−0.932 e Å^{-3}, $\Delta\sigma$ = 0.076. The structures were solved by direct methods by using SHELXS-86[19] and refined by full-matrix least-squares techniques on F^2 with SHELXL-93.[20] All non-H atoms were refined anisotropically. The crystals of **4a** were lacking diffraction ability resulting in low reflections/parameters refined ratio; thus, no H-atoms were included in the refinement. In compound **4b**, some of the H-atoms were located by difference maps and were refined isotropically; the rest were introduced at calculated positions as riding on bonded atoms. The chlorine atoms of the chloroform solvates were found disordered and were refined over two positions. In compound **5b**, all H-atoms (except those on C14, C15, and C23 which were introduced at calculated positions as riding on bonded atoms) were located by difference maps and were refined isotropically.

NMR Spectroscopy. ^{1}H (250.13 MHz) and ^{13}C (62.90 MHz) NMR spectra were recorded in $CDCl_3$ (Aldrich) on a Bruker AC 250E spectrometer equipped with an Aspect 3000 computer. Chemical shifts (δ, ppm) were referenced to TMS. Parameters for the 2D experiments (COSY, HETCOR, NOESY, etc.) have been previously reported.[21,22]

For the NMR study of complexes **5a**,**b**, the complexes were suspended in $CDCl_3$ and extracted in a small separatory funnel with 1 M NaOD in D_2O in order to release the complex from its perrhenate salt. The $CDCl_3$ solution was washed twice with D_2O, collected through cotton, and brought into the NMR tube.

Results and Discussion

Synthesis. Ligands 1 and 3. The reaction scheme leading to ligands **1** and **3** is shown in Figure 2. According to this scheme, which is commonly used for the preparation of DADT ligands,[6,12,17] 2,2′-dithio-bis(2-methylpropanal) (**6**) is condensed with ethylenediamine to form cyclic bis(imine) **7** which is subsequently reduced by sodium borohydride to the bicyclic diazolidino[1,2-*d*]dithiazepine (**8**). The use of the mild reagent $NaBH_4$, which does not reduce the disulfide bond, is necessary for the subsequent introduction of the N-alkyl substituents without competing alkylation of the thiol moieties. The intramolecular ring closure of **7** to generate **8** during the $NaBH_4$ reduction has been demonstrated in the literature.[23] In the next step, addition of the aminoalkyl chain on the nitrogen is effected by chloroacetylation with chloroacetyl chloride to give **9** followed by substitution by the appropriate amine and formation of **10**. Finally, in the last step, reduction of **10** in the presence of $LiAlH_4$ is supposed to give open dithiol ligand **1** by simultaneous breaking of the disulfide as well as of the C−N bond shared by the two rings. In our case, however, two products were isolated and identified as ligands **1** (yield 6%) and **3** (yield 35%). Ligand **1** is the expected open chain tetradentate ligand while in ligand **3** the diazolidine ring present in the cyclic disulfide has been preserved. The relative ratio of the products did not change when an up to 10-fold excess of $LiAlH_4$ was used in order to exclude the possibility of incomplete reduction.

New product **3** was characterized by NMR spectroscopy (see NMR studies); in the ^{1}H spectra, a characteristic singlet at ca. 4.4 ppm denotes the presence of the methine hydrogen. The presence of two free thiol groups in **3** was verified spectrophotometrically using *N*-ethylmaleimide.[18]

Despite the repeated preparations of DADT derivatives in the literature, the isolation of this cyclic ligand from the reaction mixture has never been reported. This product, possibly present in the preparations of complexes, but not isolated, may account for the low yields of the ^{99}TcO(DADT) complexes synthesized.[24]

The presence of the substituent ($COCH_2R$) and the simulataneous reduction of the C═O moiety on the nitrogen appear to be important in the preservation of the diazolidine ring because in its absence the $LiAlH_4$ reduction leads only to the open chain ligand.[25]

Complex 2a. The ability of **1** to act as tetradentate ligand around the ReO(V) core and generate complexes **2** of the ReO[SNN(R)S] type, analogous to those obtained with the TcO(V) core,[6] was demonstrated with ligand **1a**.

Complex **2a** was prepared by ligand exchange reaction using ligand **1a** and $ReOCl_3(PPh_3)_2$[15] as precursor in a ligand/precursor ratio of 1:1. The reaction product was extracted

(19) Sheldrick, G. M. *SHELXS-86, Structure Solving Program*; University of Göttingen: Göttingen, Germany, 1986.
(20) Sheldrick, G. M. *SHELXL-93, Program of Crystal Structure Refinement*; University of Göttingen: Göttingen, Germany, 1993.
(21) (a) Stassinopoulou, C. I.; Pelecanou, M.; Mastrostamatis, S.; Chiotellis, E. *Magn. Reson. Chem.* **1994**, *32*, 532. (b) Spyriounis, D. M.; Pelecanou, M.; Stassinopoulou, C. I.; Raptopoulou, C. P.; Terzis, A.; Chiotellis, E. *Inorg. Chem.* **1995**, *34*, 1077.
(22) Papadopoulos, M.; Pirmettis, I.; Pelecanou, M.; Raptopoulou, C. P.; Terzis, A.; Stassinopoulou, C. I.; Chiotellis, E. *Inorg. Chem.* **1996**, *35*, 7377.
(23) (a) Joshua, A. V.; Scott, J. R.; Sondhi, S. M.; Ball, R. G.; Lown, J. W. *J. Org. Chem.* **1987**, *52*, 2447. (b) Lever, S. Z. *J. Nucl. Med.* **1987**, *28*, 1064.
(24) Epps, L. A.; Burns, H. D.; Lever, S. Z.; Goldfarb, H. W.; Wagner, H. N., Jr. *Appl. Radiat. Isot.* **1987**, *38*, 661.
(25) Chryssou, K.; Pelecanou, M.; Papadopoulos, M. S.; Raptopoulou, C. P.; Pirmettis, I. C.; Chiotellis, E.; Stassinopoulou, C. I. *Inorg. Chim. Acta* **1998**, *268*, 169.

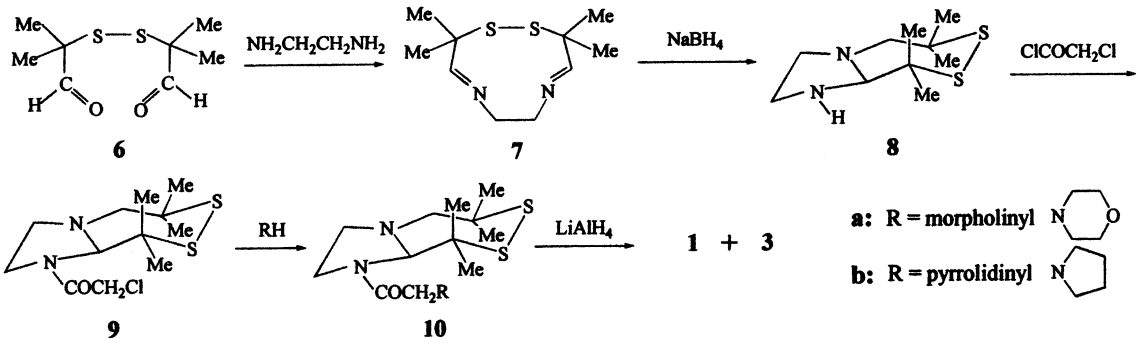

Figure 2. Synthetic scheme leading to ligands **1** and **3**.

in dichloromethane and was purified through an alumina column using 5% methanol in ether as eluent. The product was isolated as a purple solid. Because no crystals suitable for X-ray analysis were obtained, the complex was characterized by mass analysis as well as NMR spectroscopy and comparisons to NMR data of DADT complexes in the literature.[26,5c,d]

The complex is neutral, lipophilic, and soluble in acetone, chloroform, and methanol. It was stable for a long time both in the solid state and in solution. Of the two possible diastereomers resulting from the *syn* or *anti* orientation of the side chain on nitrogen with respect to the oxygen of the ReO(V) core, only the *syn* isomer was isolated. The *syn* configuration was evident from the characteristic NMR chemical shifts of the side chain.[27] No evidence for formation of the *anti* isomer was found even in the HPLC chromatograms of the reaction mixture. The *syn* configuration of the side chain on nitrogen appears to be the preferred configuration in all N-substituted oxotechnetium and oxorhenium complexes of tetradentate SNN(R)S ligands as well as of tridentate SN(R)S ligands, apparently because of thermodynamic stability.

In agreement with our experimental data, no *anti* isomer was isolated during the synthesis of the ReO(V) N−CH_3 substituted DADT complex.[14a] On the contrary, formation of both isomers was reported for the TcO(V) complexes of the described ligand,[14a] as well as of other N-substituted DADT ligands[24,26a] with the *anti* isomer always being the minor product. The difference may be due to the inherent kinetic differences between the two metals toward ligand substitution.[28] Rhenium, being more kinetically inert, exchanges ligands relatively more slowly and allows the coordinating DADT ligand to assume the preferred *syn* configuration.

Complexes 4 and 5. Ligand **3** failed to give stable complexes in the presence of the $ReOCl_3(PPh_3)_2$ precursor. Subsequently, its activity as a potential tridentate SNS ligand was tested in the presence of a monodentate thiol as coligand and $ReOCl_3(PPh_3)_2$ as precursor (ligand/coligand/precursor 1:2:1) with the aim of synthesizing "3 + 1" ReO[SNS][S][29] complexes. The reaction products were extracted in chloroform, and after successive crystallizations from chloroform/ethanol, two types of complexes, **4** and **5**, were isolated. The complexes were characterized by IR and NMR spectroscopies. Crystals suitable for X-ray analysis were obtained for **4a**,**b** as well as for **5b**.

Complex **4** is neutral, hexacoordinated, and of the ReO[SNN][S][S] type with two aromatic thiols. Complex **5** is neutral, pentacoordinated, and of the ReO[SNN][S] type with one aromatic thiol and was crystallized as the perrhenate salt. In both types of complexes, ligand **3** has undergone rearrangement with formation of a thiazolidine ring in the place of the diazolidine ring originally present.

The same products were isolated when Re(V)gluconate[16] was used as precursor.

The nature of the rearrangement of the diazolidine ring of ligand **3** to the thiazolidine ring of complexes **4** and **5** was examined. The first assumption that the rearrangement occurred during the preparation of the ligand was ruled out because, in addition to the different expected NMR spectral characteristics of the two molecules, determination of the free thiol groups of ligand **3** with the *N*-ethylmaleimide assay[18] showed that it bears two free thiol groups. If the rearrangement had occurred during the synthesis of **3**, then the assay would have indicated the presence of only one free thiol. The possibility that the rearrangement occurs in the methanolic environment during the synthesis of the complexes was examined by subjecting **3** to reaction conditions analogous to those of the synthesis of the complexes, but in the absence of the rhenium precursor. NMR analysis did not detect formation of a new compound.

Apparently, the presence of the rhenium core is necessary for the rearrangement of the diazolidine ring to thiazolidine. Metal core (Re═O or Tc═O) induced N−C bond cleavage in ligands has been reported in the literature[30] and has been

(26) Mahmood, A.; Halpin, W. A.; Baidoo, K. E.; Sweigart, D. A.; Lever, S. Z. In *Technetium and Rhenium in Chemistry and Nuclear Medicine 3*; Nicolini, M., Bandoli, G., Mazzi, U., Eds.; Raven Press: New York, p 113.
(27) Pelecanou, M.; Chryssou, K.; Stassinopoulou, C. I. *J. Inorg. Biochem.* **2000**, *79*, 347.
(28) Deutsch, E.; Libson, K.; Vanderheyden, J.-L.; Ketring, A. R.; Maxon, H. R. *Nucl. Med. Biol.* **1986**, *13*, 465.
(29) (a) Spies, H.; Fietz, T.; Glaser, M.; Pietzsch, H. J.; Johannsen, B. In *Technetium and Rhenium and in Chemistry and Nuclear Medicine 4*; Nicolini, M., Bandoli, G., Mazzi, U., Eds.; Servici Grafici Editoriali: Padova, 1994; p 243. (b) Spies, H.; Pietzsch, H. J.; Johannsen, B. In *Technetium, Rhenium and Other Metals in Chemistry and Nuclear Medicine 5*; Nicolini, M., Mazzi, U., Eds.; Servici Grafici Editoriali: Padova, Italy, 1999; p 101.
(30) (a) Glaser, M.; Spies, H.; Berger, R.; Hahn, F. E.; Lügger, T.; Johannsen, B. *Inorg. Chim. Acta* **1997**, *257*, 143. (b) Spies, H.; Pietzsch, H.-J. *Inorg. Chim. Acta* **1989**, *161*, 151.

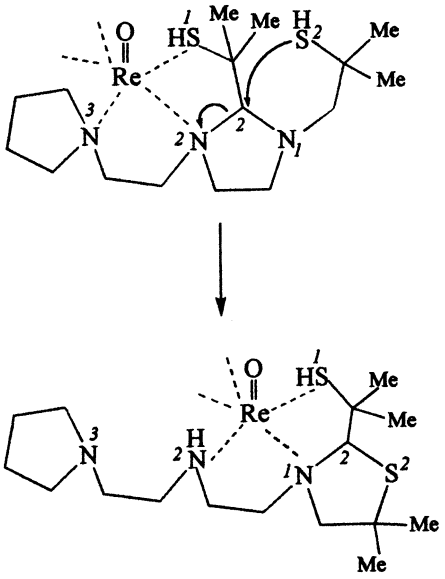

Figure 3. Possible initial approach of ligand **3** to the ReO core accounting for the observed rearrangement of the diazolidine ring to thiazolidine.

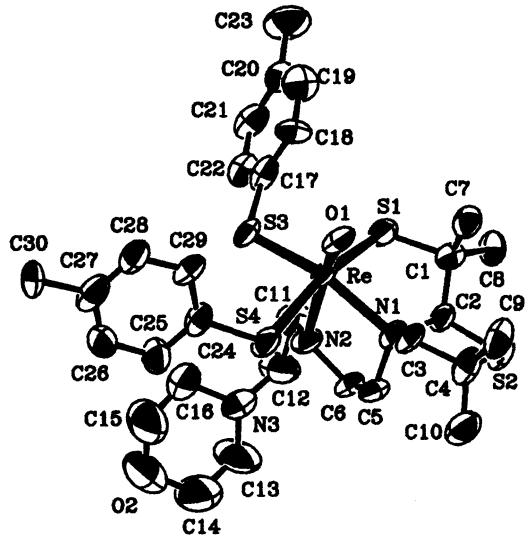

Figure 4. ORTEP diagram of compound **4a** showing 50% thermal probability ellipsoids and atom labels.

associated with the cleavage of tertiary amines in the presence of transition metals.[31] In our system, the inability of **3** to function as a tetradentate SNNS because of steric hindrance may impose a different approach to the metal center (e.g., with S-1, N-2, and even N-3 serving as donor atoms) leaving one thiol free, as shown in Figure 3. In this approach, the C-2—N-1 bond becomes highly polarized, and nucleophilic attack by the free thiol group on C-2 may occur to form the thiazolidine ring, leading eventually to the complexes isolated. Transformation of a diazolidine ring to a thiazolidine ring has been observed before in the preparation of the *N*-mercaptoethylDADT TcO(V) complexes;[32] in that case, however, the involvement of the oxometal core was not implicated.

Complexes **5a**,**b** precipitated from the reaction mixtures as perrhenate salts. The presence of the perrhenate salt became evident from the strong, broad IR peak in the range 904−890 cm^{-1} and was subsequently confirmed by X-ray crystallography. The formation of the ReO_4^{-1} anion in the reaction mixture is interesting because it can only come from oxidation of Re(V) of the precursor molecules to Re(VII) of the perrhenate. The possibility that ReO_4^{-1} is present in the precursor molecule preparations, because both the $ReOCl_3(PPh_3)_2$ and the rhenium gluconate are prepared from potassium perrhenate, was excluded by succesive recrystallizations of the precursors and analysis by IR. Apparently, the ReO_4^{-1} is generated in the reaction mixture. Isolation of ReO(V) complexes as perrhenate salts has been observed in the case of oxobis(*p*-thiocresolato)terpyridinerhenium(V) complex[33] and was accompanied by the formation of Re(III) complexes, a fact that indicates disproportionation of the initially present rhenium(V) to rhenium(III) and rhenium(VII). In the present case, however, no Re(III) complex was isolated or detected in the reaction mixture.

Neutral complexes **5** could be easily released from their perrhenate salts by suspending them in chloroform and triturating with an aqueous NaOH solution. The complexes would soon dissolve in chroroform to yield a bright green solution. For the NMR studies, deuterated solvents were used in the procedure in order to finally obtain the neutral complex in $CDCl_3$.

Even though both types of complexes, **4** and **5**, are isolated from the reaction mixtures, our experimental evidence indicates that complexes **4** are the initial products of the reaction. Specifically, gradual transformation of **4** to **5** was observed during the isolation and purification procedures, especially on the TLC plate. Gradual transformation was also evidenced by NMR in the $CDCl_3$ solutions used for the NMR studies. Apparently, complexes of the [SNN][S][S] type are kinetically favored (formed even when lower ratios of the monodentate coligand are employed, specifically, ligand/coligand/precursor 1:1:1) and are later transformed to the thermodynamically more stable complexes [SNN][S] that are further stabilized by the formation of the perrhenate salt. This is in agreement with the common belief in the literature that in oxorhenium thiolato complexes the coordination number is rarely increased to six.[33,34] Expulsion of one thiol from oxorhenium and oxotechnetium $[S][S]_3$ complexes following nucleophilic attack of a pendant amine group and conversion to the more stable $[NS][S]_2$ type has been reported in the literature.[35]

X-ray Crystallography. ORTEP diagrams of complexes **4a**, **4b**, and **5b** are shown in Figures 4−6, respectively, while a summary of crystal data, and selected bond lengths and angles are given in Tables 1 and 2, respectively. Two chloroform molecules cocrystallized with **4b**.

(31) Murahashi, S. I.; Yano, T. *J. Chem. Soc., Chem. Commun.* **1979**, 270.
(32) Alarabi, H.; Bell, R. A.; Faggiani, R.; Howard-Lock, H. E.; Lock, C. J. L.; Kramer, A. V. *Inorg. Chem.* **1995**, *34*, 1688.
(33) Chang, L.; Rall, J.; Tisato, F.; Deutsch, E.; Heeg, M. J. *Inorg. Chim. Acta* **1993**, *205*, 35.
(34) (a) Lis, T. *Acta Crystallogr.* **1976**, *B32*, 2707. (b) Fletcher, S. R.; Skapski, A. C. *J. Chem. Soc., Dalton Trans.* **1972**, 1073.
(35) Bouziotis, P.; Pirmettis, I.; Pelecanou, M.; Raptopoulou, C. P.; Terzis, A.; Papadopoulos, M.; Chiotellis, E. *Chem.—Eur. J.* **2001**, *7*, 3671.

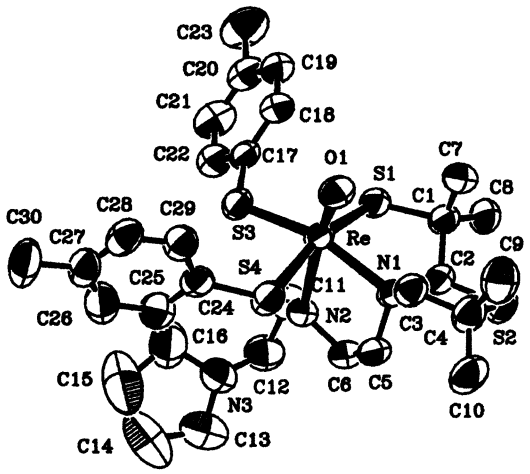

Figure 5. ORTEP diagram of compound **4b** showing 50% thermal probability ellipsoids and atom labels.

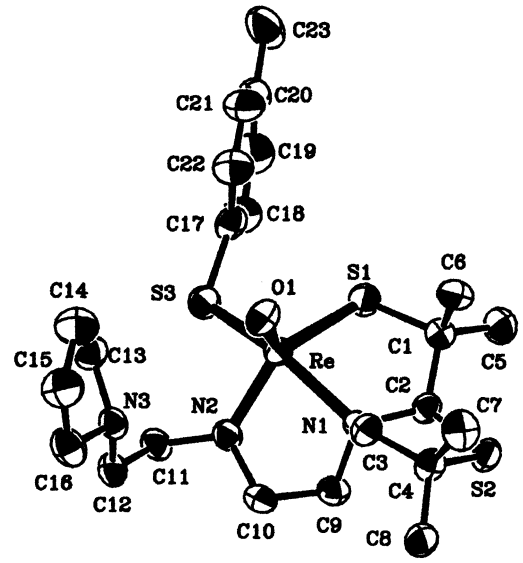

Figure 6. ORTEP diagram of compound **5b** showing 50% thermal probability ellipsoids and atom labels.

In compounds **4a** and **4b**, the coordination geometry about the metal is distorted octahedral comprising three sulfurs, two sp^3 type nitrogens, and the doubly bonded oxygen atom. The two nitrogen atoms and one of the sulfurs belong to rearranged ligand **3**, and the other two sulfurs come from two aromatic thiols used as coligands. The protonated nitrogen atom of the ligand (N2) and the oxo group occupy the axial positions of the distorted octahedron. The Re═O bond lengths are in the range observed in analogous complexes[21,22,25,35] (1.65(1) and 1.692(4) Å in **4a** and **4b**, respectively). The two aromatic thiols are directed *trans* to the sulfur and the tertiary nitrogen donor atoms of the ligand defining thus the equatorial plane of the distorted octahedron. The Re—N tertiary bond length is shorter than the corresponding Re—N protonated one (Re—N(1) = 2.26(1), Re—N(2) = 2.41(1) Å in **4a**, and Re—N(1) = 2.279(5), Re—N(2) = 2.399(5) Å in **4b**). The Re—S(1) bond distance is ca. 2.34 Å in both compounds. The Re—S thiol bond distances are quite different, the longer being *trans* to the sulfur of the ligand (Re—S(3)/Re—S(4) = 2.295(4)/2.428(4) and 2.290(2)/2.404(2) Å in **4a** and **4b**, respectively).

Table 2. Selected Bond Lengths [Å] and Angles [deg] of Complexes **4a**, **4b**, and **5b**

	4a	**4b**·2$CHCl_3$	**5b**
Re−O(1)	1.65(1)	1.692(4)	1.684(4)
Re−N(1)	2.26(1)	2.279(5)	2.204(4)
Re−S(3)	2.295(4)	2.290(2)	2.286(2)
Re−S(1)	2.336(4)	2.346(2)	2.301(2)
Re−N(2)	2.41(1)	2.399(5)	1.962(4)
Re−S(4)	2.428(4)	2.403(2)	
O(1)−Re−N(1)	96.5(4)	95.8(2)	103.2(2)
O(1)−Re−S(3)	104.9(3)	104.6(2)	106.4(1)
N(1)−Re−S(3)	158.6(3)	159.5(1)	150.3(1)
O(1)−Re−S(1)	101.0(3)	99.8(2)	114.1(2)
N(1)−Re−S(1)	82.4(3)	81.9(1)	82.0(1)
S(3)−Re−S(1)	94.0(1)	96.7(1)	88.0(1)
O(1)−Re−N(2)	168.2(4)	168.9(2)	110.6(2)
N(1)−Re−N(2)	74.8(4)	74.8(2)	79.3(2)
S(3)−Re−N(2)	84.0(3)	84.7(1)	88.2(1)
S(1)−Re−N(2)	85.9(3)	84.7(1)	134.4(1)
O(1)−Re−S(4)	95.5(3)	95.7(2)	
N(1)−Re−S(4)	87.7(3)	86.8(1)	
S(3)−Re−S(4)	89.6(1)	88.8(1)	
S(1)−Re−S(4)	161.5(1)	161.6(1)	
N(2)−Re−S(4)	76.5(3)	78.3(1)	

The two five membered rings in the coordination sphere in **4a** and **4b** defined by Re, S1, C1, C2, N1 and Re, N1, C5, C6, N2 adopt the envelope configuration with C1 and C5, respectively, being out of the mean plane of the remaining four atoms (0.76 and 0.65 Å for **4a** and 0.76 and 0.61 Å for **4b**). The five membered ring of the rearranged ligand, defined by N1, C2, S2, C4, C3, exists in the stable envelope configuration with N1 displaced by 0.53 Å out of the best mean plane of the other four atoms in both **4a** and **4b**. The morpholinyl group in **4a** adopts the stable chair conformation with N(3) and O(2) displaced by 0.74 and 0.67 Å out of the mean plane of the carbon atoms. The pyrrolidinyl group in **4b** exists in the envelope configuration with N3 being the "flap" atom (displacement 0.54 Å).

The coordination geometry about rhenium in **5b** is distorted square pyramidal with the SNN donor atom set of the ligand and the aromatic thiol defining the equatorial plane and the doubly bonded oxygen in the apex. The metal lies 0.70 Å out of the equatorial plane toward the oxo group. The angles between the opposite atoms of the basal plane (S1—Re—N2 = 134.4(1)° and N1—Re—S3 = 150.3(1)°) severely deviate from the ideal 180°. Thus, the calculated trigonality index, τ, is 0.27. The Re═O, Re—N, and Re—S bond distances (Table 2) are in the ranges observed in analogous complexes.[21,22,25,35] The nitrogen atom of the pyrrolidinyl group of the ligand is protonated, and the complex is neutralized by a perrhenate group.

The five membered rings in the coordination sphere defined by Re, S1, C1, C2, N1 and Re, N1, C5, C6, N2 adopt the envelope configuration with C1 and C5 being 0.70 and 0.58 Å, respectively, out of the mean plane of the remaining atoms. The two five membered rings defined by N1, C2, S2, C4, C3 and the pyrrolidinyl group of the ligand also adopt the envelope configuration with the corresponding nitrogen atom being 0.57 and 0.54 Å, respectively, out of

Table 3. ^{13}C and ^{1}H NMR Chemical Shifts (δ_H, ppm) for Ligand **1** in $CDCl_3$ at 25 °C

	1a	1b		1a	1b
C-1	46.18	46.10	H-2	2.56	2.49
C-2	69.85	69.89	H-3	2.72	2.68
C-3	56.66	55.19	H-4	2.72	2.62
C-4	48.32	48.23	H-5	2.59	2.52
C-5	63.76	63.71	H-7, H-8	1.34	1.28
C-6	45.32	45.21	H-9, H-10	1.36	1.30
C-7, C-8	30.73	30.64	H-11	2.72	2.68
C-9, C-10	30.57	30.50	H-12	2.48	2.55
C-11	53.30	57.00	H-13, H-16	2.47	2.43
C-12	57.00	54.32	H-14, H-15	3.69	1.68
C-13, C-16	54.07	54.32			
C-14, C-15	66.82	23.23			

Table 4. ^{13}C and ^{1}H NMR Chemical Shifts (δ_H, ppm) for Ligand **3** in $CDCl_3$ at 25 °C

	3a	3b		3a	3b
C-1	51.24	50.92	H-2	4.45	4.42
C-2	90.80	90.86	H-3, H-3′	2.80, 2.70	2.80, 2.70
C-3	50.16	50.27	H-4, H-4′	3.13, 2.96	3.06, 2.90
C-4	61.27	61.24	H-5, H-5′	3.28, 3.03	3.24, 2.92
C-5	72.31	72.30	H-7, H-8	1.40, 1.35	1.35, 1.29
C-6	57.60	57.66	H-9, H-10	1.54, 1.47	1.49, 1.42
C-7, C-8	29.28, 28.61	29.24, 28.55	H-11	2.70	2.67
C-9, C-10	28.83, 33.58	33.57, 28.81	H-12	2.50	2.58
C-11	46.17	48.63	H-13, H-16	2.45	2.46
C-12	58.49	55.96	H-14, H-15	3.71	1.72
C-13, C-16	53.83	54.27			
C-14, C-15	67.04	23.47			

Table 5. ^{13}C and ^{1}H NMR Chemical Shifts (δ_H, ppm) for complex **2a** in $CDCl_3$ at 25 °C

C-1	63.21	H-2 *endo*	3.39
C-2	74.18	H-2 *exo*	2.33
C-3	65.23	H-3 *endo*	3.64
C-4	64.83	H-3 *exo*	2.36
C-5	81.56	H-4 *endo*	4.25
C-6	61.73	H-4 *exo*	3.24
C-7	31.84	H-5 *endo*	3.88
C-8	31.02	H-5 *exo*	3.58
C-9	29.81	H-7	1.78
C-10	26.99	H-8	1.62
C-11	59.04	H-9	1.49
C-12	54.17	H-10	1.90
C-13, C-16	54.05	H-11, H-11′	4.16, 3.92
C-14, C-15	66.88	H-12	2.84
		H-13, H-16	2.53
		H-14, H-15	3.71

the mean plane of the other four atoms as in the case of compounds **4a** and **4b**.

NMR Spectroscopy. Complete ^{1}H and ^{13}C NMR assignments for ligands **1** and **3** as well as for complexes **2a**, **4**, and **5** are presented in Tables 3−7, respectively. Assignments were based on analysis of 1D and a series of 2D spectra (COSY, HETCOR, COLOC, NOESY, INADEQUATE) obtained on a Bruker AC 250 MHz instrument. Details on the assignment procedure of related complexes are given in previous publications;[25,21] so, in this work, only a few points of interest are presented. The atom numbering adopted is shown in Figure 1 and is identical to the numbering of the crystallographic structures in order to facilitate comparisons. The chemical shifts of overlapping peaks were defined from the correlation peaks of the 2D experiments.

Ligand 1. In the ^{13}C spectra, C-2 and C-5 were distinguished from the rest by their long-range couplings to the methyl protons in the COLOC experiment optimized for J = 7 Hz. Of the two, the downfield resonance was assigned to C-2 (Table 3) on the basis of the fact[36] that carbons attached to tertiary nitrogen appear downfield compared to those attached to secondary nitrogen. Similarly, of the C-3 and C-4 resonances, the downfield one was assigned to C-3 carbon bound to the tertiary nitrogen. All assignments were confirmed by the INADEQUATE experiment, shown in Figure 7, which detects signals due to $^{13}C-^{13}C$ coupling in ^{13}C spectra and allows the identification of coupled carbon pairs.

Assignment of the ^{13}C spectra led to the assignment of the ^{1}H spectra which are characterized by great overlap. The free rotation of bonds in **1** is evidenced by the singlets of

Table 6. ^{13}C and ^{1}H NMR Chemical Shifts (δ_H, ppm) for Complex **4** in $CDCl_3$ at 25 °C

	4a	4b		4a	4b
C-1	65.28	64.93	H-2	4.55	4.56
C-2	89.91	90.02	H-3, H-3′	4.22, 4.11	4.23, 4.12
				^{2}J = 13.8 Hz	^{2}J = 13.8 Hz
C-3	80.84	80.87	H-5, H-5′	4.17, 3.70	4.13, 3.73
C-4	54.58	54.62	H-6, H-6′	3.12, 2.03	3.14, 2.00
C-5	63.16	63.36	H-7	1.53	1.53
C-6	46.94	47.05	H-8	1.65	1.65
C-7	22.41	22.35	H-9	1.60	1.60
C-8	31.37	31.42	H-10	1.71	1.72
C-9	31.91	31.95	H-11, H-11′	2.30, 1.99	2.87, 2.00
C-10	33.81	33.84	H-12, H-12′	2.88, 1.97	2.68, 1.91
C-11	54.80	52.94	H-13, H-16	2.64, 2.23	2.16, 2.35
C-12	50.05	52.25	H-14, H-15	3.80	1.86
C-13, C-16	53.45	54.14	H-18, H-22	7.30	7.29
C-14, C-15	67.00	23.85	H-19, H-21	7.12	7.11
C-17	135.69	135.52	H-23	2.38	2.37
C-18, C-22	132.83	132.92	H-25, H-29	7.62	7.60
C-19, C-21	128.22	128.14	H-26, H-28	7.08	7.09
C-20	151.45	151.54	H-30	2.32	2.33
C-23	21.09	21.14	NH	3.38	3.41
C-24	134.83	134.91			
C-25, C-29	135.25	135.52			
C-26, C-28	128.88	128.77			
C-27	140.57	140.51			
C-30	21.09	21.14			

Table 7. ^{13}C and ^{1}H NMR Chemical Shifts (δ_H, ppm) for Complex **5** in $CDCl_3$ at 25 °C

	5a	5b		5a	5b
C-1	65.23	64.95	H-2	4.17	4.17
C-2	95.57	95.59	H-3, H-3′	3.93, 3.73	3.94, 3.73
				^{2}J = 13.2 Hz	^{2}J = 13.8 Hz
C-3	72.49	72.05	H-5, H-5′	3.68, 2.48	3.64, 2.45
C-4	55.13	54.95	H-6, H-6′	4.31, 3.63	4.29, 3.64
C-5	66.51	66.44	H-7	1.62	1.61
C-6	70.34	70.25	H-8	1.36	1.36
C-7	27.62	27.67	H-9	1.62	1.61
C-8	30.79	30.79	H-10	1.79	1.78
C-9	31.87	31.97	H-11, H-11′	4.62, 3.98	4.63, 3.98
C-10	34.83	34.90	H-12, H-12′	2.65, 2.73	2.88, 2.76
C-11	61.04	63.18	H-13, H-16	3.73	2.63
C-12	60.54	57.80	H-14, H-15	2.58	1.79
C-13, C-16	54.30	54.50	H-18, H-22	7.43	7.44
C-14, C-15	67.23	23.55	H-19, H-21	7.16	7.17
C-17	135.75	135.68	H-23	2.40	2.39
C-18, C-22	133.24	133.17			
C-19, C-21	128.68	128.61			
C-20	150.07	150.37			
C-23	21.10	21.17			

(36) Wehrli, F. W.; Wirthlin, T. *Interpretation of Carbon-13 NMR Spectra*; Heyden: London, 1978.

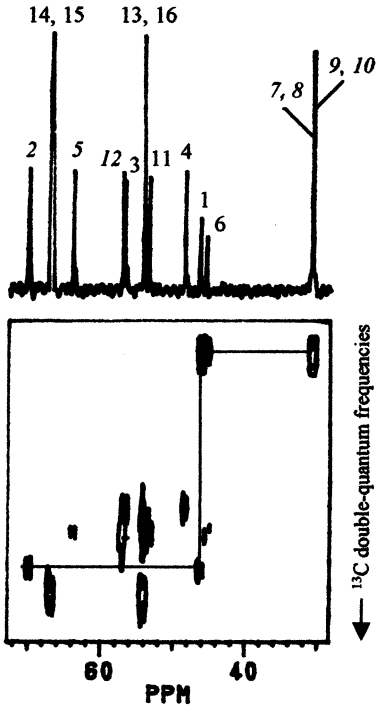

Figure 7. ^{13}C (range δ_C 72.3−28.0) INADEQUATE spectrum of ligand **1a**. The solid line traces the carbon sequence C-2−C-1−C-7(C-8).

H-2 and H-5 as well as by the chemical shift equivalence of the methyl groups on C-1 and C-6.

Ligand 3. The presence of the diazolidinyl ring introduces asymmetry to the molecule resulting in chemical shift differentiation of the geminal protons on C-5 as well as differentiation of protons and carbons of the four methyl groups (Table 4). Even though the two sets of methyl groups CH_3-7, CH_3-8 and CH_3-9, CH_3-10 are readily distinguishable from their correlations to neighboring protons and carbons in the NOESY and COLOC spectra, no distinction of methyl groups within the set is possible, and the order they are reported in Table 4 is not position specific.

Complex 2a. In the spectra of complex **2a**, identification of protons H-12 from their NOE correlations to H-13, H-16 of the morpholinyl and pyrrolidinyl moieties serves as the starting point in the assignment procedure and subsequently leads to the assignment of protons and carbons of the side chain on nitrogen (Table 5). NOE correlations of protons of the DADT backbone with the side chain on nitrogen were essential in distinguishing the H-2 and H-3 protons facing toward the oxygen of the ReO core (*endo* protons) from their geminals facing away from the oxygen of the ReO core (*exo* protons). Because it is evident from the chemical shifts of the H-11 protons that the side chain on nitrogen is *syn* with respect to the ReO core,[27] H-2 and H-3 protons exhibiting correlation peaks to protons of the chain were considered *endo* (Figure 8). H-4 and H-5 *endo/exo* protons were distinguished by analogy. The assignments are in agreement with existing literature data on DADT complexes according to which *endo* protons of the DADT backbone appear downfield compared to their *exo* geminals.[27]

Complex 4. Complex **4** represents a completely new system, as yet not reported. The high asymmetry of the

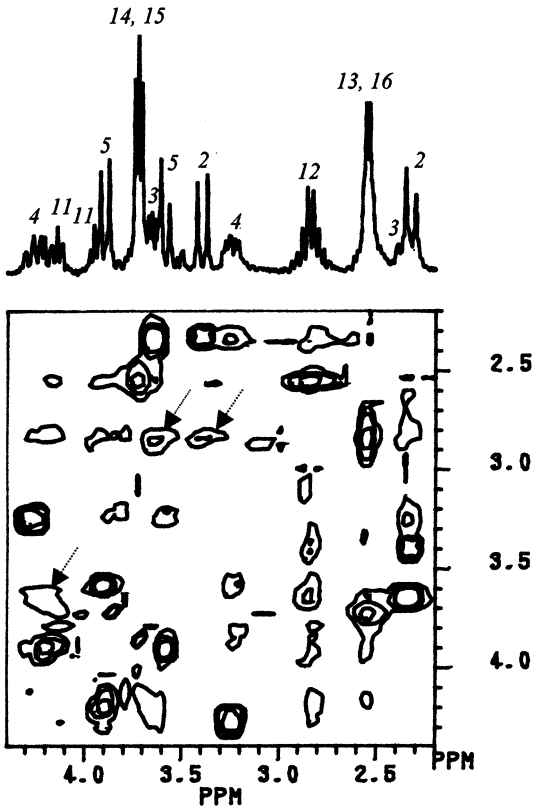

Figure 8. Phase-sensitive NOESY spectrum (range δ_H 4.39−2.20) of complex **2a**. Only positive levels are plotted. The arrows mark from left to right the correlation peaks between H-3$_{endo}$−H-11, H-3$_{endo}$−H-12, H-2$_{endo}$−H-12.

molecule causes the geminal protons of the side chain to be magnetically nonequivalent and differentiates the, usually coinciding, H-13 from H-16 in the morpholinyl and pyrrolidinyl moieties (Table 6).

The singlet belonging to proton H-2 as well as the doublet of doublets coming from the AB spin system of the H-3 geminal protons served as the starting points for the assignment of protons and carbons of the ligand backbone in this type of complex. C-5 was distinguished from C-6 by its long-range coupling to H-2, and C-12 was distinguished from C-11 through the NOE interaction of one of the H-12 protons to protons H-13, H-16 of the morpholinyl (**4a**) or pyrrolidinyl (**4b**) moieties. C-4 was distinguished from C-1 on the basis of its long-range couplings to H-3 protons.

Because of the asymmetry of the molecule, the two aromatic cresols are in different magnetic environments and appear at different chemical shifts. Distinction of the two aromatic rings was achieved from the presence of an NOE correlation peak between the aromatic H-25/H-29 and protons on the morpholinyl and pyrrodininyl moieties.

Complex 5. Assignment of the peaks was achieved following arguments similar to those presented previously for complexes **4** (Table 7). In these molecules, distinction of the H-5/H-6 spin system from the H-11/H-12 was based on the presence of an NOE correlation peak between the H-2 singlet and a signal that was consequently assigned to one of the H-5 protons.

In conclusion, this is a detailed reexamination of the known synthetic scheme leading to the widely used N-substituted

DADT ligands of the type of **1**.[6,12,17] We have shown that the DADT ligand is the minor product of the synthetic scheme and, as anticipated, leads to stable, neutral, and lipophilic ReO[SNNS] complexes when reacted with the ReO(V) core. These ReO[SNNS] complexes are suitable for the development of oxorhenium radiopharmaceuticals exploiting the existing knowledge of the properties and the biodistribution of their oxotechnetium counterparts. However, the major product of the synthetic scheme is the cyclic ligand **3** which has never been isolated before. During complexation to the ReO(V) core in the presence of monodentate thiols, the diazolidine ring of **3** undergoes rearrangement to thiazolidine and yields two new types of neutral and lipophilic complexes **4** and **5** of the ReO[SNN][S][S] and ReO[SNN]-[S] type, respectively. Complexes **5** are stable, and they offer an alternative approach to the design of specific radiopharmaceuticals utilizing the versatile "3 + 1" concept that allows fast and simple access to ligand−biomolecule conjugates.[29]

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Supporting Information Available: Crystallographic data for the structures of complexes **4a**, **4b**, and **5b** as well as of product **10** with R = piperidinyl. This material is available free of charge via the Internet at http://pubs.acs.org.

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