Selective Formation of Heterodimeric Bis-Bidentate Aminothiol–Oxometal Complexes of Rhenium(V)

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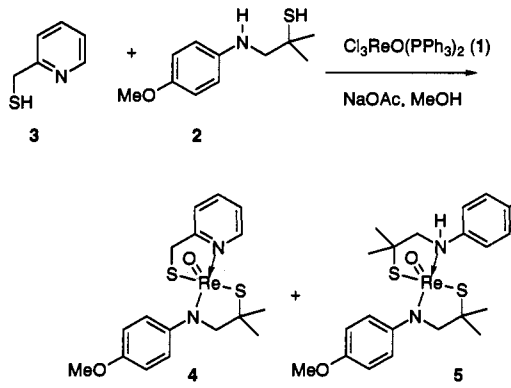
Complexes of γ-emitting isotopes of technetium and rhenium have been studied extensively in the development of agents for diagnostic imaging and radiotherapy.[1] In many cases, these complexes involve a chelate molecule that donates four heteroatoms (most often two nitrogen and two sulfur atoms) to an oxometal(V) core. Useful complexes may be formed from bis-bidentate (NS) and tetradentate (N_2S_2) ligands. While several bis-bidentate complexes have been prepared, for example, with S_2 (ethane-1,2-dithiol,[2] thiomercaptoacetic acid[3]), OS (2-mercaptoethanol[4]), and NS (2-mercaptoethylamine[5]) ligands, a number of factors have limited the further development of these systems: (1) introduction of substituents onto the carbon atom backbone of the bis-bidentate ligand creates stereogenic centers, with the number of possible stereoisomeric complexes being higher in the bis-bidentate than in the tetradentate case; (2) because the bis-bidentate complex is symmetrical, one cannot easily modify just one side of the complex in a controlled fashion; and (3) the bis-bidentate complex may be more labile to ligand exchange[6] and may therefore be less stable than the tetradentate complex.[7] Because of these difficulties, bis-bidentate technetium and rhenium oxo complexes have not been studied extensively.

We have recently described the preparation of two tetradentate rhenium and technetium complexes conjugated to a synthetic progestin.[8] While they retained nanomolar binding affinity for the progesterone receptor, the overall size of these conjugates is about twice that of normal ligands for steroid receptors, a fact that appears to impair their receptor-selective distribution in vivo; this compromises the potential of these radiolabeled complexes for diagnostic (Tc-99m) and therapeutic (Re-186 and -188) applications. Therefore, we have begun to investigate the preparation of heterodimeric bis-bidentate aminothiol complexes of technetium and rhenium that might in themselves more closely mimic the size and shape of certain steroidal and nonsteroidal ligands for steroid receptors, in particular for the estrogen receptor.

Scheme I



Here we report the synthesis of some novel homodimeric oxorhenium(V) complexes of aminothiols, as well as the first selective synthesis and characterization of two heterodimeric complexes. The preparation of these complexes, particularly the heterodimeric ones, raises interesting issues of competitive complexation kinetics of different aminothiols.

The general method for the preparation of rhenium complexes in solution is by substitution reaction of oxotrichlorobis(triphenylphosphine)rhenium(V) (**1**, $Cl_3ReO(PPh_3)_2$) in the presence of coordinating ligand. 1-(4′-Methoxyphenyl)amino-2-methylpropane-2-thiol (**2**) was prepared according to procedures similar to those used by D'Amico and Corbin.[9] The ligands **2** (42.2 mg, 0.20 mmol) and pyridine-2-methanethiol[10] (**3**, 25.0 mg, 0.20 mmol) are added to **1** (166.6 mg, 0.20 mmol) in 2 mL of 1 M NaOAc in methanol (Scheme I). The mixture is heated at 75 °C for 20 min and cooled to ambient temperature, resulting in the formation of a brownish purple precipitate. Recrystallization of collected precipitate from $MeOH/CHCl_3$ provides crystalline (*N*-(2-mercapto-2-methylpropyl)-*N*-(4′-methoxyphenyl)aminato)-(2-mercaptomethylpyridinato)oxorhenium(V) (**4**)[11] in essentially quantitative yield.

The results shown in Table I demonstrate the selective formation of heterodimer **4** at various concentrations and ratios of the two aminothiols **2** and **3**. As the concentration of ligand **3** is increased, the yield of heterodimer **4** is reduced to some degree (entries 3–1), but even at a 1:4 ratio of **2**:**3**, the heterodimer **4** forms in 50% yield (entry 1). Despite this preference for heterodimer formation, the reaction of **1** (166.6 mg, 0.20 mmol) with only ligand **2** (84.4 mg, 0.40 mmol) under the same conditions (entry 7) does provide a quantitative yield of the homodimer complex bis(*N*-(2-mercapto-2-methylpropyl)-*N*-(4′-methoxyphenyl)aminato)oxorhenium(V) (**5**).[11] In the absence of ligand **2**, 2 equiv of ligand **3** will react with **1**, providing a powdery tan product which is very polar but has not yet been characterized;[12] this material is not detected in our HPLC analysis.

The experiments presented in Table I demonstrate that heterodimeric complex **4** is formed in strong preference to the homodimeric complex **5**, as the homodimeric complex **5** begins to form only when the ratio of **2**:**3** becomes very large (entries

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(7) While most N_2S_2 technetium(V) oxo complexes used for in vivo imaging are tetradentate, complexes of technetium in other valence states may be bis-tridentate (e.g., Tc(III)–HIDA (Loberg, M. D.; Fields, A. T. *Int. J. Appl. Radiat. Isotopes* **1978**, *29*, 167)) or even hexakis-monodentate (e.g., Tc(I)–hexaisonitrile (Abrams, M. J.; Davison, A. J.; Jones, A. G.; Costello, C. E.; Pang, H. *Inorg. Chem.* **1983**, *22*, 2798).

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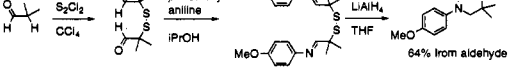
(9) (a) D'Amico, J. J.; Dahl, W. E. *J. Org. Chem.* **1975**, *40*, 1224. (b) Corbin, J. L.; Work, D. E. *J. Org. Chem.* **1976**, *41*, 489. (c) The synthesis of aminothiol ligand **2** is as follows:



(10) Pyridine-2-methanethiol (10% in EtOH) was purchased from Penta Manufacturing Company (Fairfield, NJ).

(11) ^1H NMR, ^{13}C NMR, low- and high-resolution mass spectra, and some 2D NMR spectroscopic data are available as supplementary material.

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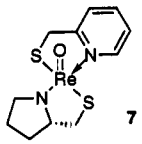
Table I. Product Distributions with Various Concentration of Ligands for the Reaction Shown in Scheme I[a]

entry	2 (μmol)	3 (μmol)	ratio 2:3 (relative to 1)	yield of 4 (%)[b]	yield of 5 (%)[b]
1	20	80	1:4	50	0
2	20	40	1:2	85	0
3	20	20	1:1	99	0
4	40	20	2:1	97	2
5	80	20	4:1	86	4
6	80	80	4:4	99	0
7	40		2:0	0	99

[a] Reaction condition: the ligands 2 and 3 are added to 1 (16.6 mg, 20 μmol) and NaOAc (200 μmol) in 1 mL of methanol. The mixture is heated at 75 °C for 20 min. [b] Product total yields were determined by isolation, and product ratios by normal-phase HPLC (cyanopropyl silica gel column) on a completely soluble sample of crude product. Under these conditions, the proposed homodimeric complex from 3[12] is too polar to elute. Yields are based on the quantity of 1, and product ratios are based on response facts at 400 nm, calibrated against standard samples of 4 and 5.

4 and 5). The preferential formation of the heterodimeric complex 4 under these relatively mild conditions reflects a strong kinetic preference.

We have synthesized another heterodimer (*S*)-(2-mercaptomethylpyridinato)-(2-mercaptomethylpyrrolidinato)oxorhenium-(V) (7)[11] from ligand 3 and (*S*)-2-mercaptomethylpyrrolidine hydroiodide (6).[13] Because ligand 6 was prepared as the hydroiodide salt, 1 equiv of Et_3N is added as an acid scavenger. Complex 7 is formed in 63% yield in the presence of Et_3N and in 41% yield without any base.



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In principle, NS–bis-bidentate complexes can exist as cis or trans isomers. In the case of other homodimeric NS–bis-bidentate complexes reported in the literature,[5,14] only the trans isomer has been reported; in the case of one OS–bis-bidentate complex, the cis isomer could be isolated, although the trans isomer was also detected by NMR in the unfractionated reaction product.[4]

With our heterodimeric bis-bidentate complexes 4 and 7, isolation of the major product, which appears as one spot on silica gel and basic alumina TLC and one peak by HPLC on cyanopropyl silica gel, gives a material that shows only one set of NMR signals. On the other hand, ^1H NMR of homodimeric bis-bidentate complex 5 shows two sets of signals in the ratio of 85:15, which may indicate the presence of a small amount of the cis isomer. The results of an X-ray structure determination of a single crystal of complex 4 (Figure 1),[15] obtained from $MeOH/CHCl_3$, shows the trans configuration; the other complexes 5 and 7 are assumed to be trans by analogy. This is consistent with the general preference for the dative bond (i.e., the Re–NHR_2 bond in 5 and the Re–N(pyridine) bond in 4) to be trans to the most electron-withdrawing donor (N as opposed to S), the "trans effect".[16]

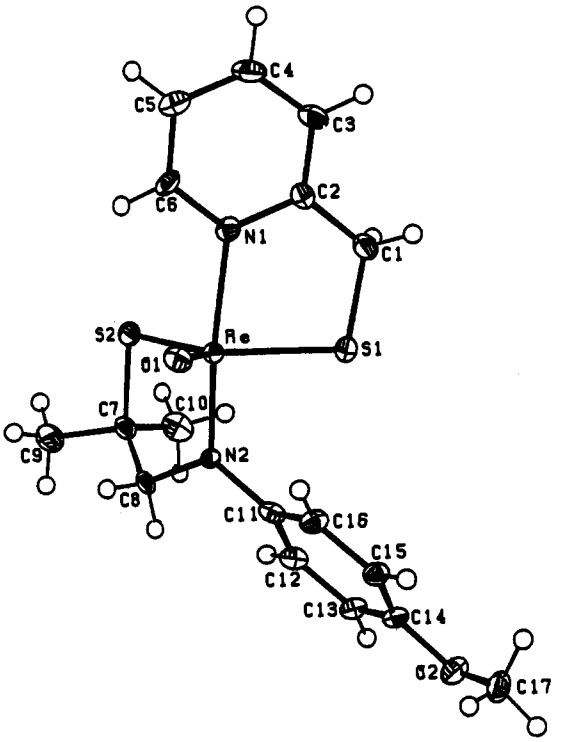

Figure 1. Molecular structure of 4.

Bis-bidentate complexes generally have lower kinetic and thermodynamic stability than tetradentate complexes.[6,7] The heterodimeric rhenium complexes 4 and 7 are, however, remarkably stable under ambient conditions, and, in a preliminary study, a technetium-99m complex analogous to 4 appears to have reasonable stability in vivo as well (Chi, D. Y.; O'Neil, J. P.; Anderson, C. J.; Welch, M. J.; Katzenellenbogen, J. A., unpublished results).

It is hoped that this work, which demonstrates that NS–bis-bidentate heterocomplexes of oxorhenium can be prepared in a selective and controlled fashion, will stimulate a more thorough investigation of structurally novel square pyramidal technetium and rhenium oxo complexes, with the ultimate aim of designing complexes whose size, shape, and disposition of functional groups provide good mimics of ligands for binding sites in important biomolecules. We are currently investigating the stability and distribution properties of these homo- and heterodimeric technetium and rhenium complexes in vivo.

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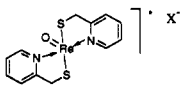
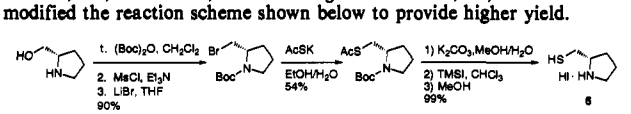
Supplementary Material Available: Description of the spectroscopic characteristics of compounds 4, 5, and 7 (selected ^1H and ^{13}C NMR, 1D and 2D spectra) and crystal data and selected structural parameters for 4 (12 pages). Ordering information is given on any current masthead page.

(12) We expected to isolate the homodimeric complex from 1 and 3 alone as the salt shown below. A molecular ion peak was not detected by FI or FAB mass spectroscopy, although the ^1H NMR spectrum of this unidentified product shows two doublets due to CH_2S at δ 4.14 (J = 16.8 Hz) and 4.81 (J = 16.8 Hz), consistent with the structure shown.



(13) (*S*)-2-Mercaptomethylpyrrolidine was prepared from (*S*)-prolinol according to the method of Searles, Jr., et al.: Searles, S., Jr.; Roelofs, G. E.; Tamres, M.; McDonald, R. N. *J. Org. Chem.* **1965**, *30*, 3443. We have modified the reaction scheme shown below to provide higher yield.



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