A New and Unexpected Arrangement for a $Re^{V}=O(N_2S_2)$ Complex. The Donor Set in the Basal Plane Is NOS_2

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Received February 2, 1995

Bis(amino thiol) (BAT) tetradentate ligands form complexes with $[M^{V}O]^{3+}$ (Re, Tc) centers that are commonly square pyramidal. In extensive structural studies of such complexes with N_2S_2 tetradentate ligands as well as with two NS bidentate ligands, the two N and two S donor atoms have always been found to coordinate at the four corners of the basal plane with the oxo ligand at the apex. The ^{99m}Tc derivatives of such ligands are potentially useful as cerebral[1-4] and myocardial[5] blood perfusion imaging agents. An important example is ^{99m}TcO-(LL-ECDH), which is currently used in clinical trials as a brain perfusion imaging agent (LL-ECDH = trianionic form of ethylenedi-L-cysteine diethyl ester, LL-$ECDH_4$, where a subscript on H designates the number of dissociable protons remaining).[6,7] A related ^{99m}Tc complex formed with LL-ECH_6 (ethylenedi-L-cysteine) shows promise as an imaging agent for evaluating renal function.[8,9] Renal agents normally possess dangling carboxyl groups, which are recognized by the organic anion tubular transport system in the kidneys. Such groups either do not coordinate or bind weakly *trans* to the oxo ligand. For example, we recently reported the solid-state structure of a neutral Re complex with LL-ECH_6, ReO(LL-ECH_3).[10] The C_2 symmetry of the LL-EC ligand is lowered on coordination by the presence of the oxo ligand; one carboxyl group is *anti* while the other is *syn* to the oxo group. ReO(LL-ECH_3) is six-coordinate with the *anti*-carboxyl group coordinated *trans* to the oxo ligand through a long Re–O bond (2.252(9) Å). ^{99}TcO-(*anti*-D-$penH_2$)(*syn*-D-$penH_3$) (D-$penH_2$ = dianionic form of D-penicillamine; D-$penH_3$ = monoanionic form of D-penicillamine) has a coordination geometry similar to that of ReO(LL-ECH_3) with a long Tc–O(*anti*-CO_2) bond (2.214(4) Å).[11] In both compounds, the *syn*-CO_2 is protonated and not coordinated.

Since chirality often significantly influences the renal clearance of ^{99m}Tc complexes, we initiated an investigation of $[M^{V}O]^{3+}$ (M = ^{99m}Tc, Re) derivatives of DL-ECH_6. When the chiralities of the two amino acid moieties differ in $M{=}O(N_2S_2)$ complexes, there are two expected configurations, one with both carboxyls *syn* and one with both *anti*.

Racemic thiazolidine-4-carboxylic acid[12] was coupled by sodium reduction in liquid ammonia,[13] resulting in a mixture of DD-, LL-, and DL-ECH_6 isomers (isolated as the dihydrochloride salt). A solution of this mixture, 1 equiv of $ReIO_2(PPh_3)_2$,[14] and 7 equiv of KOH in aqueous methanol (50%) was heated at reflux for 1 h. Analysis of the reaction solution by reverse phase HPLC showed two peaks for ReO(DD-ECH_3)/ReO(LL-ECH_3) and ReO(DL-ECH_3) [DD+LL:DL ratio ~1:2, 254 nm). Column chromatography using a cation exchange resin eluted with 1 N HCl gave two fractions. After concentration to ~10 mL and desalting by gel filtration, the second fraction yielded violet plates of ReO(DL-ECH_3) (**1**) by slow solvent evaporation of the aqueous solution (pH 3).[15]

Under high-pH conditions, **1** was the only ReO(DL-ECH_3) species obtained, a finding similar to that reported for a DL-dicarboxylic ^{99}TcO(N_2S_2) complex closely related to ReO-(ECH_3).[16] The isomer obtained was the *syn,syn* species. The ^{1}H NMR spectrum of **1** in D_2O at pH 12[15] is consistent with a mirror plane between the halves of the ligand; i.e., there was only one set of cysteine signals (H_α, $H_{\beta'}$, and $H_{\beta''}$) and two ethylene multiplets (*anti*-CH and *syn*-CH). This spectrum is consistent with either the *anti,anti* or the *syn,syn* isomer, both with the normal N_2S_2 basal donor set. We recently interpreted the NMR spectral changes which accompany the lowering of the pH for solutions of $[ReO(LL\text{-}EC)]^{3-}$.[10] The spectra become

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(15) Crystals of **1** readily lost 3 water molecules per formula unit on vacuum drying (yield: 19 mg, 8%). Anal. Calcd for $C_8H_{13}N_2O_5ReS_2$: C, 20.55; H, 2.80; N, 5.99. Found: C, 20.52; H, 2.81: N, 5.95. ^{1}H NMR (NaOD/D_2O, pH 12): δ 4.15 (m, 2H, *anti*-CH_2CH_2), 3.65 (dd, 2H, H_α), 3.55 (dd, 2H, $H_{\beta'}$) 3.38 (m, 2H, *syn*-CH_2CH_2), 2.83 (t, 2H, $H_{\beta''}$). X-ray parameters for *syn*-ReO(DL-ECH_3)·$3H_2O$ (**1**): $C_8H_{19}N_2O_8ReS_2$, mol. wt. 521.6, $P2_1/c$; a = 6.605(2) Å, b = 21.518(4) Å, c = 11.205(2) Å, β = 106.71(3)°; V = 1525.3(6) Å^3; Z = 4; ϱ_{calc} = 2.27 Mg/m^3; λ(Mo Kα) = 0.710 73 Å; absorption coefficient 8.28 mm^{-1}, min/max transmission = 0.15/0.63. Intensities of 3291 independent reflections ($3 < 2\theta < 55°$) were collected at −150 °C on a Siemens P4 instrument. Intensity data were corrected for Lorentz and monochromator polarization and absorption (semiempirical method based on azimuthal scans). The structure was solved by Patterson methods and refined by full-matrix least-squares procedures on F^2 using SHELXL 93. All non-hydrogen atoms were refined anisotropically. The amine, carboxylic, and water H atoms were located from difference maps and refined with idealized bond lengths (d(N–H) = 0.90 Å, d(O–H) = 0.85 Å). One water was disordered and was modeled using two sets of atomic positions for the O and one H atom with 60% (O8, HO8A) and 40% (O9, HO9B) occupancies. The second H atom, within bonding distance of both O8 and O9, was refined with 100% occupancy (HO9A). All other H atoms were generated at calculated positions (d(C–H) = 0.96 Å). All H atoms were constrained using a riding model with isotropic thermal parameters 20% greater than the U(eq) of the bonded heavy atom. Two strong low-angle reflections (100, 002) were supressed in the final refinement due to low intensity ($F_o << F_c$). Final indices: R = 4.60%, R_w = 11.89% (all data); R = 4.20%, R_w = 11.47% ($I > 2\sigma(I)$).
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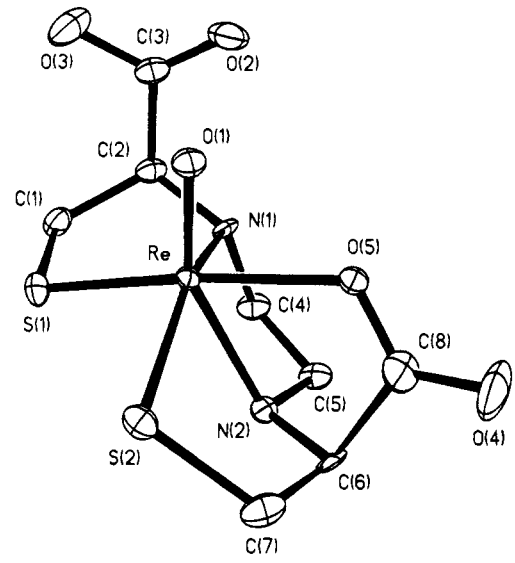

Figure 1. Perspective drawing of *syn*-ReO(DL-ECH$_3$) (**1**) with 50% probability for the thermal ellipsoids.

broad, and our analysis showed that the broadening is due to an *anti*-carboxyl group ligation−deligation process occurring on the NMR time scale. The spectra were sharp at low pH. In other studies we have found that the [ReO(D-penH$_2$)(L-penH$_2$)]$^-$ species has well-defined NMR spectra at low pH but broad spectra at intermediate pHs. These spectra are consistent with a similar carboxyl group ligation−deligation process.[17] Thus we expected similar spectral behavior if **1** was the *anti,anti* species. We expected sharp signals throughout the pH range if **1** was the *syn,syn* species. Instead, upon lowering of the pH of the pH 12 solution of **1**, the spectra of **1** were broad near neutral pH and remained broad even at low pH.

These unexpected solution findings prompted us to determine the solid-state structure of **1**.[15] The structure has new and unexpected features, Figure 1.[15] Most notably, one carboxyl group is bound *cis* to the oxo ligand in the six-coordinate complex in which both carboxyl groups are *syn*. S(1), S(2), and N(1) complete the basal coordination plane, giving an unusual NOS$_2$ donor set. N(2) is bound in the axial position *trans* to the oxo group with a very nonlinear O(1)−Re−N(2) bond angle (151.6(2)°). The metal is displaced (0.60 Å) toward the oxo ligand with respect to N(1), S(1), and S(2); the O(1)−Re−N(1) (103.3(2)°), O(1)−Re−S(1) (107.2(2)°), and O(1)−Re−S(2) (107.7(2)°) bond angles are >90°. However, the O(1)−Re−O(5) bond angle in **1** is only 80.9 (2)°.

Protonation of both N(1) and N(2) is reflected in the Re−N(1) (2.159(5) Å) and Re−N(2) (2.217(5) Å) bond lengths, which are outside the range of M−N bond lengths (1.921(3)−2.024(6) Å) observed in complexes with deprotonated nitrogen donor atoms.[10,16,18−21] The H atom on N(1) is *syn* to the oxo ligand, and the H atom on N(2) is directed down, away from the metal center. The Re−N(2) bond length is significantly longer than the Re−N(1) bond length due to the widely recognized structural *trans* influence of the oxo ligand. However, the Re−N(2) bond in **1** is significantly shorter than the axial M−N bonds found in related complexes.[22,23] These comparisons suggest that the Re−N(2) bond in **1** is influenced by chelation.

The Re−O(5) (2.198(5) Å) bond is long for an M−O bond in the basal plane (1.913(15)−2.141(1) Å)[24−28] but significantly shorter than the Re−O$_{carboxyl}$ bond (2.252(9) Å) in ReO(LL-ECH$_3$),[10] the latter bond being *trans* to the oxo ligand. The Re−O(1) (1.701(4) Å), Re−S(1) (2.252(2) Å), and Re−S(2) (2.306(2) Å) bond lengths are normal.

The structure of **1** allows us to suggest a reason for the broad NMR spectra we observed over a wide pH range. Evidently, when neither carboxyl group is positioned to coordinate to the axial position and the pH is sufficiently low to favor protonation of the coordinated nitrogen(s), the *syn* carboxyl group can coordinate to a basal position. This process could readily explain the observed line broadening if, as for axial ligation,[10] it occurs on the NMR time scale. Surprisingly, in both solution and the solid state, *syn*-CO_2^- coordination seems to be competitive with maintaining the almost universal N_2S_2 basal donor set.

The new results combined with previous results suggest some general themes concerning such N_2S_2 complexes. A number of five-coordinate cationic M^V=O(N_2S_2) complexes are known in which both the amine donor atoms are neutral.[5,29−31] The six-coordinate M=O(N_2S_2) complexes, *syn*-ReO(DL-ECH$_3$) (**1**), ReO(LL-ECH$_3$),[10] and ^{99}TcO(*anti*-D-penH$_2$)(*syn*-D-penH$_3$),[11] all have two neutral N (amine) donor atoms and pendant CO_2 groups. Our work suggests that N_2S_2 ligands with a pendant carboxyl group form five-coordinate complexes with [M^VO]$^{3+}$ centers when both N donor atoms are deprotonated.[10] Thus, there is a bias toward five-coordinate species, even when the N donors are neutral. However, from the present study and our recent work,[10] we expect six-coordinate geometries to be found more frequently in M=O (M = Re, ^{99}Tc) complexes with N_2S_2 ligands with a pendant anionic donor (A). When both N donor atoms are neutral (protonated or alkylated N's), the ligands become quinquedentate. Basal coordination of relevant new ligands with pendant anionic groups is expected to be N_2S_2 for *anti*-pendant groups and NAS_2 for *syn*-pendant groups, e.g. the NOS_2 basal donor set found here for *syn*-ReO(DL-ECH$_3$) (**1**). It is not clear how pendant carboxyl group ligation and coordination number vary when only one nitrogen is deprotonated. Analysis of this situation requires additional study.

Acknowledgment. This work was supported by the National Institutes of Health (Grant No. DK38842-08). We thank the NIH and NSF for supporting the purchase of instruments.

Supporting Information Available: For **1**, tables of crystal data and experimental parameters, atomic coordinates with equivalent isotropic displacement coefficients, bond lengths, bond angles, displacement coefficients, and H atom parameters and a view in $P2_1/c$ (7 pages). Ordering information is given on any current masthead page.

IC950129N

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