Synthesis of Bis-Thiolato-Bridged Ru(III) Dimers. The Crystal Structure of $[Ru(H_2edta)(\mu\text{-}SC_6H_5)]_2$

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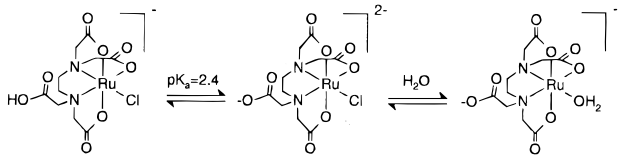
Introduction

Owing to their antitumor[1,2] and antisepsis[3] activity, small molecule ruthenium complexes have been the focus of increasing attention. Our interest in the reactivity of ruthenium-based nitric oxide scavengers[4,5] led us to investigate the reaction of K[Ru(Hedta)Cl] and Ru(Hedta)(OH_2) with various sulfur-containing ligands. It has been established that Ru(Hedta)(OH_2) is generated by the rapid substitution of the bound chloride of $[Ru(Hedta)Cl]^-$ in aqueous solution,[6] and thus, it is generally accepted that edta is coordinated to ruthenium as a pentadentate ligand with the sixth coordination site occupied by a water molecule (Chart 1).

The extreme lability of this coordinated water molecule has been attributed to the hydrogen bonding of the pendant carboxylate group to the water molecule, thereby weakening the Ru−OH_2 bond and/or creating an open site for an associative attack of the incoming ligand.[7,8] Substitution reactions of K[Ru(Hedta)Cl] with thiol(ate)[8−11] ligands have not been investigated to the extent of other[7,8,12] (N-donor) ligands. In the course of our investigations, we have isolated a thiolato-bridged Ru(III)-(H_2edta) dimer (**II**) possessing a Ru(III)−Ru(III) single bond. Thiolato bridged diruthenium complexes are rare, and those reported that contain a ruthenium−ruthenium bond consist of mixed-valence oxidation states,[13] Ru(I)[14] dimers, or Ru(II) dimers.[15] Generally, these complexes contain π-acidic donors in the ligand framework. Few examples of thiolato-bridged Ru(III)−Ru(III) dimers possessing a Ru−Ru bond exist, and these are limited to complexes containing Cp* in the coordination sphere.[16−23] Single-bonded Ru(III)−Ru(III) dimers containing other bridging ligands (RCO_2^-, OH^-, and dppm/Cl^-) have been reported.[24−26]

Chart 1



Experimental Details

General Information. All reagents were purchased from Aldrich and used without further purification. K[Ru(Hedta)Cl]·$2H_2O$ was prepared according to published procedures.[6] ^{1}H NMR (300 MHz) spectra were recorded on a Bruker Avance 300 spectrometer with chemical shifts relative to Me_4Si. Spectrophotometric measurements were performed on a Perkin-Elmer LAMBDA 2S spectrophotometer. Electrospray mass spectra were recorded on a Bruker-HP Esquire-LC Ion Trap mass spectrometer. FAB mass spectra were measured by M-Scan (West Chester, PA). Elemental analyses were carried out by Atlantic Microlab Inc. (Norcross, GA).

Synthesis of Product I (K[Ru(Hedta)(SCH_2CH_2OH)]·$4H_2O$). K[Ru(Hedta)Cl]·$2H_2O$ (0.5 g, 1 mmol) was suspended in HCl (10^{-3} M, 100 mL) and heated at 50 °C until completely dissolved. Mercaptoethanol (0.07 mL, 1 mmol) was added, at which time the solution turned deep magenta. The reaction mixture was stirred for an additional 20 min before the solvent was removed in vacuo. The residue was dissolved in a minimum amount of HCl (1 mmol), and the product precipitated upon the addition of ethanol. Yield: 0.235 g (44%). ES-MS (-ve) *m*/*z*: $[Ru(Hedta)(SCH_2CH_2OH)]^-$, 468; $[Ru(edta)]^-$, 390. Anal. Calcd for $C_{12}H_{18}N_2O_9RuSK\cdot 4H_2O$: C, 24.91; H, 4.53; N, 4.84; S, 5.54. Found: C, 25.03; H, 4.19; N, 5.09; S, 5.53.

Synthesis of Product II ($[Ru(H_2edta)(\mu\text{-}SPh)]_2$). K[Ru(Hedta)Cl]·$2H_2O$ (0.5 g, 1 mmol) was dissolved in deionized water at 50 °C. Once completely dissolved, the reaction mixture was removed from heat, and thiophenol (0.102 mL, 1 mmol) was added. A dark red solution formed immediately. A dark blue solution formed on continuous stirring, and finally, a dark green solution formed after 30 min. The reaction mixture was left to stand at room temperature, during which time a green crystalline solid precipitated from the solution. This was collected by filtration, washed with diethyl ether, and dried in air. Yield: 0.29 g (27%). FAB (+ve) *m*/*z*: $[M + H]^+$, 1003; $[M + Na]^+$, 1025. ^{1}H NMR (D_2O/K_2CO_3, 25 °C): δ 7.83−8.02 (ArH, br m, 4H), 7.60−7.63

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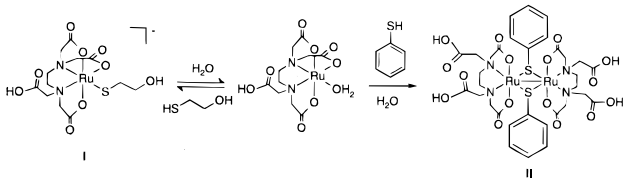
Chart 2. Reaction of Ru(Hedta)(OH_2) with Thiols



(ArH, br m, 6H), 4.77−4.79 (CH_2, br m, 2H), 4.76 (CH_2, br s, 6H), 3.70−4.32 (CH_2, br m, 12H), 3.15 (CH_2, br s, 4H). Anal. Calcd for $C_{32}H_{38}N_4O_{16}Ru_2S_2 \cdot 4H_2O$: C, 35.82; H, 4.32; N, 5.22; S, 5.98. Found: C, 35.42; H, 4.20; N, 5.19; S, 5.81.

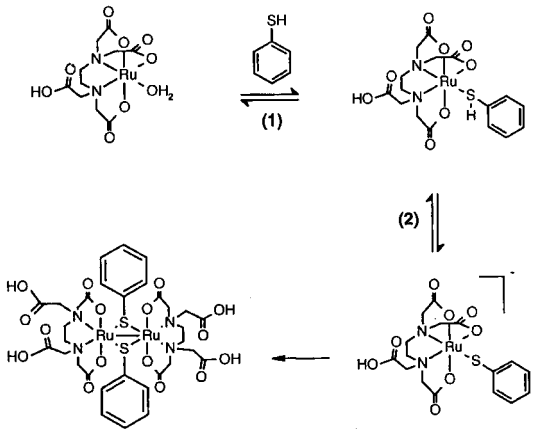
Solution Studies. The reversibility of the thiolate ligand in complex **I** was monitored spectrophotometrically. A solution of complex **I** (10^{-4} M, 0.1 M phosphate-buffered saline (PBS), pH 7.4) was prepared and allowed to equilibrate overnight, during which time the absorbance peak at 509 nm gradually disappeared. A spectrophotometric titration of K[Ru(Hedta)Cl] with thiophenol was performed in the following manner: 100 μL of a 10^{-3} M solution of K[Ru(Hedta)Cl] (0.1 M PBS, pH 7.4, 10% MeOH) was mixed with varying amounts (0−5 equiv) of thiophenol (2.5×10^{-3} M). The total volume was brought to 1 mL so that the final concentration of K[Ru(Hedta)Cl] remained constant at 10^{-4} M and the HSPh/Ru ratio varied from 0 to 5. The UV−vis spectrum was measured immediately after mixing. A 1:1 solution of K[Ru(Hedta)Cl] and thiophenol (both reactants at 10^{-4} M, 0.1 M PBS, pH 7.4, 10% MeOH) was mixed and allowed to equilibrate, during which time the absorbance peak at 610 nm disappeared.

X-ray Crystal Structure Analysis. For product **II**, intensity data were measured on a Bruker SMART system with Mo-Kα radiation (λ = 0.71073 Å, ω mode, θ range 2.03−28.24°) at 295 K. Data collection and reduction were performed using the SAINT processing program. Direct methods solution and refinements (full-matrix least squares on F^2) were performed using the SHELXTL program. The structure was refined to R1 = 0.0714, wR2 = 0.0976, and goodness of fit = 1.395 for 4779 unique observed data points and 300 parameters.

Results and Discussion

The reaction of K[Ru(Hedta)Cl]·$2H_2O$ with an aliphatic thiol such as mercaptoethanol results in substitution of the aqua ligand (generated in solution) to give the monomeric ruthenium complex **I** (Chart 2) in an isolated yield of 44%. To verify that mercaptoethanol coordinates through the sulfur atom and not the oxygen atom, we treated K[Ru(Hedta)Cl] with 1 equiv of ethanethiol. The solution immediately turned the same magenta color as that in the reaction with mercaptoethanol. Due to the presence of water in the lattice of **I**, the OH stretch (from the mercaptoethanol ligand) in the infrared region cannot be isolated. Solution studies of **I** show that the substitution reaction is a reversible process in aqueous solution, and a solution of **I** will slowly convert to Ru(Hedta)(OH_2) over an extended period of time.

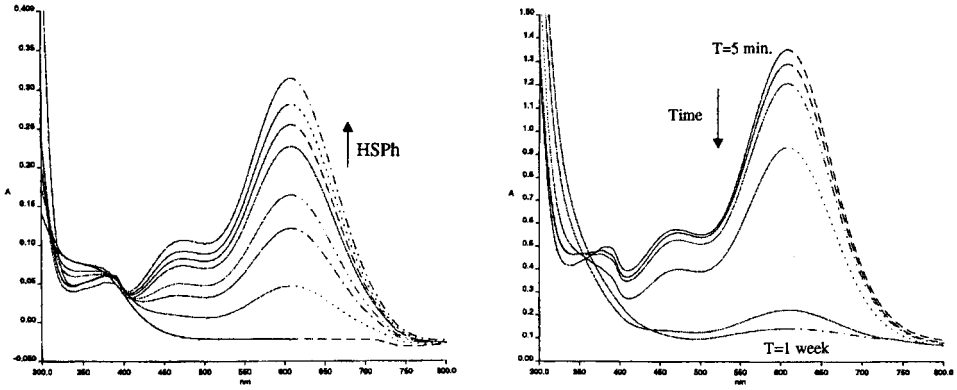
Chart 3. Proposed Stepwise Formation of **II**



Similarly, a spectrophotometric titration of K[Ru(Hedta)Cl] with thiophenol (Figure 1a) in a pH 7.4 buffered solution (close to the pK_a of thiophenol (7.8)) results in the appearance of an absorbance peak at 610 nm (as the number of equivalents of thiophenol increased), corresponding to the monomeric ruthenium−thiophenolate complex. These studies demonstrate that the reaction of K[Ru(Hedta)Cl] with thiophenol yields the thiophenolato-substituted monomer in 1:1 stoichiometry. When a dilute 1:1 mixture of K[Ru(Hedta)Cl] and thiophenol is allowed to stand for extended periods of time, the monomeric [Ru(Hedta)SPh]$^-$ complex also reverts to the original aqua species (Figure 1b), indicating reversibility of the coordinated thiophenolate ligand.

However, a preparatory reaction of K[Ru(Hedta)Cl] with thiophenol in unbuffered aqueous solution (both reactants at 0.1 M) resulted in the formation of **II** (Chart 2), a bis-thiolato-bridged Ru(III)−Ru(III) dimer. The color changes observed during the reaction provide evidence for the proposed stepwise formation of **II** (Chart 3). Upon the initial mixing of K[Ru(Hedta)Cl] and thiophenol, the solution turns dark red in color; after a few minutes, the solution turns blue, and then, within 30 min, the solution turns green, and a precipitate forms, corresponding to the dimer **II**.

The structure of complex **II** was verified by X-ray crystallographic refinement (Table 1), mass spectrometry, ^{1}H NMR



a **b**

Figure 1. Spectrophotometric titrations of (a) K[Ru(Hedta)Cl] (10^{-4} M) with thiophenol (0−5 equiv) and (b) 1:1 K[Ru(Hedta)Cl]:thiophenol in aqueous solution over time.

Table 1. Details of Data Collection and Structure Refinement for **II**

chemical formula	$C_{32}H_{46}N_4O_{20}Ru_2S_2$
a	10.4398(1) Å
b	10.4398(1) Å
c	36.2157(7) Å
V	3946.98(9) Å^3
Z	4
formula weight	1072.99
space group	$P4_12_12$
T	293(2) K
λ	0.71073 Å
density$_{calcd}$	1.806 Mg/m^3
μ (Mo-Kα)	0.960 mm^{-1}
R1[a]	0.0714
wR2[b]	0.0976

[a] $R1 = \sum(F_o - F_c)/F_o$. [b] $wR2 = [\sum(F_o^2 - F_c^2)^2/\sum wF_o^2]^{1/2}$.

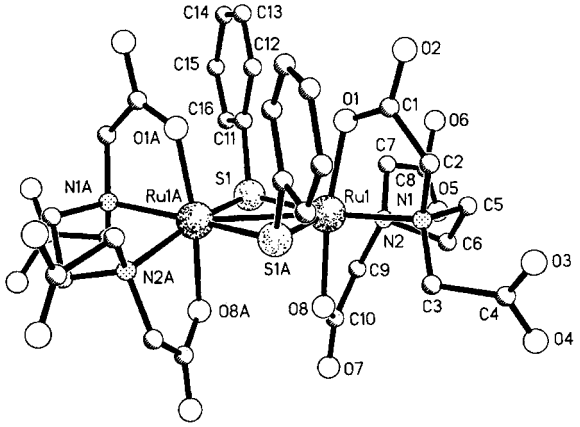


Figure 2. Perspective of complex **II**.

spectroscopy, and elemental analysis. Figure 2 shows the crystal structure of **II** with selected bond lengths and angles given in Table 2.

Each ruthenium atom is coordinated to H_2edta through two nitrogen atoms and two carboxylate oxygen atoms. It is difficult to predict the geometry the bridging thiolates will adopt in these types of complexes. In **II**, the two thiophenolate ions coordinate such that the aromatic rings are syn to one another with respect to the equatorial plane of the Ru_2S_2 four-membered ring. This syn coordination is also prevalent in the [Cp*Ru$-(\mu$-SR$)_2-$RuCp*] dimers, in which there is no Ru−Ru bond. However, in a recently reported complex, [Cp*ClRu$-(\mu$-SR$)_2-$RuClCp*], which does have a Ru(III)−Ru(III) single bond, the bridging thiolate ions adopt an anti geometrical configuration.[23] The most important structural feature of complex **II** is the characteristic Ru(III)−Ru(III) single bond distance (2.866 Å), consistent with reported values for Ru−Ru single bonds (2.6−2.9 Å). It is also noteworthy that the metrical parameters associated with the Ru−O and C−O distances are consistent with those previously reported for Ru(III)−carboxylate complexes.[27,28] There is no evidence for the Ru−O bond lengthening of ca. 0.15−0.20 Å, which would occur concomitant to protonation at the metal-bonded oxygen atoms in a Ru(II) analogue. Similarly, the C−O distances are unexceptional and indicative of deprotonation of the metal-bound carboxylate groups. Mass spectral data are consistent with the molecular formula assigned to complex **II** and follow calculated isotopic distribution patterns of the parent complex. If there were protonation of the carboxylate oxygen atoms (and thus, a Ru(II)−Ru(II) dimer), this would be reflected in the mass spectra.

Table 2. Selected Bond Lengths (Å) and Angles (deg) for **II**

Ru(1)−O(1)	2.061(4)	O(1)−Ru(1)−O(8)	171.3(2)
Ru(1)−O(8)	2.076(3)	N(1)−Ru(1)−S(1)	165.2(2)
Ru(1)−N(1)	2.186(5)	N(2)−Ru(1)−S(1A)	161.9(2)
Ru(1)−N(2)	2.198(5)	O(1)−Ru(1)−S(1A)	96.5(2)
Ru(1)−S(1)	2.290(1)	O(1)−Ru(1)−N(1)	78.1(2)
Ru(1)−S(1A)	2.323(2)	O(1)−Ru(1)−N(2)	97.5(2)
Ru(1)−Ru(1A)	2.866(1)	O(1)−Ru(1)−S(1)	95.7(1)
S(1)−Ru(1)−S(1A)	103.2(6)		

The ^{1}H NMR spectrum (D_2O) of **II** also supports the diamagnetic nature of structure **II**, indicating coupling between the two Ru(III) centers. The chemical shifts are within the normal diamagnetic range (0−10 ppm), although they are slightly broadened at room temperature.

All experimental evidence supports that the structure of complex **II** is a Ru(III)−Ru(III) dimer. This does not, however, rule out the fact that in the reaction mixture there may have been some reduction of Ru(III) to Ru(II) by thiophenol, which could account for the low yield (27%) of complex **II**.

In conclusion, we have demonstrated that a bis-thiolato-bridged Ru(III)−Ru(III) dimer possessing a Ru−Ru single bond has been formed from an aqueous solution. This is the first example of a thiolato-bridged Ru(III)−Ru(III) dimeric complex that does not contain Cp* in the coordination sphere. Recently, an intermediate complex in the catalytic transformation of organic disulfides, [Cp*RuCl(μ-SPh)]$_2$, which also has a Ru(III)−Ru(III) single bond (2.860 Å), has been isolated.[23] The biological active precursor (Ru(Hedta)(OH_2)) remains intact in dilute aqueous solution and is not scavenged by the presence of RSH groups (e.g., glutathione, cysteine, etc.). This is an inherent property of the reversibility of eqs 1 and 2 in Chart 3 at pH 7.4. Dimer formation and, hence, removal from the biological reactivity profile only occur at high concentrations of K[Ru(Hedta)Cl]. These are excellent properties in the development of metal-based drugs.

Supporting Information Available: An X-ray crystallographic file in CIF format for the structure of **II** ([Ru(H_2edta)(μ-SPh)]$_2$). This material is available free of charge via the Internet at http://pubs.acs.org.

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