Inorg. Chem. **2003**, *42*, 661–663

Isolation of the Novel Dirhodium(II/II) Thiolate Compound $Rh_2(\eta^1\text{-}C_6H_5S)_2(\mu\text{-}C_6H_5S)_2(bpy)_2$

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Received October 16, 2002

The reaction of the anticancer active compound $[Rh_2(\mu\text{-}O_2CCH_3)_2(bpy)_2(CH_3CN)_2][BF_4]_2$ (**1**) (bpy = 2,2′-bipyridine) with NaC_6H_5S under anaerobic conditions yields $Rh_2(\eta^1\text{-}C_6H_5S)_2(\mu\text{-}C_6H_5S)_2(bpy)_2\cdot CH_3OH$ (**2**), which was characterized by UV–visible, IR, and ^1H NMR spectroscopies as well as single-crystal X-ray crystallography. Compound **2** crystallizes as dark red platelets in the monoclinic space group *C*2/*c* with cell parameters $a = 20.398(4)$ Å, $b = 11.861(2)$ Å, $c = 17.417(4)$ Å, $\beta = 108.98°$, $V = 3984.9(14)$ Å^3, $Z = 4$. The main structural features are the presence of a $[Rh_2]^{4+}$ core with a Rh–Rh distance of 2.549(2) Å bridged by two benzene thiolate ligands in a butterfly-type arrangement. The axial positions of the $[Rh_2]^{4+}$ core are occupied by two terminal benzene thiolates. Cyclic voltammetric studies of **2** reveal that the compound exhibits an irreversible oxidation at +0.046 V in CH_3CN, which is in accord with the fact that the compound readily oxidizes in the presence of O_2. The fact that this unusual dirhodium(II/II) thiolate compound is formed under these conditions is an important first step in understanding the metabolism of dirhodium anticancer active compounds with thiol-containing peptides and proteins.

The mechanism of action of the platinum-containing chemotherapeutic drugs *cis*-$[PtCl_2(NH_3)_2]$, carboplatin, and oxaliplatin, vis-à-vis their cellular targets, has been under investigation for many years.[1] For example, the reactivity of cisplatin and analogues with SH-containing compounds has been explored in substantial detail.[1d] Structures of Pt(II) complexes containing SH-based biomolecules, namely, $Pt_2(\mu\text{-accys-S})_2(bpy)_2$ (accys-S = *N*-acetyl-L-cysteinate; bpy = 2,2′-bipyridine) and $[\{Pt(en)(\mu\text{-SG})\}_2]$ (SG = deprotonated glutathione; en = ethylenediamine), have been reported.[4] The main structural feature of these complexes is the presence of bridging thiolate ligands.[4] Although the metabolism of these drugs is known to involve reactions with sulfur-containing molecules, such as glutathione, it is generally accepted that nuclear DNA is the main target.[1−3] In fact, there is compelling structural evidence that Pt complexes form strong intrastrand cross-links which serve to interrupt the local structure of the double helix, a situation that leads to an increase in binding affinity of key proteins to these platinated sites.[1b] The ultimate outcome of this cascade of events is that DNA replication ceases and the cell dies.

In spite of the obvious importance of the medicinal chemistry of metal-containing compounds, relatively little is known about the biological activity of anticancer active transition metal compounds other than those of platinum.[1c] Work in our laboratories over the past 10 years has endeavored to build a database of structural information on products of reactions between $Rh_2(\mu\text{-}O_2CCH_3)_4L_2$ (L = solvents), $[Rh_2(\mu\text{-}O_2CCH_3)_2(N\text{-}N)_2L_2]X_2$ (N-N = 2,2′-bipy-

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10.1021/ic020630x CCC: $25.00
Published on Web 01/10/2003

ridine and 1,10-phenanthroline; X = halides), and $Rh_2(\mu\text{-}O_2CCF_3)_2(DTolF)_2$ (DTolF = ditolylformamidinate) and various biomolecules. Although these compounds are not in clinical use, they are known to exhibit potent anticancer activity against Ehrlich ascites, leukemia, sarcoma, and human oral carcinoma KB tumors.[2] Seminal work in this area was carried out by Bear and co-workers in the 1970s, the results of which support the conclusion that DNA is affected by the presence of $Rh_2(\mu\text{-}O_2CR)_4$ compounds.[3]

Although there is general consensus that DNA is the primary molecular target of anticancer active transition metal compounds, the chemistry of these metal complexes with sulfur molecules of biological importance must also be considered. Typically these studies require a combination of solution data obtained on the metal complex of a biomolecule coupled with definitive structural evidence on a model ligand that allows for crystallization of the product.[4a] In this vein, we are exploring reactions of metal compounds with cysteine (Cys) and glutathione (GSH) as well as thiolate ligands, such as 2-aminothiophenol (amp) and benzene thiolate. In an earlier study, we reported that Rh^{III} compounds are formed in aerobic reactions between $[Rh_2(\mu\text{-}O_2CCH_3)_2(N\text{-}N)_2(CH_3CN)_2]^{2+}$ and amp.[5] We further proposed that the putative intermediate in the reaction pathway is a thiolate-bridged dirhodium(II/II) complex that oxidizes to the structurally characterized $Rh_2^{III/III}$ and Rh^{III} compounds. Herein we report that the reaction of $[Rh_2(\mu\text{-}O_2CCH_3)_2(bpy)_2(CH_3CN)_2][BF_4]_2$ with thiolate ligands in the absence of O_2 does, indeed, produce a $Rh_2^{II/II}$ compound. This compound, which contains a Rh−Rh bond, is unprecedented in the dirhodium-(II/II) family of compounds.

A greenish brown solution of $[Rh_2(\mu\text{-}O_2CCH_3)_2(bpy)_2(CH_3CN)_2][BF_4]_2$ (**1**) in dry, degassed CH_3OH reacts with excess NaC_6H_5S at room temperature to yield a dark red microcrystalline product.[6] An X-ray crystallographic study of the compound revealed the identity of the product to be $[Rh(\eta^1\text{-}C_6H_5S)(\mu\text{-}C_6H_5S)(bpy)]_2{\cdot}CH_3OH$ (**2**).[7] The molecular structure of **2** consists of a central Rh_2S_2 butterfly core that is further coordinated to two terminal $C_6H_5S^-$ and two chelating bpy ligands (Figure 1). The Rh−Rh distance is 2.549(2) Å, which is in the typical range for a Rh−Rh single bond (2.4−2.9 Å).[8] The Rh−S distances are 2.243(4) and 2.275(4) Å, and the angles subtended by the bridging thiolate ligands are ∠S−Rh−S = 84.41(2)° and ∠Rh−S−Rh = 68.70(13)°. The coordination environment of the Rh_2 unit in **2** is completed by the presence of chelating bpy ligands in the equatorial positions, and two terminal $C_6H_5S^-$ molecules occupying the axial positions. The Rh−S distances for the axial positions of 2.424(4) Å are longer, as expected, due to the strong trans influence of the metal−metal bond.[10] The Rh_2S_2 core is reminiscent of the structures of several known organometallic compounds, but, to our knowledge, this represents the first example of a mixed thiolate diimine compound to have been crystallographically characterized.[9] The neutral molecules pack in an overall pseudohexagonal arrangement and do not show any significant intermolecular interactions.

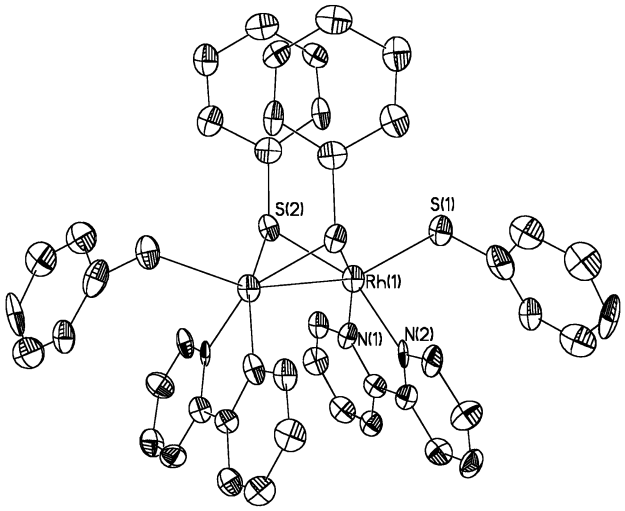

Figure 1.

A ^1H NMR spectrum of **2** in a CD_3OD solution contains two sets of multiplet resonances in the ranges 6.2−7.6 and 7.2−8.5 ppm for the C_6H_5S and bpy ligands, respectively.[11] The assignments are based on a comparison of the chemical shifts observed for the resonances of the parent compound **1** as well as those of free C_6H_5SH. The electrochemical properties of **2** were investigated by cyclic voltammetry in CH_3CN,[12] which revealed the presence of an accessible irreversible oxidation at +0.046 V along with minor anodic and cathodic features. It is interesting to note that the starting material $[Rh_2(\mu\text{-}O_2CCH_3)_2(bpy)_2(CH_3CN)_2][BF_4]_2$ exhibits remarkably different electrochemical behavior, namely, a reversible one-electron reduction at −0.89 V.[14] Clearly, the

(5) (a) Sorasaenee, K.; Galán-Mascarós, J. R.; Dunbar, K. R. *Inorg. Chem.* **2002**, *41*, 433. (b) ^1H NMR spectrum of the decomposition product of compound **2**, δ (ppm; CD_3CN): 6.94 (m), 7.21 (m), 7.35 (m), 7.38 (m), 7.76 (m), 7.88 (m), 8.18 (m), 8.32 (d), 8.52 (d).

(6) A CH_3CN solution of $[Rh_2(\mu\text{-}O_2CCH_3)_2(bpy)_2(CH_3CN)_2][BF_4]_2$ (**1**) (0.11 mmol) was slowly added to a MeOH solution of excess C_6H_5SNa (1.1 mmol) under N_2, during which time the solution color changed from orange-brown to dark red. The solution was stirred at rt for 6 h, concentrated to dryness, and recrystallized from MeOH/Et_2O to yield dark red crystalline plates. Yield before recrystallization = 70 mg (percent yield = 65).

(7) Crystal data for $[Rh(\mu\text{-}C_6H_5S)(C_6H_5S)(bpy)]_2{\cdot}CH_3OH$ (**2**) at 110(2) K: $C_{45}H_{40}N_4ORh_2S_4$, MW = 985.86, dark red platelet, 0.303 × 0.252 × 0.193 mm^3, *C2/c*, a = 20.398(4) Å, b = 11.861(2) Å, c = 17.417(4) Å, β = 108.98°, V = 3984.9(14), Z = 4, ρ_{calc} = 1.625, Mo Kα radiation (λ = 0.71069 Å), μ = 1.079 mm^{-1}. Data were collected on a Bruker SMART CCD area detector diffractometer equipped with a graphite-monochromated Mo anode in the range 4.0° < 2θ < 56.5°. A total of 8966 reflections were collected, of which 4331 were unique and 1980 were in the range $F_o^2 \geq 4\sigma(F_o^2)$. The frames were used to refine 251 parameters to R1 (wR2) = 0.0756 (0.1424), GOF = 0.980, F^2 refinement in SHELXTL-5.0. All non-hydrogen atoms were refined anisotropically, with the exception of a disordered methanol solvent molecule which was modeled over two positions and refined isotropically.

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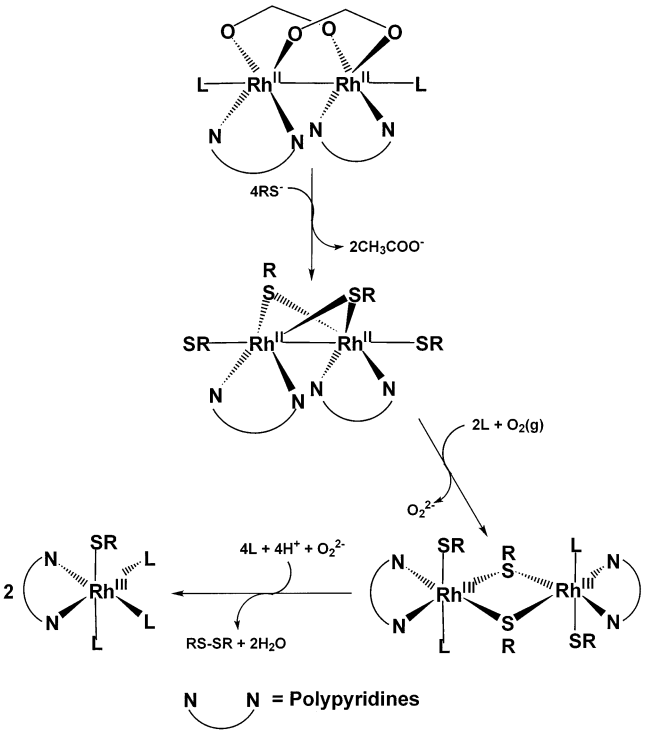
Scheme 1



electrochemical properties of **2** have been dramatically affected by the replacement of two carboxylate ligands with four thiolate ligands which are much more electron rich. The accessibility of the oxidation process for **2** supports our observation that the compound decomposes in air, and the irreversible nature of the process suggests that the oxidized product will be structurally quite different from **2**.[13] Indeed, we have evidence for this hypothesis from a related study of the reaction of **1** with 2-aminothiophenol in air to yield the dinuclear and mononuclear Rh^{III} cations $[Rh_2^{III/III}(\mu\text{-}C_6H_6NS)_2(\eta^1\text{-}C_6H_6NS)_2(bpy)_2]^{2+}$ and $[Rh^{III}(\eta^2\text{-}C_6H_6NS)_2(bpy)]^+$, respectively.[5] In this earlier study we proposed that the reaction proceeds via the formation of a thiolato-bridged dirhodium compound followed by oxidation of the $Rh_2^{II/II}$ core to Rh^{III} compounds and release of disulfide upon exposure to O_2 (Scheme 1).

We are now in a position to further defend the proposed reaction scheme by providing a previously missing piece of evidence, namely, the oxidatively unstable intermediate of the type represented by compound **2** crystallized under anaerobic conditions. The decomposition of **2** in air is readily apparent by a color change from dark red-brown to yellow-orange,[5] and the concomitant formation of the disulfide byproduct $C_6H_5S-SC_6H_5$.[16] No suitable single crystals of the Rh^{III} decomposition product were obtained in this study, but the identity of the product shows a similarity to those formed with 2-aminothiophenol based on the ^1H NMR spectroscopic data.[5]

The current results are important for our general understanding of the fate of anticancer active dirhodium bis-polypyridine compounds in the presence of thiol groups. Reactions with cysteine and glutathione proceed with the same color changes and redox reactions as noted for the 2-aminothiophenol and benzenethiol ligands, which we take as a promising sign that such model studies are relevant. An even more compelling observation is that reactions of **1** with both Cys and GSH yield dark blue precipitates.[17] Preliminary characterization of the blue solids by elemental analyses and IR spectroscopy[18] indicates that the products with cysteine and glutathione also contain thiolate ligands bound to a dirhodium core.

Acknowledgment. We thank the National Science Foundation for the equipment grants to purchase the CCD X-ray diffractometer (CHE-9807975), as well as the state of Texas (Grant ARP-010366-0277-1999) and the Welch Foundation for financial support. J.R.G.-M. thanks the Ministerio de Educación y Cultura for a postdoctoral fellowship. K.R.D. acknowledges Johnson-Matthey for a generous loan of rhodium. K.S. thanks Prof. Marcetta Y. Darensbourg for helpful discussion.

Note Added after ASAP: The version of this paper posted ASAP on January 10, 2003, contained the wrong Scheme 1. The correct Scheme 1 is present in the version posted on January 17, 2003.

Supporting Information Available: Crystallographic data (CIF). This material is availiale free of charge via the Internet at http://pubs.acs.org.

IC020630X

(11) IR (CsI pellets) and solution electronic spectra with matching quartz cuvettes were recorded on Nicolet Nexus model 470-FTIR and Shimadzu UVPC-1601 spectrophotometers, respectively. ^1H NMR spectra were recorded on a Mercury-300 MHz spectrometer. IR, ν (cm^{-1}; CsI): 308, 321, 483 (Rh−S vibrational frequencies). Electronic absorption, λ (nm; CH_3OH): 408.5 (s). ^1H NMR, δ (ppm; CD_3OD): 6.2−7.6 (m), 7.2−8.5 (m). Anal. Calcd for $C_{45}H_{40}N_4ORh_2S_4$: C, 54.77; H, 4.09; N, 5.68. Found: C, 53.50; H, 3.68; N, 5.03.

(12) Electrochemistry was performed with an HCH Instruments electrochemical analyzer employing a standard three-electrode cell (Pt working, Pt wire auxiliary, and Ag/AgCl reference electrodes). The supporting electrolyte is $[NBu^n_4][PF_6]$. The $Cp_2Fe/[Cp_2Fe]^+$ couple occurs at +0.44 V vs Ag/AgCl under the same conditions.

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(15) The most likely stepwise reaction to form **2** involves binding of RS^- to $[Rh_2(\mu\text{-}O_2CCH_3)_2(N\text{-}N)_2L_2]X_2$ through the axial positions to yield an axial adduct, followed by rearrangement to bridging sites with displacement of the bridging acetate ligands. Precedence for the formation of an axial adduct of $Rh_2(\mu\text{-}O_2CCH_3)_4$ and $C_6H_5CH_2SH$ is the following paper: Christoph, G. C.; Tolbert, M. *Am. Cryst. Assoc. Symp.* **1980**, *7*, 39.

(16) The disulfide byproduct was obtained as pale yellow crystals after the solution mixtures were exposed to O_2 and was characterized by single-crystal X-ray methods.

(17) Reactions of **1** (0.11 mmol) with cysteine (0.44 mmol) and glutathione (0.44 mmol) were performed in degassed aqueous solutions under an inert atmosphere. The reaction mixtures rapidly turned an opaque brown color with a formation of a dark precipitate. All volatile compounds were removed *in vacuo*, and the dark blue solids were collected. Reaction between **1** and cysteine: IR, ν (cm^{-1}; CsI): 315, 334, 352, 422 (Rh−S vibrational frequencies). Anal. Calcd for $C_{32}H_{42}B_2F_8N_8O_8Rh_2S_4$: C, 32.73; H, 3.60; N, 9.54. Found: C, 32.66; H, 3.68; N, 8.97. Reaction between **1** and GSH: IR, ν (cm^{-1}; CsI): 312, 323, 423 (Rh−S vibrational frequencies). Anal. Calcd for $C_{60}H_{100}B_2F_8N_{16}O_{33}Rh_2S_4$: C, 34.07; H, 4.68; N, 10.84. Found: C, 34.63; H, 4.84; N, 10.77.

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