Isolation of the Novel Dirhodium(II/II) Thiolate Compound
Rh2(η1-C6H5S)2(μ-C6H5S)2(bpy)2

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The reaction of the anticancer active compound [Rh2(μ-O2CCH3)2-
(bpy)2(CH3CN)2][BF4]2 (1) (bpy = 2,2’-bipyridine) with NaC6H5S
under anaerobic conditions yields Rh2(η1-C6H5S)2(μ-C6H5S)2(bpy)2-
CH3OH (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 C2/c with cell parameters a = 20.398(4) Å, b = 11.861(2) Å, c = 17.417(4) Å, β = 108.98°, V = 3984.9(14) Å3,
Z = 4. The main structural features are the presence of a [Rh2]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 [Rh2]4+ core are occupied by two terminal benzene thiocyanates.

The mechanism of action of the platinum-containing
chemotherapeutic drugs cis-[PtCl2(NH3)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
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 intranuclear 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 Rh2(μ-O2CCH3)2L2 (L =
solvents), [Rh2(μ-O2CCH3)2(N-N)2L2]X2 (N-N = 2,2’-bipy-

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ridine and 1,10-phenanthroline; \(X = \text{halides}\), and \(\text{Rh}_2(\mu-O_2CCF_3)_2(DToIF)_2\) (DToIF = 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 \(\text{Rh}_2(\mu-O_2CR)\_4\) 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.\(^4\)

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 \(\text{Rh}_2(\mu-O_2CCCH_3)_2-(\text{N-N})_2(\text{CH}_3\text{CN})_2\)\(^2\) and amp.\(^3\) 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 \(\text{Rh}_2^{III/III}\) and \(\text{Rh}^{III}\) compounds. Herein we report that the reaction of \([\text{Rh}_2(\mu-O_2CCCH_3)_2(bpy)_2(\text{CH}_3\text{CN})_2][\text{BF}_4]_2\) with thiolate ligands in the absence of \(O_2\) does, indeed, produce a \(\text{Rh}^{II/II}\) complex. This compound, which contains a \(\text{Rh}^{-}\text{Rh}\) bond, is unprecedented in the dirhodium-(II/II) family of compounds.

A greenish brown solution of \([\text{Rh}_2(\mu-O_2CCCH_3)_2(bpy)_2(\text{CH}_3\text{CN})_2][\text{BF}_4]_2\) (1) in dry, degassed \(\text{CH}_3\text{OH}\) reacts with excess \(\text{NaC}_6\text{H}_5\text{S}\) at room temperature to yield a dark red microcrystalline product.\(^5\) An X-ray crystallographic study of the compound revealed the identity of the product to be \([\text{Rh}^{II}(\mu-\text{C}_6\text{H}_5\text{S})(\text{C}_6\text{H}_5\text{S})(\text{bpy})_2]\text{CH}_3\text{OH}\) (2).\(^7\) The molecular structure of 2 consists of a central \(\text{Rh}_2\text{S}_2\) butterfly core that oxidizes to the structural model ligand that allows for crystallization of the product.\(^4\)

The Rh\(^{II}\) unit in 2 is completed by the presence of chelating bpy ligands in the equatorial positions, and two terminal \(\text{C}_6\text{H}_5\text{S}\) molecules occupying the axial positions. The Rh\(^{II}\) distances for the axial positions of 2.424(4) \(\AA\) are longer, as expected, due to the strong trans influence of the metal–metal bond.\(^10\) The \(\text{Rh}_2\text{S}_2\) 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.\(^8\) The neutral molecules pack in an overall pseudohexagonal arrangement and do not show any significant intermolecular interactions.

A \(^1\)H NMR spectrum of 2 in a CD\(_3\)OD solution contains two sets of multiplet resonances in the ranges 6.2–7.6 and 7.2–8.5 ppm for the \(\text{C}_6\text{H}_5\text{S}\) 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 \(\text{C}_6\text{H}_5\text{SH}\). The electrochemical properties of 2 were investigated by cyclic voltammetry in CH\(_3\)CN,\(^12\) 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 \([\text{Rh}_2(\mu-O_2CCCH_3)_2(bpy)_2(\text{CH}_3\text{CN})_2][\text{BF}_4]_2\) exhibits remarkably different electrochemical behavior, namely, a reversible one-electron reduction at −0.89 V.\(^13\) Clearly, the

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\(^{(5)}\) (a) Sorasaenee, K.; Galán-Mascarós, J. R.; Dunbar, K. R. Inorg. Chem. 2002, 41, 433. (b) \(^1\)H NMR spectrum of the decomposition product of compound 2, \(\delta\) (ppm; CD\(_3\)CN): 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\(_3\)CN solution of \([\text{Rh}_2(\mu-O_2CCCH_3)_2(bpy)_2(\text{CH}_3\text{CN})_2][\text{BF}_4]_2\) (1) (0.11 mmol) was slowly added to a MeOH solution of excess \(\text{C}_6\text{H}_5\text{SH}\) (1.1 mmol) under \(\text{N}_2\), during which time the solution color changed from orange-brown to dark red. The solution was stirred at \(\text{rt}\) for 6 h, concentrated to dryness, and recrystallized from MeOH/ Et\(_2\text{O}\) to yield dark red crystalline plates. Yield before recrystallization = 70 mg (percent yield = 65).

\(^{(7)}\) Crystal data for \([\text{Rh}(\mu-\text{C}_6\text{H}_5\text{S})(\text{C}_6\text{H}_5\text{S})(\text{bpy})_2]\text{CH}_3\text{OH}\) (2) at 110(2) K: \(\text{C}_{64}\text{H}_{44}\text{N}_4\text{O}_9\text{Rh}_2\text{S}_3\text{W}\) = 985.86, dark red platelet, 0.303 \(\times\) 0.252 \(\times\) 0.193 \(\text{mm}^3\), \(\varepsilon_{2\text{E}}\); \(\alpha = 20.398(4)\) \(\AA\), \(\beta = 11.861(2)\) \(\AA\), \(\gamma = 17.417(4)\) \(\AA\), \(V = 3984.6(14)\) \(\text{Å}^3\), \(Z = 4\), \(\rho_{\text{calc}} = 1.625\). Mo \(\text{K\alpha}\) radiation (\(\lambda = 0.71069\) \(\text{Å}\)), \(\mu = 1.079\) 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 < \(\theta < 26.5\)°. A total of 8966 reflections were collected, of which 4331 were unique and 1890 were in the range \(F^2\geq 4\sigma(F^2)\). The frames were used to refine 251 parameters to \(R = 0.0756(0.1424)\), \(GOF = 0.980, F^2\) refinement in SHEXLTL-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.


the dinuclear and mononuclear Rh III cations [Rh₂III/III (respectively. 5 In this earlier study we proposed that the evidence, namely, the oxidatively unstable intermediate of reaction scheme by providing a previously missing piece of information. Specifically, the oxidatively unstable intermediate of the reaction scheme is a thiolato-bridged dirhodium core to Rh III compounds and release of disulfide upon exposure to O₂ (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, and the concomitant formation of the disulfide byproduct C₆H₂S₂, which is not 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. The current results are important for our general understanding of the fate of anticancer active dirhodium bis-polypyrrole 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. Preliminary characterization of the blue solids by elemental analyses and IR spectroscopy indicates that the products with cysteine and glutathione also contain thiolate ligands bound to a dirhodium core.

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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 available free of charge via the Internet at http://pubs.acs.org.


(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. Electronic absorption, λ (nm; CH₃OH): 408.5 (s). ¹H NMR, δ (ppm; CD-OD): 6.2–7.6 (m), 7.2–8.5 (m). Anal. Calcd for C₅₆H₅₀B₂F₈N₈O₁₆S₄Rh₂: C, 34.07; H, 4.68; N, 10.84. Found: C, 33.92; H, 4.68; N, 10.78.

(12) Electrochemistry was performed with an HCH Instruments electroanalyser employing a standard three-electrode cell (Pt working, Pt wire auxiliary, and Ag/AgCl reference electrodes). The supporting electrolyte is [NBun4][PF₆]. The Cp₂Fe[Cp₂Fe]⁺ couple occurs at +0.34 V vs Ag/AgCl under the same conditions.


(15) The transition stepwise reaction to form 2 involves binding of RS⁻ to [Rh₂(μ-O₂CCH₃)₂(N-N)₂L₂]⁺ through the axial positions to yield [Rh₂(μ-O₂CCH₃)₂(N-N)₂L₂(X)²]⁴⁺, followed by rearrangement to bridging sites with displacement of the bridging acetate ligands. Precedence for the formation of an axial adduct of Rh₄(μ-O₂CCH₃)₄ 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 O₂ and was characterized by single-crystral 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 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 C₃₂H₂₅B₂F₈N₄O₂Rh₂S₂: 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 C₆₀H₄₀B₂F₄N₄O₂Rh₂S₂: C, 34.07; H, 4.68; N, 10.84. Found: C, 34.63; H, 4.84; N, 10.77.