

Electrochemical and Chemical Oxidation of Gold(I) Thiolate Phosphine Complexes: Formation of Gold Clusters and Disulfide

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The biological activity of gold–sulfur complexes is well established and has led to the development of highly effective antiarthritis drugs, as well as complexes that show antitumor activity and inhibition of the HIV virus.¹ However, the targets and mechanisms of action of gold complexes remain elusive. Since rheumatoid arthritis has an oxidative pathology,^{2–4} we have been studying the oxidative reactivity and electronic structure of complexes of the form $\text{LAu}(\text{SC}_6\text{H}_4\text{CH}_3)$ and $\text{LL}[\text{Au}(\text{SC}_6\text{H}_4\text{CH}_3)]_2$, where L and LL are mono- and bisphosphines.^{5–14} These complexes are related to the antiarthritis drug, Auranofin, which contains gold(I) coordinated to triethylphosphine and tetracetylthioglucose. The study reported below demonstrates that mild oxidation of gold–sulfur complexes produces gold clusters and disulfide by way of an electron-transfer mechanism that occurs with unexpected n values. These results suggest an oxidative reactivity for gold–sulfur centers that has not been previously recognized.

The results of cyclic voltammetry experiments for $\text{LAu}(\text{SC}_6\text{H}_4\text{CH}_3)$ and $\text{LL}[\text{Au}(\text{SC}_6\text{H}_4\text{CH}_3)]_2$ [L = PPh_3 ; LL = dppe, dppp, dppb, dpppn] show two irreversible anodic processes at $+0.8 \pm 0.1$ V and $+1.6 \pm 0.1$ V (vs SCE).^{9,15} Constant potential electrolysis experiments on $\text{Ph}_3\text{PAu}(\text{SC}_6\text{H}_4\text{CH}_3)$ show n values of 0.5 and >2 for the first and second oxidations, respectively. Similarly, n values obtained for the dinuclear complexes, $\text{LL}[\text{Au}(\text{SC}_6\text{H}_4\text{CH}_3)]_2$, are approximately 1 and >4 for the first and

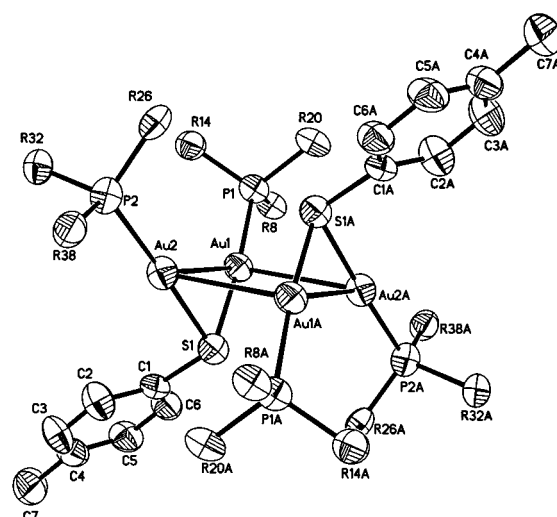


Figure 1. ORTEP drawing of the cationic portion of $[(\text{PPh}_3)_4\text{Au}_4(\mu\text{-SC}_6\text{H}_4\text{CH}_3)_2](\text{PF}_6)_2$ (**1**) (50% probability ellipsoids). For clarity, only the ipso-carbons of the phenyl rings (designated R) are shown. Selected distances (Å) and angles (deg): Au(1)–P(1), 2.275(2); Au(1)–S(1), 2.342(2); Au(1)–Au(2), 3.152(1); Au(1)–Au(2A), 3.173(1); P(1)–Au(1)–S(1), 174.59(5).

second oxidations, respectively. The nonintegral n value of 0.5 for the first oxidation of $\text{Ph}_3\text{PAu}(\text{SC}_6\text{H}_4\text{CH}_3)$ is unexpected insofar as complete oxidation of a single type of redox center, i.e., phosphine, gold, or thiolate, would lead to an n value of 1 or greater. The same logic suggests that an n value of 1.0 for the dinuclear complexes, $\text{LL}[\text{Au}(\text{SC}_6\text{H}_4\text{CH}_3)]_2$, is half of the expected value. These results suggest that a chemical reaction occurs following the first oxidation.

Monitoring the first oxidation for $\text{Ph}_3\text{PAu}(\text{SC}_6\text{H}_4\text{CH}_3)$ by ^1H NMR during constant potential electrolysis experiments¹⁶ reveals that disulfide, $(\text{SC}_6\text{H}_4\text{CH}_3)_2$, forms in significant quantities.¹⁷ Chemical titration experiments on $\text{Ph}_3\text{PAu}(\text{SC}_6\text{H}_4\text{CH}_3)$ using the mild oxidant, $(\text{Cp}_2\text{Fe})\text{PF}_6$,¹⁸ also confirms the nonintegral n values and the formation of significant quantities of disulfide. Chemical oxidation afforded the opportunity to isolate the products of the first oxidation process. Reaction of 0.5 mmol of $\text{Ph}_3\text{PAu}(\text{SC}_6\text{H}_4\text{CH}_3)$ and 0.25 mmol of $(\text{Cp}_2\text{Fe})\text{PF}_6$ in CH_2Cl_2 resulted in formation of $[(\text{Ph}_3\text{P})_4\text{Au}_4(\mu\text{-SC}_6\text{H}_4\text{CH}_3)_2](\text{PF}_6)_2$ (**1**), $(\text{SC}_6\text{H}_4\text{CH}_3)_2$, and Cp_2Fe .¹⁹ X-ray quality crystals of **1** were obtained from a $\text{CH}_2\text{Cl}_2/\text{Et}_2\text{O}$ solution.²⁰ Figure 1 shows the ORTEP drawing of **1**, which can be thought of as consisting of two monocationic $\text{Au}_2(\text{PPh}_3)_2(\mu\text{-SC}_6\text{H}_4\text{CH}_3)^+$ units that dimerize via Au(I)–Au(I) interactions to form a tetranuclear cluster. The four Au atoms form a square with angles about Au(1) and Au(2) near 90° (Au(2)–Au(1)–Au(2A) = 87.5° , Au(1)–Au(2)–Au(1A) = 92.5°). The structure is similar to that of $[\text{Au}_2(\text{PPh}_3)_2(\mu\text{-SCH}_2\text{Ph})_2](\text{NO}_3)_2$ reported by Wang and Fackler.²¹ The structural patterns and

(16) Conditions for electrolysis: Pt mesh electrode, +1.0 V, saturated KPF₆/CD₃CN.

(17) Bromine oxidation of a related complex containing a propanedithiol ligand, $\text{LLAu}_2(\text{pdt})$, also leads to formation of disulfide and $\text{LL}(\text{AuBr})_2$. See ref 9.

(18) The oxidation potential for $\text{Cp}_2\text{Fe}^{\text{O}+}$ in $[\text{Bu}_4\text{N}][\text{PF}_6]/\text{CH}_2\text{Cl}_2$ is +0.46 V vs SCE. See: Connelly, N. G.; Geiger, W. E. *Chem. Rev.* **1996**, *96*, 877–910.

(19) The disulfide, $(\text{SC}_6\text{H}_4\text{CH}_3)_2$, forms in 48% yield based on starting gold complex and was characterized by comparison of its ^1H NMR spectrum with an authentic sample (Aldrich). ^1H NMR (CDCl_3 , ppm): δ 7.37 (d); 7.09 (d); 2.31 (s).

(20) X-ray data (293 K): colorless needles of **1** from $\text{CH}_2\text{Cl}_2/\text{Et}_2\text{O}$, orthorhombic ($Pbca$), $a = 18.6416(2)$ Å, $\alpha = 90^\circ$, $b = 18.8457(4)$ Å, $\beta = 90^\circ$, $c = 24.1510(4)$ Å, $\gamma = 90^\circ$, $V = 8484.6(2)$ Å³, $Z = 4$, $R = 0.0365$, GOF = 0.804.

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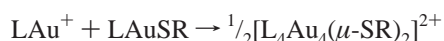
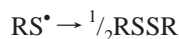
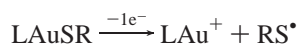
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(15) The gold(I) complexes were prepared as described in ref 13. dppe = diphenylphosphinoethane, dppp = diphenylphosphinopropane, dppb = diphenylphosphinobutane, dpppn = diphenylphosphinopentane.

bonding in digold(organo)sulfonium salts have been discussed previously.^{21–25}

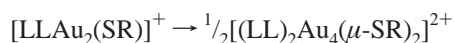
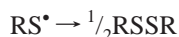
A sequence of reactions producing the stoichiometry that is consistent with the observed nonintegral n value of 0.5 for the mononuclear gold(I) complex is illustrated in Scheme 1. One-electron oxidation of $\text{Ph}_3\text{PAu}(\text{SC}_6\text{H}_4\text{CH}_3)$ results in homolytic cleavage of the Au–S bond and formation of Ph_3PAu^+ and thiyl radical, $\cdot\text{SC}_6\text{H}_4\text{CH}_3$, which rapidly dimerizes to produce disulfide.²⁶ Previous studies on the electronic structure of gold(I) thiolate phosphine complexes have assigned the HOMO orbitals of these complexes as having significant sulfur character.^{10,13,14} The cation, Ph_3PAu^+ , reacts with a molecule of the starting mononuclear gold(I) complex to form a digold complex with thiolates bridging two gold(I) centers, which then dimerizes via Au–Au bonds to form the observed tetragold cluster. The last step in the mechanism is supported by an independent synthesis of the tetragold cluster. Thus, treatment of $\text{Ph}_3\text{PAu}(\text{SC}_6\text{H}_4\text{CH}_3)$ with Ph_3PAu^+ yields $[(\text{PPh}_3)_4\text{Au}_4(\mu\text{-SC}_6\text{H}_4\text{CH}_3)_2]^{2+}$.

Scheme 1 (L = Ph_3P , R = $\text{C}_6\text{H}_4\text{CH}_3$)



Oxidation of the dinuclear complex, $\text{dppe}[\text{Au}(\text{SC}_6\text{H}_4\text{CH}_3)_2]$ (0.4 mmol), with $(\text{Cp}_2\text{Fe})\text{PF}_6$ (0.4 mmol) resulted in formation of $[(\text{dppe})_2\text{Au}_4(\mu\text{-SC}_6\text{H}_4\text{CH}_3)_2](\text{PF}_6)_2$ (**2**), $(\text{SC}_6\text{H}_4\text{CH}_3)_2$, and Cp_2Fe . X-ray quality crystals of **2** were obtained from a $\text{CH}_2\text{Cl}_2/\text{Et}_2\text{O}$ solution.²⁷ Figure 2 shows the ORTEP drawing of **2**, which can be thought of as consisting of two monocationic $\text{dppeAu}_2(\mu\text{-SC}_6\text{H}_4\text{CH}_3)^+$ units which dimerize to form a tetranuclear cluster. The Au_4S_2 core adopts a chair configuration with a gold single bond between $\text{Au}(1)\text{--Au}(2) = 2.961(1)$ Å and a sulfur-bridged nonbonded $\text{Au}\cdots\text{Au}$ interaction of 3.844 Å. A consistent sequence of reactions producing the stoichiometry and observed n values of 1.0 for oxidation of the dinuclear gold complexes is illustrated in Scheme 2.

Scheme 2 (LL = dppe, R = $\text{C}_6\text{H}_4\text{CH}_3$)



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(27) X-ray data (270 K): colorless striated plates of **2**·2H₂O from $\text{CH}_2\text{Cl}_2\text{-Et}_2\text{O}$, monoclinic ($P2_1/c$), $a = 14.0845(3)$ Å, $\alpha = 90^\circ$, $b = 13.2873(2)$ Å, $\beta = 97.516(1)^\circ$, $c = 19.6109(3)$ Å, $\gamma = 90^\circ$, $V = 3638.55(11)$ Å³, $Z = 2$, $R = 0.0530$, GOF = 1.002.

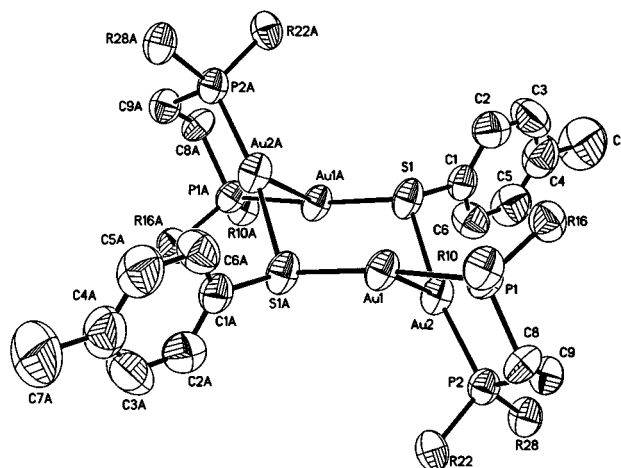


Figure 2. ORTEP drawing of the cationic portion of $[(\text{dppe})_2\text{Au}_4(\mu\text{-SC}_6\text{H}_4\text{CH}_3)_2](\text{PF}_6)_2$ (**2**) (50% probability ellipsoids). For clarity, only the ipso-carbons of the phenyl rings (designated R) are shown. Selected distances (Å) and angles (deg): Au(1)–P(1), 2.274(2); Au(1)–S(1A), 2.328(3); Au(1)–Au(2), 2.961(1); P(1)–Au(1)–S(1A), 173.88(9).

Further support for Schemes 1 and 2 is provided by comparison of the electrochemistry of the neutral vs cluster complexes. According to the schemes, one-electron oxidation of $\text{PPh}_3\text{Au}(\text{SC}_6\text{H}_4\text{CH}_3)$ and $\text{dppe}[\text{Au}(\text{SC}_6\text{H}_4\text{CH}_3)_2]$ converts the complexes to gold clusters and disulfide. Assuming the chemical reactions after one-electron oxidation (+0.8 V) are fast, cyclic voltammograms of $\text{PPh}_3\text{Au}(\text{SC}_6\text{H}_4\text{CH}_3)$ and $\text{dppe}[\text{Au}(\text{SC}_6\text{H}_4\text{CH}_3)_2]$ should contain the appropriate gold cluster and disulfide, in the potential region $> +0.8$ V. Additionally, if one-electron oxidation of $\text{PPh}_3\text{Au}(\text{SC}_6\text{H}_4\text{CH}_3)$ and $\text{dppe}[\text{Au}(\text{SC}_6\text{H}_4\text{CH}_3)_2]$ results in oxidation of terminal thiolates, these redox processes may be absent in **1** and **2**, since the clusters contain only bridging thiolates. Cyclic voltammetry experiments show that the *first* oxidation of $\text{PPh}_3\text{Au}(\text{SC}_6\text{H}_4\text{CH}_3)$ and $\text{dppe}[\text{Au}(\text{SC}_6\text{H}_4\text{CH}_3)_2]$ at +0.8 V is, indeed, absent in **1** and **2**. Furthermore, bulk electrolysis experiments on **1** at +1.0 V show $n \approx 0$. Cyclic voltammetry experiments also show that **1**, **2**, and $(\text{SC}_6\text{H}_4\text{CH}_3)_2$ all oxidize at +1.6 V, approximately the same potential as the *second* oxidation of $\text{PPh}_3\text{Au}(\text{SC}_6\text{H}_4\text{CH}_3)$ and $\text{dppe}[\text{Au}(\text{SC}_6\text{H}_4\text{CH}_3)_2]$.

The oxidative reactivity of gold–sulfur complexes suggests some intriguing possibilities for the biochemistry of gold. For example, oxidation of gold complexes bound to cysteine-rich proteins may lead to formation of disulfide bonds that would cause substantial changes in reaction chemistry. Recently, we reported that the oxidative reactivity of Auranofin is similar to that of $\text{Ph}_3\text{PAuSC}_6\text{H}_4\text{CH}_3$.¹² Preliminary experiments in our laboratory suggest that mild oxidation of Auranofin also results in formation of disulfide and a gold cluster.²⁸

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Supporting Information Available: Experimental details for the chemical titration experiments, syntheses, cyclic voltammograms, spectroscopic data (PDF). X-ray crystallographic files, in CIF format, are also available for **1** and **2**. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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