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Redox studies on the anti-rheumatoid arthritis gold drugs: auranofin and solganol

Ahmed A. Mohamed

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REDOX STUDIES ON THE 
ANTI-RHEUMATOID ARTHRITIS GOLD DRUGS: 
AURANOFIN AND SOLGANOL

By

Ahmed A. Mohamed

M.Sc., Zagazig University, Egypt, 1993

A THESIS

Submitted in Partial Fulfillment of the
Requirements for the Degree of
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(in Chemistry)

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December, 2000

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REDOX STUDIES ON THE ANTI-RHEUMATOID ARTHRITIS GOLD

DRUGS: AURANOFIN AND SOLGANOL

By Ahmed A. Mohamed

Thesis Co-Advisors: Dr. Alice E. Bruce
Dr. Mitchell R. M. Bruce

An Abstract of the Thesis Presented
in Partial Fulfillment of the Requirements for the
Degree of Doctor of Philosophy
(in Chemistry)
December, 2000

The oxidative behavior of Auranofin, 2,3,4,6-tetra-O-acetyl-L-thio-β-D-glucopyranosato-S(triethylphosphine)gold(I), was investigated by using cyclic voltammetry (CV) in 0.1 M Bu4NBF4/CH2Cl2 and 0.1 M Bu4NPF6/CH2Cl2 solutions using Pt working and auxiliary electrodes and a Ag/AgCl reference. CV studies at scan rates from 50-2,000 mVs⁻¹ and Auranofin concentrations between 1 and 4 mM, show two irreversible oxidation processes occurring at +1.1 V and +1.6 V vs. Ag/AgCl.

Treatment of Auranofin with the one electron oxidizing agent [Cp2Fe]PF6 gave a μ-thiolato digold cluster, [(Et3PAu)2(μ-SR)]2⁺ and the disulfide, bis(tetraacetlythioglucose). A mechanism for Auranofin oxidation is proposed on the basis of chemical and electrochemical studies. The p-thiolato species is also obtained by treatment of Auranofin with Et3PAuNO3 in CH3CN or addition of methanolic silver nitrate to an equimolar mixture of Auranofin and Et3PAuCl followed by product
isolation. The X-ray structure is reported for the Auranofin analogue,
\([\text{Au}(\text{PMe}_3)_2(\text{thioglucose})_2]\)(\text{NO}_3)_2. The structure of the cluster confirms the coordination of two \(\text{Me}_3\text{PAu}^+\) to a bridging thiolato moiety and the two-thiolates are on opposite sides and trans to each other. The gold-gold distances are \(\text{Au}_1\text{-Au}_2=3.106(7), \text{Au}_1\text{-Au}_\Lambda=3.171(11),\) and \(\text{Au}_2\text{-Au}_\Lambda=3.144(12)\text{Å}\.\)

The cyclic voltammetry of Solganol, aurothioglucose, was investigated in 0.5 M \(\text{NaClO}_4/\text{H}_2\text{O}\) solutions using a three-electrode system consisting of a platinum working electrode, a platinum-wire auxiliary electrode, and a silver-silver chloride reference electrode. A broad peak obtained at +1.2 V, which affected by scan rate and pH changes. Multiple CV scans of Solganol showed an enhancement in current due to a possible filming on the electrode surface. Bulk electrolysis of Solganol showed \(n=2\). Chemical oxidation using \([\text{Cp}_2\text{Fe}]\text{PF}_6\) showed no change in the NMR peaks and there was no change in the color of the mixture. Based on bulk electrolysis, resistance to chemical oxidation, and pH studies, the peak at +1.2 V vs Ag/AgCl was assigned as \(\text{Au}^{\text{IIIi}}\)\).

A series of binuclear Au(I) halide and thiolate complexes \((\text{AuX})_2\text{dppbz}\) \((X=\text{Cl, Br, I, } \rho-\text{SC}_6\text{H}_4\text{CH}_3)\) were synthesized. All of the newly synthesized complexes gave satisfactory elemental analysis and characterized by \(^1\text{H}\) and \(^{31}\text{P}\) NMR. The complex \((\text{AuCl})_2\text{dppbz}\) crystallized in the orthorhombic space group Pbca with \(a=16.955(3), \) \(b=18.160(2), \) \(c=22.225(1)\text{Å}, \) \(\alpha=\beta=\gamma=90^\circ, Z=8\) (at 293 K). The Au…Au bond length of 2.99Å, is in the range of gold-gold interaction distance.
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CHAPTER 1

Introduction

Oxidation States of Gold

Gold can be found in several oxidation states; 0, I, and III are the most common but complexes containing gold in the –I, II, IV, V states are known. Gold coordination chemistry is dominated by the oxidation states I and III. Gold(I), with the electron configuration of \([\text{Xe}]^4 4f^4 5d^{10}\), usually forms linear compounds with sp hybridization at gold; however trigonal planar (sp\(^2\) hybridization) and tetrahedral (sp\(^3\) hybridization) coordination geometries are known. The first example of a tetrahedral gold(I) center characterized by X-ray crystallography, is the bis chelated diphosphine complex \([\text{Au(dppe)}_2]^{2+}\), where dppe is \(1,2\)-bis(diphenylphosphino)ethane.\(^1\)

Gold(I) is a soft metal ion and therefore has a preference for soft donor atoms, such as sulfur, over hard ligands such as nitrogen and oxygen. Compounds of gold(III), with electron configuration of \([\text{Xe}]^4 4f^4 5d^6\), i.e. isoelectronic with platinum(II), are square planar with four donor atoms. Gold(III) is a hard metal ion and favors hard donor atoms such as nitrogen and oxygen more than gold(I).\(^1\)

In the absence of stabilizing ligands gold(I) disproportionates to gold(0) and gold(III), a powerful oxidizing agent. It is this property which precludes the use of gold(III) as a useful pharmaceutical in the reducing mammalian environment. Ligands
that stabilize gold(I) include cyanide, phosphines, arsines and a range of sulfur-containing ligands (sulfides and thiols for example).”’

**History of Gold in Medicine**

Gold is an ancient metal with a long medical history. The biological benefits attributed to gold in history may surpass its monetary attraction. Gold has been used in a variety of forms as a medicine by ancient civilizations. In medieval Europe alchemists had a variety of prescriptions known as aurum potabile, which contained small amounts of gold. In the 17th century, a gold cordial was used for the treatment of ailments, such as fever which was believed to be caused by a decrease in the vital spirit. A mixture of gold chloride and sodium chloride, Na[AuCl₄] was used in the 19th century to treat syphilis. Gold cyanide, K[Au(CN)₂], discovered by the German bacteriologist Robert Koch in the twentieth century, was used as a bacteriostatic toward the tubercle bacillus. Gold therapy for tuberculosis was subsequently introduced in the 1920s. The suggestion that the tubercle bacillus was the causative agent for rheumatoid arthritis led to the use of gold therapy for this disease, which led the Empire Rheumatism Council in 1960 to confirm the effectiveness of gold compounds against rheumatoid arthritis.³,⁴

**Gold(I) Drugs in the Treatment of Rheumatoid Arthritis, Cancer, and AIDS**

Rheumatoid arthritis is a chronic inflammatory disease characterized by erosion of peripheral joints. It is a systemic autoimmune disorder of unknown etiology.³ The early gold drugs used for treatment of rheumatoid arthritis, for almost six decades, were
water-soluble gold(I) thiolate complexes such as Myochrysine and Solganol. These drugs are administered by deep intramuscular injection at weekly intervals. They provide considerable pain relief, decrease joint inflammation, and more importantly, restore joint function. Improvement in the disease is not expected for at least four months after beginning a course of injections. During treatment with Myochrysine, gold was found in much higher concentrations in the red blood cells of smokers than in the same cells in non-smokers. The reason is that hydrogen cyanide is inhaled by smokers and forms the very stable complex, gold cyanide which allows the gold to be taken up and bound to red cells. Serious side effects were noticed such as nephrotoxicity, mouth ulcers, skin reactions, and blood disorders. The high toxicity and serious side effects led to the search for a drug with reduced toxicity and higher pharmacological activity.

In 1985, Auranofin (Figure 1.1) was reported to be orally effective in human rheumatoid arthritis conditions. The advantages of oral Auranofin over injectable drugs include lower gold levels in blood and kidney and less toxicity. That the anti-arthritic action of Auranofin is due to gold is proven by the fact that the non-gold-containing substructures of Auranofin administered to rats have no effect. The orally active Auranofin drug is slightly less effective than the injectable drugs but causes fewer serious side effects.

There is no unique mechanism of action for antiarthritic gold drugs due to the lack of understanding of rheumatoid arthritis. From a practical point of view, the main advantage of understanding the mechanism of action would be to improve the therapeutic to toxic ratio of gold drugs.
Figure 1.1. Structure of gold(I) drugs used as anti-rheumatoid arthritis.
Gold compounds such as the tetrahedral complex $[\text{Au(dppe)}_2]\text{Cl}$ have also shown promising medical activity as antitumor drugs. The proposed mechanism of action was the formation of DNA-protein cross-links. Although this compound had remarkable activity against cancer cells; it was not entered for clinical trials due to problems with cardiotoxicity during toxicology studies.$^4$

The demonstration of antitumor activity of $[\text{Au(dppe)}_2]\text{Cl}$ encouraged wider studies on other gold complexes (Figure 1.2). $[\text{AuCl}_2(\text{damp})]$, damp = dimethylaminomethylphenyl (Figure 1.2) has been evaluated for human tumor cells.$^{1b}$ Initial studies indicated that this new drug demonstrated modest antitumor activity, seen as a reduction in tumor growth, against breast cancer. An evaluation of the antitumor activity of Auranofin showed that it was active against some tumor models $\text{in vivo}$ but ineffective against solid tumors.$^{1b}$

The design and testing of gold complexes for antitumor activity over the past several decades has been based on three rationales$^{6-9}$: (1) analogies between square planar complexes of Pt(II) and Au(III), both of which are $d^8$ ions; (2) analogy to the immunomodulatory effects of gold(I) antiarthritic agents; (3) complexation of gold(I) and gold(III) with known antitumor agents to form new compounds with enhanced activity. The discovery that Auranofin had activity against HeLa cells $\text{in vitro}$ and P388 leukemia cells $\text{in vivo}$ led to the screening of many Auranofin analogues.$^7$

The retrovirus, which causes AIDS, is human immunodeficiency virus (“HIV”). HIV is part of a group of slow viruses, which cause diseases that develop extremely slowly. A powerful means to attack the AIDS virus would be to find a specific inhibitor
Au(damp)X₂ (X = Cl−, OAc−, etc.)

damp = dimethylaminomethylphenyl

dppe(AuCl)₂  [Au(dppe)₂]⁺

dppe = bis(diphenylphosphino)ethane

Figure 1.2. Structure of gold(I) complexes used as anticancer.
for the replication process of the HIV virus. Gold cyanide, \([\text{Au(CN)}_2^-]\), is found at varying levels in patients treated with common antiarthritis drugs. The observation that infected cells incubated with gold cyanide showed rapid uptake of gold suggested the possibility that gold cyanide might be useful in the treatment of AIDS. \(^9\) Gold cyanide can readily enter cells and attack the replication process of the retrovirus in an infected host. Interestingly, only 20 ppb of gold cyanide were required to inhibit the replication of HIV in vitro. \(^10\)

The chemistry of gold is intriguing in its history, which is one of the most interesting and colorful stories in chemistry. There is little wonder that gold easily occupied an honored place when it was considered for therapeutic purposes.

Many questions remain to be answered in gold chemistry: How are gold drugs distributed in the body's organs? How does gold produce its toxic effects? What effects do gold drugs have on the immune system? The search for the answer for these questions is challenging in studying gold drugs.

**X-ray Structure of Gold(I) Drugs**

The X-ray crystallography of Auranofin shows a monomer with a near linear \(\text{S-Au-P}\) linkage (173.6°) and virtually identical \(\text{S-Au (2.29 Å)}\) and \(\text{Au-P (2.26 Å)}\) bond lengths (Table 1.1 and Figure 1.3). \(^11\) The glucopyranose ring is not planar but exists in the chair conformation. The gold side chain is oriented markedly toward the ring oxygen suggesting some type of attraction (Figure 1.3), perhaps Van der Waals nature, between gold and oxygen atom.
After many decades of effort, the Myochrysine analogue [CsNa₂HAu₂(STm)₂]ₙ, Figure 1.4, has been crystallized and its structure determined by X-ray crystallography. Using vapor phase deposition, Bau was able to isolate tiny colorless crystals in the form of thin square tiles or, more commonly, stubby needles in about two weeks. The crystals were allowed to grow slowly over a 2 months period to a size adequate for X-ray collection. The structure is polymeric with two interpenetrating spirals. Helices of opposite handiness occur in equal numbers: the right-handed helices contain exclusively S-thiomalate. The bridging Au-S bond distances are 2.28 and 2.26 Å. Table 1.1 shows the bond lengths (Å) and angles (°) of Auranofin, Myochrysine, and related structures. 

**Table 1.1.** Bond lengths (Å) and Angles (°) of Auranofin, Myochrysine, and related structures.

<table>
<thead>
<tr>
<th>Compound</th>
<th>dₘₐₜₜ</th>
<th>&lt;S-Au-S/P</th>
<th>dₘₜₜₜ</th>
<th>&lt;Au-S-Au</th>
<th>Ref</th>
</tr>
</thead>
<tbody>
<tr>
<td>Myochrysine</td>
<td>2.28</td>
<td>170, 179</td>
<td>3.23,</td>
<td>99</td>
<td>12</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>3.48</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Auₙ(STm)ₘ</td>
<td>2.30</td>
<td></td>
<td>3.35</td>
<td>94</td>
<td>13</td>
</tr>
<tr>
<td>[Au(SR)]ₙ</td>
<td>2.29</td>
<td>176</td>
<td>3.56</td>
<td>102</td>
<td>14</td>
</tr>
<tr>
<td>Auranofin</td>
<td>2.29(S)</td>
<td>174</td>
<td></td>
<td></td>
<td>15</td>
</tr>
<tr>
<td></td>
<td>2.26(P)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

R = C₆H₃Pr₃, Tm = Thiomalate.
Figure 1.3. X-ray structure of Auranofin.\textsuperscript{15}
Figure 1.4. X-ray structure of Myochrysine analogue.\textsuperscript{12}
Bioinorganic Pharmacology of Gold Drugs

A considerable body of evidence suggests that in vivo gold exists primarily as gold(I).\textsuperscript{13,14,15} Gold drugs exposed to body fluids and proteins react predominantly by ligand exchange reactions that preserve the gold(I) oxidation state.\textsuperscript{13,14} Aurosomes (lysosomes that accumulate large amounts of gold and undergo morphological changes) from gold-treated rats contain predominantly gold(I), even when gold(III) has been administered.\textsuperscript{15} Thiols and thioethers, including cysteine and methionine residues in proteins and peptides, are capable of reducing gold(III) to gold(I) (Figure 1.5).\textsuperscript{16,17} Even disulfide bonds react rapidly to reduce gold(III).\textsuperscript{16} Thus, it appears that the bulk of gold present in vivo is likely to be gold(I). Nonetheless, the potential for oxidizing gold(I) to gold(III) in vivo has long been recognized.\textsuperscript{14,16}

![Diagram](image)

**Figure 1.5.** Biological Redox Cycling of gold(I) and gold(III).\textsuperscript{4,16}

The high affinity of gold(I) for sulfur and selenium ligands suggests that proteins, including enzymes and transport proteins, will be critical in vivo targets. In addition, it is
clear that extracellular gold in the blood is primarily protein bound, suggesting protein-mediated transport of gold during therapy.\textsuperscript{16,17}

Serum albumin, the principal extracellular protein of blood, binds between 80% and 95% of the gold in serum and functions as a defacto transport agent. Thirty-four of its 35 cysteine residues are present as 17 disulfide bonds. Auranofin reacts with the \textit{a} cys-34 in albumin via a ligand exchange reaction that displaces the sulfhydryl groups (Figure 1.6) to form AlbSAuPEt3. The same product is obtained if Et3PAuCl reacts with albumin.\textsuperscript{18,19,20} The product showed \textsuperscript{31}P NMR peak at 38.8 ppm (Table 1.2).

\[
\text{Albumin-S} + \text{Auranofin} \rightarrow \text{Albumin-S-Au-PEt}_3 + \text{TATG}
\]

\[
\text{Et}_3\text{P} + \text{H}_2\text{O} \rightarrow \text{Et}_3\text{PO} + \text{HS-CH}_2\text{ Albumin} \rightarrow \text{HS-CH}_2\text{ Albumin} + \text{Et}_3\text{PO}
\]

\textbf{Figure 1.6.} Reactions of serum albumin with Auranofin in buffered aqueous solutions at pH values near physiological pH.\textsuperscript{19}

The free acetylthioglucose liberated from Auranofin reacts further with the cysteine-34 disulfide bonds to liberate cysteine and also displaces the Et\textsubscript{3}P ligand, leading to its oxidation (Figure 1.6).\textsuperscript{20} Under conditions approximating those in vivo, complex formation is first-order in Auranofin and has a rate constant of 2.9 ± 0.2 s\textsuperscript{-1}, which
indicates that Auranofin will have a short lifetime after entering the bloodstream where albumin is present in large excess.

Sadler and colleagues reported a conformational change in albumin that accompanies gold binding to cys-34. The rate of gold binding may correspond either to the rate of opening of the cys-34 crevice to solvent molecules or to the rate of the conformational change that accommodates gold binding.

Hemoglobin reacts with Et$_3$PAu$^+$ taken up by red cells exposed in vitro to Et$_3$PAuCl although it may not be a significant red cell binding site at the lower concentrations that prevail during clinical use of Auranofin. $^{31}$P NMR evidence is consistent with the formation of S-Au-P coordination by displacement of chloride at the hemoglobin cysteine $\beta$93 residues, which are on the surface of the $\beta$ subunits. $^{31}$

**Table 1.2. $^{31}$P NMR of Gold-Protein Complexes.**

<table>
<thead>
<tr>
<th>Complex</th>
<th>$^{31}$P NMR</th>
<th>Ref</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alb-S-(AuPEt3)</td>
<td>38.8</td>
<td>23,24</td>
</tr>
<tr>
<td>Alb-N$<em>{his}$-$(AuPEt_3)</em>{0.78}$</td>
<td>27-28</td>
<td>24</td>
</tr>
<tr>
<td>Alb-S-(AuPEt3)$_2$</td>
<td>36.5</td>
<td>24</td>
</tr>
<tr>
<td>Hb-(SAuPEt3)$_1$</td>
<td>34.0</td>
<td>25</td>
</tr>
</tbody>
</table>

Previous studies have demonstrated that Auranofin can undergo facile thiol-exchange reactions with biological ligands. In acidic medium, like the stomach, the reactivity of the thiolate ligand of Auranofin can be enhanced. $^{21}$ Auranofin reacts with
HCl in aqueous solution and in 50% methanol/water to form chloro(triethylphosphine)gold(I) and the product reacts with Auranofin to form a thiolate-bridged dinuclear gold complex with two gold triethylphosphine moieties bound to a single thioglucose ligand (Figure 1.7). The thermodynamics and kinetics of these reactions have been studied in water and in 50% methanol/water. The equilibrium constants for the formation of Et₃PAuCl are $4.6 \times 10^{-4}$ M⁻¹ in water and $2.0 \times 10^{-3}$ M⁻¹ in 50% methanol/water. The equilibrium constant for the formation of the thiolate-bridged digold complex is $1.2 \times 10^3$ (water), $1.3 \times 10^2$ (50% methanol/water), and $0.7 \times 10^2$ (95% methanol). The kinetics for the formation of the thiolate-bridged digold complex is too rapid to be observed by ordinary mixing techniques.

**Figure 1.7.** Reaction of Auranofin with HCl in water or 50% methanol/water.²⁶
Previous Redox Studies of Gold(I) Drugs

Hypochlorus acid (HOCl), which is generated by the enzyme myeloperoxidase during the oxidative burst at inflammed sites, can oxidize the gold in Myochrysine to gold(III) in vitro.\textsuperscript{27,28} This finding has been extended to additional gold compounds. For example, gold(I) thiolates including Auranofin are oxidized to Au(III) with preliminary or concomitant oxidation of the ligands.\textsuperscript{27}

\[
\text{Et}_3\text{PAuSAtg} + 5 \text{OCI}^- + 2\text{H}^+ \rightarrow \text{AuCl}_4^- + \text{AtgSO}_3^- + \text{Et}_3\text{PO} + \text{H}_2\text{O} + \text{Cl}^- \quad 1.1
\]

\[
\frac{1}{n}[\text{AuSR}]_n + 4 \text{OCI}^- + 2\text{H}^+ \rightarrow \text{AuCl}_4^- + \text{RSO}_3^- + \text{H}_2\text{O} \quad 1.2
\]

The dc and differential pulse polarography studies of Auranofin by Perez and coworkers at a dropping mercury electrode, establishes that Auranofin undergoes a diffusion controlled and reversible reductive redox process at \(-0.5\) V \textit{vs.} SCE at pH greater than 9.5.\textsuperscript{29} Bulk electrolysis at \(-0.8\) V yields an \(n\) value of 1 indicative that reduction involves the \(\text{Au}^{10}\) couple. Below a pH of about 8.5, a proton dependent pathway occurs. Protonation of triethylphosphine \((pK_a = 8.69)\) is believed to be responsible for the shift in potential as a function of pH. A linear relationship between the limiting current and Auranofin concentration was also noted in the concentration range 3.63 \(x\) \(10^{-5}\) to 5.1 \(x\) \(10^{-4}\) M.\textsuperscript{29}

The reducing properties of antiarthritic drugs such as Auranofin, Solganol, and Myochrysine were investigated by Huck and coworkers.\textsuperscript{30} The standard redox potentials of drugs which instantly react with the oxidant, 5,5'-dithiobis-(2-nitrobenzoic acid), were
determined by titration with potassium hexacyanoferrate(III) in a 0.1 M phosphate buffer (pH 7.0, 25°C), at a dropping mercury electrode using a SCE reference. Unfortunately, none of the gold-containing compounds reacted very quickly with the oxidant and the standard potentials could not be measured directly even after long incubation periods in phosphate buffer at 37°C.30

**Photophysical Studies of Gold(I) Drugs**

The study of the excited state of gold drugs could also lead to significant advances in the understanding of the mechanism of Au(I) drugs in the body which are used for the treatment of rheumatoid arthritis.31 According to Corey and Khan, several gold drugs have been shown to quench singlet oxygen, ¹O₂ (Table 1.3). They propose that it is by this action that gold compounds are capable of aiding in the treatment of the disease which appears to be oxygen related.31

Emission from singlet oxygen occurs at 7752 cm⁻¹.32 The molecule is converted to its lower lying triplet state. The quenching of singlet oxygen is thought to occur by energy transfer to species with electronic or vibrational states that are energetically compatible or by the interaction of singlet oxygen with heavy atoms that have large spin orbit coupling. The proposals for the action of gold drugs in the quenching mechanism of ¹O₂ have led our group and others to study the photophysical properties of gold(I) complexes.33,34
Auranofin is luminescent in the solid state and in EtOH glasses at 77K ($\lambda_{\text{max}} = 618$ nm). Auranofin is also photoreactive ($\lambda_{\text{max}} = 254$ nm) in acetonitrile, undergoing photodecomposition that appears not to include production of elemental gold.

**Table 1.3.** Rate constants for the quenching of $^{1}$O$_2$ by various agents.

<table>
<thead>
<tr>
<th>Quencher</th>
<th>$K_q$ (M$^{-1}$ sec$^{-1}$)</th>
<th>Method A</th>
<th>Method B</th>
</tr>
</thead>
<tbody>
<tr>
<td>Auranofin</td>
<td>$0.75 \times 10^7$</td>
<td></td>
<td>$0.2 \times 10^7$</td>
</tr>
<tr>
<td>Et$_3$PAuSCH$_3$</td>
<td>$4.5 \times 10^7$</td>
<td>$3.7 \times 10^7$</td>
<td></td>
</tr>
<tr>
<td>$\beta$-Carotene</td>
<td>$1.1 \times 10^{10}$</td>
<td>$1.5 \times 10^{10}$</td>
<td></td>
</tr>
</tbody>
</table>

dimethylnaphthalene-1,4-endoperoxide at 30°C. Method B: solvent, benzene; $^{1}$O$_2$ generated by self-sensitized photooxidation of rubrene at 30°C.

**Electrochemistry Overview**

Over the past couple of decades potential sweep techniques, such as cyclic voltammetry, have been applied to an ever-interesting range of systems, and at the same time the mathematical description of these techniques have been developed sufficiently to enable kinetic parameters to be determined for a wide variety of mechanisms.

**Reversible Systems.** A simple reversible reaction can be described by Equation 1.6 and O is the only species present in solution. As soon as a potential where O is reduced is reached the surface concentration of O decreases from its bulk value in order to satisfy
the Nernst equation and a concentration gradient is set up (Figure 1.8). The surface concentration of O is further decreased until it effectively reaches zero. Reversible cyclic voltammogram can only be observed if both O and R are stable and the kinetics of the electron transfer process are fast.\textsuperscript{35}

$$\text{O} + n \text{e}^- = \text{R} \quad 1.6$$

Diagnostic tests for cyclic voltammograms of reversible processes are as follows:\textsuperscript{35}

1. $\Delta E_p = E_p^A - E_p^C = 59/n \text{mV}$
2. $E_p - E_{p/2} = 59/n \text{mV}$
3. $I_A/I_p^C = 1$
4. $I \propto v^{1/2}$ (v is scan rate)
5. $E_p$ is independent of v

---

**Irreversible Systems.** The most marked feature of a cyclic voltammogram of a totally irreversible system is the total absence of a reverse peak. Whereas for the reversible case the value of $E_p^C$ is independent of the sweep rate, $v$, for the irreversible case $E_p^C$ is found to vary with the sweep rate (Figure 1.9). It can be seen in Figure 1.9 that increasing the scan rate increases the peak separation and the peak height is slightly reduced from that for a reversible system.\textsuperscript{35}
Diagnostic tests for cyclic voltammograms of an irreversible processes are as follows:\textsuperscript{35}

1. No reverse peak
2. $I' \propto \sqrt{v}$ (v is scan rate)
3. $E_p - E_{p/2} = 48/\alpha_c n \alpha \text{ mV}$
4. $E_p^C$ shifts $-30/\alpha_c n \alpha \text{ mV}$ for each decade increase in v

**Quasi-reversible Systems.** It is quite common for a process that is reversible at low sweep rates to become irreversible at higher ones after having passed through a region known as quasi-reversible at intermediate values (Figure 1.10). This transition from reversibility occurs when the relative rate of the electron transfer with respect to that of mass transport is insufficient to maintain Nernestian equilibrium at the electrode surface.

Diagnostic tests for cyclic voltammograms of quasi-reversible processes are as follows:\textsuperscript{35}

1. $\Delta E_p$ is greater than $59/\Omega \text{ mV}$ and increase with increasing v
2. $I_p^{A}/I_p^{C} = 1$ provided $\alpha_c = \alpha_A = 0.5$
3. $I_0$ increases with $\sqrt{v}$ but not proportional to it
4. $E_p^{C}$ shifts negatively with increasing v

**As** a general conclusion, the extent of irreversibility increases with increase in sweep rate, while at the same time there is a decrease in the peak current relative to the reversible case and an increasing separation between anodic and cathodic peaks.
Figure 1.8. Cyclic voltammogram for a reversible process, $\text{O} + e^* = \text{R}$. (a) $\nu$, (b) $10\nu$, (c) $50\nu$, and (d) $100\nu$.\(^{35}\)
Figure 1.9. Cyclic voltammogram for an irreversible process, \(\text{O} + e^- = \text{R}\).

Potential sweep rates (a) 0.13 \(\text{Vs}^{-1}\), (b) 1.3 \(\text{Vs}^{-1}\), (c) 4 \(\text{Vs}^{-1}\), (d) 13 \(\text{Vs}^{-1}\).
Figure 1.10. Transition from a reversible to an irreversible system on increasing scan rate.
Goals of This Work

Little is known concerning the redox behavior of the anti-rheumatoid arthritis gold thiolate drugs. Hoping to contribute to understanding the possible sources of toxic and therapeutic causes of gold drugs, we conducted chemical and electrochemical redox studies on Auranofin and Solganol. An understanding of the oxidative properties of gold drugs is important in light of the proposed toxic side effects of Au(III) in vivo. In a broad sense, the goals of this thesis stem from the poor understanding of the fate of gold thiolate drugs in the oxidizing biological environment.

Our group has been studying the electronic structure and thermal, electronic, and photochemical reactivity of d^{10} gold(I) complexes, especially those containing phosphine and thiolate ligands.^{36,37} Recently our group studied the chemical oxidation of gold thiolates using [Cp_{2}Fe]PF_{6} in methylene chloride.^{36} Chemical titration experiments on Ph_{3}PAu(SC_{6}H_{4}CH_{3}) using the mild oxidant, [Cp_{2}Fe]PF_{6} confirms the formation of significant quantities of disulfide, (SC_{6}H_{4}CH_{3})_{2}. Chemical oxidation afforded the opportunity to isolate the products of the first oxidation process. Reaction of 0.5 mmol of Ph_{3}PAu(SC_{6}H_{4}CH_{3}) and 0.25 mmol of [Cp_{2}Fe]PF_{6} in CH_{2}Cl_{2} resulted in formation of [(Ph_{3}P)_{4}Au_{4}(_{2}SC_{6}H_{4}CH_{3})_{2}]PF_{6}, (SC_{6}H_{4}CH_{3})_{2}, and Cp_{2}Fe.^{36} Similar oxidation studies have been carried out on dinuclear gold thiolates. Disulfide and tetranuclear gold clusters were isolated.^{36,37}

My first project involved the electrochemical oxidation and bulk electrolysis studies of Auranofin in 0.1 M Bu_{4}NPF_{6}/CH_{2}Cl_{2} and 0.1 M Bu_{4}NBF_{4}/CH_{2}Cl_{2} solutions.
using Pt working and auxiliary electrodes and a Ag/AgCl reference. Results are discussed in chapter 2.

My next project involved treatment of Auranofin with the one electron oxidizing agent, \([\text{Cp}_2\text{Fe}]\text{PF}_6\). The oxidation resulted in a \(\mu\)-thiolato digold cluster \([\text{Et}_3\text{PAu}]_2(\mu\text{-SR})_2^{2+}\) and the disulfide, \(\text{bis(tetraacetylthioglucose)}\). The \(\mu\)-thiolato species was obtained several by independent procedures involving the treatment of Auranofin with \(\text{Et}_3\text{PAuNO}_3\) in \(\text{CH}_3\text{CN}\) or \(\text{CH}_2\text{Cl}_2\) or addition of methanolic silver nitrate to an equimolar mixture of Auranofin and \(\text{Et}_3\text{PAuCl}\). The cluster was characterized using \(^1\text{H} \text{NMR}, ~^{31}\text{P} \text{NMR}, \text{mass spectroscopy, and elemental analysis. Disulfide exchange reactions of the tetragold cluster with \(\text{bis(tetraacetylthioglucose)}, \text{(SC}_6\text{H}_4\text{Cl)}_2, \text{(SC}_6\text{H}_4\text{CH}_3)_2, \text{and glutathione disulfide were studied. I tried growing x-ray quality crystals of the cluster by varying the counter anion from PF}_6^{-} \text{to NO}_3^{-}, \text{BF}_4^{-}, \text{CF}_3\text{SO}_3^{-}, \text{Sn(Ph)}_2(\text{NO}_3)_3^{-}. The results of these trials are presented in chapter 3. Successful trial to grow X-ray quality crystals was acheived by changing the triethylphosphine group to trimethylphosphine. X-ray structure of the tetragold(I) cluster is discussed in chapter 3.}

The electrochemical and chemical oxidation of the polymeric gold(I) thiolate drug Solganol will provide the literature with a broad understanding of the oxidative behavior or the source of toxicity of monomeric (Auranofin) versus polymeric (Solganol) gold drugs.
The last project involves the synthesis, characterization, and investigation of the photophysical behavior of a new class of halo and thiolato gold(I) complexes of the formula \((\text{AuX})_2\text{dppbz}, X = \text{Cl, Br, I, } p-\text{SC}_6\text{H}_5\text{CH}_3\).

Hopefully my thesis will stimulate further studies in the biochemistry of gold drugs.
References


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CHAPTER 2

Electrochemical Oxidation of Auranofin: An Anti-arthritic Gold (I)-Sulfur Drug

Introduction

The medicinal effects of gold drugs have been extensively investigated during the last two decades. However, a recent review of the electrochemical literature shows that the redox data for biologically important gold and silver complexes is generally still lacking. This is especially significant for gold drugs, where the redox reactivity, especially oxidation, has been invoked in partial explanation of both therapeutic and toxic side effects.

Auranofin

Auranofin, (2,3,4,6-tetra-O-acetyl- l-thio-β-D-glucopyranosato-S)(triethylphosphine)gold(I), is a water insoluble phosphine gold thiolate complex that is
used as an orally active anti-arthritic drug in both experimental animals and man. Reductive polarography of Auranofin has been previously reported. Auranofin has been investigated by a variety of techniques. X-ray crystallography shows that Auranofin is monomeric with a nearly linear S-Au-P linkage (173.6’) and virtually identical Au-S (2.29 Å) and Au-P (2.26 Å) bond lengths. The triethylphosphine group appears to stabilize the gold-thiol moiety. The ¹⁹⁷Au Mossbauer for Auranofin shows relatively high parameters (IS = 3.55 mm/sec, QS = 8.64 mm/sec, relative to gold) compared to Myocrisin and Solganol, intrinsic to the Au-P bond. Auranofin is luminescent in the solid state and in EtOH glasses at 77K (λmax = 618 nm). Auranofin is also photoreactive (λmax = 254 nm) in acetonitrile, undergoing photodecomposition that appears not to include production of elemental gold. The dc and differential pulse polarography studies of Auranofin by Perez and coworkers at a dropping mercury electrode, establishes that Auranofin undergoes a diffusion controlled and reversible redox process at −0.5 V (vs. SCE) at pH greater than 9.5. Bulk electrolysis at −0.8 V leads to an n value of 0.9 electrons per molecule and suggests that the reduction involves the AuI/O couple.

Oxidation of Auranofin with hypochlorite, a strong oxidant released by phagocytic cells, has also been studied by Shaw and coworkers. Sulfonate and Et₃PO formed first followed by oxidation of Au(I) to Au(III).

The electrochemistry of a series of neutral phosphine gold(I) thiolate complexes has been investigated in our laboratory. The series includes cyclic dinuclear gold(I) complexes formed from 1,2-propanedithiolate (pdt) and bis-chelating phosphines, Au₂(LL)(pdt) (LL= dppe and dpppn), open dinuclear gold(I) complexes formed from
para-thiocresolate (p-tc) and bis-chelating phosphines, \( \text{Au}_2(\text{LL})(\text{p-tc})_2 \) (\( \text{LL}= \text{ddpe}, \text{dppp}, \text{dppb}, \text{dpppn} \)), and a mononuclear complex, \( \text{Au}(\text{PPh}_3)(\text{p-tc}) \). Oxidative cyclic voltammetry experiments were performed at Pt and glassy carbon electrodes in 0.1 M \( \text{Bu}_4\text{NPF}_6/\text{CH}_3\text{CN} \) and \( \text{CH}_2\text{Cl}_2 \) solutions. Adsorption effects occurred in all electrode/solvent combinations investigated and were minimized by wiping the electrode between each CV experiment. The position and wave shape of the oxidation processes were somewhat dependent on the electrode/solvent combination.

Our goal is to report oxidative cyclic voltammetry and bulk electrolysis studies of Auranofin.

**Experimental Section**

**Reagents.** Methylene chloride and the supporting electrolytes, tetra-N-butylammonium hexafluorophosphate (\( \text{Bu}_4\text{NPF}_6 \)) and tetra-N-butylammonium tetrafluoroborate (\( \text{Bu}_4\text{NBF}_4 \)) were used as received (Aldrich). Auranofin was purchased from Pfanstiehl Laboratories, Inc., IL. \( \text{PPh}_3\text{Au-p-tc} \) was prepared according to previously published methods.\(^5\)

**Abbreviations.** The following abbreviations are used: p-tc = p-thiocresol, pdt = propane dithiolate, dppe = bis(diphenylphosphine) ethane, rev = reversible, irr = irreversible.
**Figure 2.1.** Cell for cyclic voltammetry experiments.

**Cyclic Voltammetry (CV) Experiments.** CV experiments were conducted using an EG&G Princeton Applied Research 273 potentiostat/galvanostat under computer control. CV measurements were performed in methylene chloride with 0.1 M Bu₄NPF₆ or 0.1 Bu₄NBF₄ as supporting electrolyte. Fresh solutions containing electrolyte (10 ml) were prepared prior to each CV experiment. Each solution was deoxygenated by purging with nitrogen for 2-5 minutes. Background CV’s were acquired before the addition of gold complex. A three-electrode system was used, comprised of a platinum (1.6 mm diameter) working electrode, a platinum wire or paddle auxiliary electrode, and a silver/silver chloride (Ag/AgCl) reference electrode (Figure 2.1). The working electrode was wiped prior to each experiment. The auxiliary electrode was lightly sanded before each set of experiments with fine sand paper. Potentials are reported vs. Ag/AgCl at room
temperature and are not corrected for junction potentials. Each CV experiment was repeated a number of times.

**Bulk Electrolysis Experiments.** Bulk electrolysis experiments were performed using an EG&G Princeton Applied Research 273 potentiostat/galvanostat in CH$_2$Cl$_2$/0.1 M Bu$_4$NBF$_4$ solutions. The electrolytic cell divided into three compartments with a fine porosity glass frit between the compartments (Figure 2.2). The main compartment contained a cylindrical platinum mesh working electrode and Teflon stir bar centered within the platinum mesh. The other two compartments contain the platinum counter electrode and the silver-silver chloride reference electrode.

The electrolytic cell was assembled after oven drying at 110$^0$C. A CH$_2$Cl$_2$/0.1 M Bu$_4$NBF$_4$ solution was introduced into the cell, stirred, and degassed with nitrogen for 10 minutes. Auranofin was added (10 to 20 mg) and the solution was stirred and degassed for 10 minutes.

The total number of electron equivalencies (n) passed was calculated by assuming that the background current constant during the electrolysis experiment. The total number of coulombs (Q = I x time) was subtracted from the total number of coulombs passed during the experiment (Q$_{total}$):

\[ N = \frac{(Q_{total} - Q_{background})}{(F)(Mol)} \]

\[ F = \text{Faraday constant.} \]

\[ \text{Mol} = \text{number of added Auranofin moles.} \]
Figure 2.2. Cell for bulk electrolysis experiments
Results

Cyclic Voltammetry Experiments. The results of cyclic voltammetry experiments on Auranofin are shown in Figure 2.3. Figure 2.3 a-b are the current-voltage responses for 1 mM Auranofin in 0.1 M Bu₄NBF₄/CH₂Cl₂ solutions at scan rates of (a) 50 mV/s and (b) 500 mV/s, respectively. In each CV, there are two anodic processes. In Figure 2.3a they occur at about +1.1 V (vs. Ag/AgCl) and +1.6 V, while in Figure 2.3b, they occur at somewhat higher potentials. The two redox processes were found to be irreversible at all scan rates, concentrations, and switching potentials (e.g. +1.2 V) investigated. Both processes appear characteristic of an EC mechanism, with the following reaction being quite fast. CV experiments with ferrocene, a reversible one-electron redox couple, at 50 mV/s and 500 mV/s show a potential shift of similar magnitude as seen for Auranofin (Figure 2.3a-b). This result suggests that the shift originates from the electrochemical cell used, such as from cell resistance (iR drop), and not from kinetic effects of a following reaction.

Figure 2.4a-c shows the effect of change of concentration as well as of electrolyte. The current-voltage response for 1 mM Auranofin in 0.1 M Bu₄NPF₆/CH₂Cl₂ solution at scan rates of 50 mV/s is shown in Figure 2.4a. This CV is the result of the same experimental procedure used to generate the CV for Figure 2.3a, except for a change of electrolyte (Bu₄NPF₆ vs. Bu₄NBF₄). At first glance, the CV wave-shapes of Figure 2.4a vs. 2.3a appear significantly different. However, close inspection of Figure 2.3a shows similar anodic processes to 2.3a, i.e. one starting at about +1.0 V as well as
Figure 2.3A. Cyclic voltammogram of 1 M ammonium using Pt working and auxiliary electrodes and \( \text{AF/AgI} \) reference in 0.1 M Bu4NBF4/CH3Cl2 at 50 mV/s.
Figure 2.3b. Cyclic voltammogram of 1 mM Auranofin using Pt working and auxiliary electrodes and Ag/AgCl reference in 0.1 M Bu₄NBF₄/CH₂Cl₂ at 500 mV/s.
Reference in 0.1 M Bu₄NPF₆/CH₂Cl₂ at 50 mV/s:
(a) 1 mM, (b) 2 mM, (c) 4 mM.

Figure 2.4. Cyclic Voltammogram of Au nanostructures using Pt working and auxiliary electrodes and Ag/AgCl.

Voltage vs. Ag/AgCl (V)

Current (μA)
one at +1.65 V. What is also apparent is the great diminution of the current response of Figure 2.4a compared to Figure 2.3a. It has been previously demonstrated that the CV wave-shapes for phosphine gold thiolate complexes are sensitive to the type of electrode as well as to solvent owing to the effects of adsorption at the electrode.\(^6\) Repeated CV cycling of Auranofin also leads to filming of the electrode, indicative of adsorption at the electrode. Presumably, the filming process is affected during oxidation by the rate at which oxidized (positively charged) complexes are removed from the surface of the electrode. It is therefore not unexpected that changing the anion (PF\(_6^-\) vs. BF\(_4^-\)) would also effect the wave-shape. The data suggests that the PF\(_6^-\) anion is not as efficient as BF\(_4^-\) in keeping the electrode clear of oxidation products, leading to an increase in filming rate and thus leading to a great reduction in the current response. The effect of increasing concentration of Auranofin from 1 mM, 2 mM, and 4 mM is seen in Figures 2.4a, 2.4b, and 2.4c, respectively. The increase in the current response of both oxidation processes demonstrates that the observed electrochemistry originates from the analyte and not the solvent or electrolyte. Cyclic voltammetry experiments were also performed on Ph\(_3\)PAu(p-thiocresolate) under similar conditions used for Auranofin (0.1 M Bu\(_4\)NBF\(_4/\)CH\(_2\)Cl\(_2\) solutions at scan rates of 50 mV/s) (Figure 2.5). The results allow comparison to other electrochemical investigations reported for phosphine gold thiolate complexes.\(^6\) The electrochemistry of gold(I) complexes with pyridine-2-thiolate was investigated by Laguna and coworkers.\(^{6c}\) The gold(I) cationic complexes [Au\(_2(dppm)(2\)-pyS)]\(^+\) and [Au\(_2(dppe)(2\)-pyS)]\(^+\) undergo irreversible oxidations at +1.42 V and +1.46 V vs. SCE, respectively, during cyclic voltammetry experiments at a Pt disk
Figure 2.5. Cyclic Voltammogram of 1 mM Ph₃PAu(p-thiocresolate) using Pt working and auxiliary electrodes and Ag/AgCl reference in 0.1 M Bu₄NBF₄/CH₂Cl₂ at 50 mV/s.
working electrode recorded at 200 mVs⁻¹ in 0.1 M Bu₄NPF₆/CH₂Cl₂ solution.⁶c

**Bulk Electrolysis Experiments.** Bulk electrolysis of Auranofin at +1.2 V vs. Ag/AgCl in 0.1 M Bu₄NBF₄/CH₂Cl₂ showed that the first oxidation is 0.5 electron process (data based on 9 runs; 0.44, 0.65, 0.25, 0.6, 0.54, 0.54, 0.49, 0.38, and 0.61). The data supports the irreversible oxidation at +1.1 V is due to a fast chemical reaction, which is the oxidation of thiolate to the corresponding disulfide and rapid rearrangement of the gold product to a cluster. Bulk electrolysis results on Auranofin at +1.6 V showed the process is consistently >2 electrons. Completion of electrolysis experiments after the first oxidation was checked by CV experiments. The first oxidation wave disappears completely in the cyclic voltammogram of electrolysis product solution, while the last oxidation remains almost the same as for the initial Auranofin cyclic voltammogram. Figure 2.6 is an example of bulk electrolysis curve obtained during the experiment.

**Discussion**

This work reports oxidative cyclic voltammetry studies on Auranofin in a non-aqueous solvent (CH₂Cl₂). There are two oxidation processes that occur at +1.1 V and +1.6 V. Both appear to be irreversible at all scan rates investigated (50-2,000 mV/s). Table 2.1 shows the results of CV studies on Auranofin and related phosphine gold thiolate complexes.⁷ All of the complexes show two irreversible oxidation processes that are separated by 400-800 mV. The first oxidation process for the PPh₃ and dppe complexes have been assigned as a sulfur based oxidation.⁶a,b
in 0.1 M Bu₄NBF₄/CH₂Cl₂

Figure 2.6: Bulk electrolysis plot of current (mA) vs. time (s) for activation at +1.2 V vs. Ag/AgCl

Time (s)

Current (mA)

0 0.5 1.0 1.5 2.0 2.5 3.0 3.5 4.0 4.5 5.0

0 1000 2000 3000 4000 5000 6000
### Table 2.1. Cyclic Voltammetry Data for Auranofin and Related Complexes.

<table>
<thead>
<tr>
<th>Complex</th>
<th>Oxidation</th>
<th>Reduction</th>
<th>Solvent</th>
<th>Ref. Elec.</th>
<th>Ref</th>
</tr>
</thead>
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<tr>
<td>Auranofin</td>
<td>+1.1 (irr)</td>
<td></td>
<td>CH₂Cl₂</td>
<td>Ag/AgCl</td>
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<tr>
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<td>Ag/AgCl</td>
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<td>b</td>
</tr>
<tr>
<td></td>
<td>+1.50 (irr)</td>
<td></td>
<td>CH₂Cl₂</td>
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</tr>
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<td>SCE</td>
<td>6a</td>
</tr>
<tr>
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<td>SCE</td>
<td>6a</td>
</tr>
<tr>
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<td></td>
<td>CH₂Cl₂</td>
<td>SCE</td>
<td>6a</td>
</tr>
<tr>
<td>Me₃PAu(p-tc)</td>
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<td></td>
<td>CH₃CN</td>
<td>Ag/AgCl</td>
<td>6b</td>
</tr>
<tr>
<td></td>
<td>+1.55 (irr)</td>
<td></td>
<td>CH₃CN</td>
<td>Ag/AgCl</td>
<td>6b</td>
</tr>
</tbody>
</table>

a. CV experiment at 1 mM Auranofin and 50 mVs⁻¹ using 0.1 M Bu₄NBF₄ solution. b. This work.

b. Reversible at pH > 9; assigned to the Au⁺⁺ couple. d. Pt wire working electrode and 0.1 M TBAH solution; scan rate of 50 mVs⁻¹.
Recent results from our laboratory on binuclear as well as on mononuclear phosphine gold thiolate complexes indicate that after an initial one-electron sulfur-based oxidation, the gold complex rapidly undergoes rearrangement to form a gold cluster and disulfide.\(^1\) This suggests the possibility that one-electron oxidation of Auranofin may provide a pathway to higher molecular weight gold complexes as well as a mechanism to increase disulfide concentration. Characterization of the one electron oxidation products will be discussed in chapter 3.
References

1. Mohamed, A.; Bruce, A. E.; Bruce, M. R. M. Metal-Based Drugs, 1999, 6, 233


10. Conversion of SCE to Ag/AgCl reference electrodes can be approximated by adding +0.045 V.

CHAPTER 3

The Formation of a Gold(I) Cluster and Disulfide

From Oxidation of the Antiarthritic Gold Drug: Auranofin

Introduction

Gold compounds have been successfully used in the treatment of rheumatoid arthritis (RA) for over half a century. The antitumor activity of gold compounds in several tumor models such as P388 leukemia was also investigated. Recently a few gold compounds showed high potency in the treatment of AIDS. Auranofin (‘Ridura’ from Smith Kline and French Laboratories) is one of the orally active groups of the slow-acting anti-arthritic gold drugs, and is used mainly to delay progression of the arthritis and prevent or reduce subsequent damage to the joints.

Despite its extensive clinical investigation, the mechanism by which Auranofin, 2,3,4,6-tetra-O-acetyl-1-thio-β-D-glucopyranosato-S)(triethylphosphine)gold(I), inhibits rheumatoid inflammation and alters disease pathophysiology is poorly understood. This is mainly due to a lack of understanding of the etiology of the arthritis disease. Previous studies on the interaction of gold drugs with albumin, a thiol containing protein, identified cysteine-34 as the preferred binding site of gold(I). Free triisopropylphosphine oxide was obtained from triisopropylphosphine (2,3,4,6-tetra-O-acetyl-1-thio-β-D-glucopyranosato-S)gold(I), an Auranofin
analogue, in the reaction with serum albumin via a protein-bound phosphonium intermediate.\textsuperscript{6}

\begin{center}
\includegraphics[width=0.5\textwidth]{figure3.png}
\end{center}

\textbf{Figure 3.1.} Structure of Auranofin showing numbering scheme for ring protons.

Auranofin, (Et\textsubscript{3}P)Au(TATG), TATG = Tetraacetylthioglucose, is monomeric, lipid soluble, and nonconductive.\textsuperscript{1} The X-ray structure shows that gold(I) is equidistant between thiolate (Au-S = 2.29 Å) and phosphine (2.26 Å) ligands and the S-Au-P linkage is nearly linear (173.6 °).\textsuperscript{7} The Et\textsubscript{3}P unit plays a role in stabilizing the gold-thiolate moiety.\textsuperscript{7} The \textsuperscript{197}Au Mossbauer spectroscopy has been used successfully to determine oxidation state, type of ligand, and degree of coordination of anti-arthritic gold drugs.\textsuperscript{2} The IS and QS values of Auranofin (3.55 and 8.64 mm s\textsuperscript{-1}) are closer to the characteristic values for bis(triethylphosphine) gold (3.06 and 8.93 mm s\textsuperscript{-1}) than those for the polymeric gold thiolate drugs (1.40 and 6.2 mm s\textsuperscript{-1}).\textsuperscript{8}

Studying the redox behavior of gold(I) thiolate drugs emerged as an effective approach in understanding their pharmaceutical effects in rheumatoid arthritis.\textsuperscript{5,9,10} Oxidizing conditions \textit{in vivo} are believed to play a role in the therapeutic effect of the anti-rheumatoid drugs.\textsuperscript{5,9,10} In plasma the thioglucose moiety undergoes exchange with
other thiolates and the triethylphosphine ligand releases to form the very stable Et$_3$PO.$^5$
Sadler et al. reported on the formation of Et$_3$PO from Auranofin in the presence of albumin.' Colloidal gold and gold(I), in the presence of oxygen and penicillamine, undergo a redox reaction of importance in cryotherapists models.$^1$ Chemical oxidation of Auranofin by hypochlorite, a strong oxidant released by phagocytic cells, has been studied by Shaw et al.$^{10}$ Sulfonate and the very stable Et$_3$PO formed first followed by oxidation of gold(I) to gold(III).$^{10}$ Biooxidation of metals other than gold(I) is known such as Hg(0) oxidation to Hg(II) in vivo.$^{12}$

A recent review of the electrochemistry of gold and silver complexes shows that studies of the redox behavior of gold compounds related to medicinal effects are still lacking.$^{13}$ The electrochemical reduction of Auranofin in C$_2$H$_5$OH/H$_2$O reported at $-0.5$ V vs. SCE, involves one electron reduction, i.e., Au.$^{10}$ The oxidation of Auranofin in 0.1 M Bu$_4$NBF$_4$/CH$_2$Cl$_2$ solution was reported recently. There are two irreversible processes at 1.1 and 1.6 V vs. Ag/AgCl (Chapter 2).$^{15}$ Hemple et al. studied the effect of aqueous HCl on Auranofin, (Et$_3$P)Au(TATG), TATG = Tetraacetylthiglucose, to mimic its behavior in stomach acid.$^{16}$ The ionic [(Et$_3$PAu)$_2$(TATG)]Cl was proposed as one of the products; however, trials to isolate the ionic structure resulted only in (Et$_3$P)Au(TATG) and Et$_3$PAuCl.$^{16}$ The formation of the ionic complex, [(Et$_3$PAu)$_2$(TATG)]Cl, involves two reversible steps; the first step involves formation of Et$_3$PAuCl with the stability constant, $K_1 = 4.6 \times 10^4$ M$^{-1}$ and the second step involves formation of the ionic digold complex with the stability constant, $K_2 = 2.0 \times 10^3$ M$^{-1}$.
water at 37°C while $K_1 = 7.8 \times 10^{-3} \text{ M}^{-1}$ and $K_2 = 1.3 \times 10^2 \text{ M}^{-1}$ in 50% methanol/water.\textsuperscript{16}

A thorough examination of Chemical Abstracts showed many trials to detect disulfide as a possible product from the redox reactions of gold(I) thiolate drugs.\textsuperscript{10,17,18,19} Formation of disulfide along with gold(0) from Solganol, (aurothioglucose) in aqueous medium was proposed by Shaw.\textsuperscript{11,17} Reglinński et al. studied the disulfide produced from Myochrysine (aurothiomalate) as a source of oxidative stress in arthritic patients.\textsuperscript{11,12}

Chemical and electrochemical results from our lab indicated formation of a gold(I) cluster and disulfide upon oxidation of phosphine gold(I) thiolates in non-aqueous medium.\textsuperscript{9} The irreversible electrochemical oxidation processes of Auranofin imply a possible chemical change upon oxidation, i.e., an EC mechanism.\textsuperscript{15} We decided to investigate the possible redox activity at the thiolate center using the well-known one-electron oxidizing agent, $[\text{Cp}_2\text{Fe}]\text{PF}_6$, which has an oxidation potential comparable to the thiolate center in Auranofin.\textsuperscript{20} The results of the oxidative study on the thiolate center in Auranofin, which are presented in this chapter, may help to understand the possible sources of toxic and therapeutic effects.

**Experimental Section**

**Materials.** All solvents are reagent grade and used without purification. Auranofin was purchased from Pfanstiehl, IL. HAuCl$_4$ is a gift from Johnson Matthey. Et$_3$PAuCl was a gift from Dr. David T. Hill, Temple University. AgNO$_3$, CF$_3$SO$_3$Ag, AgPF$_6$, and AgBF$_4$ were purchased from Aldrich. Oxidized glutathione for disulfide exchange experiments
was purchased from Sigma. Solvents for NMR studies, CDCl₃, D₂O, and DMSO were purchased from Aldrich. [Cp₂Fe]PF₆ for chemical oxidation was purchased from Aldrich and was finely grounded before use.

**3¹P NMR Measurements.** The ³¹P{¹H}NMR resonances were recorded at 81 MHz using a Gemini 300 spectrometer. The ³¹P NMR chemical shifts were referenced to an external sample of 85% H₃PO₄.

**¹H NMR Measurements.** The 'H NMR resonances were recorded at 81 MHz using a Gemini 300 spectrometer. Chemical shifts were measured relative to the solvent resonance at room temperature. About 10 mg of the desired complex was dissolved in CDCl₃ and spectra were recorded directly. In the chemical oxidation studies a downfield shift for the triethylphosphine ligand was noticed with some overlapping with the resonances for the tetraacetyl groups on the thioglucose ligand. Thus this upfield (aliphatic) region is not very informative. Data will be reported for the downfield region only, which corresponds to H1-H6 of the thioglucose ligand.

**Electrochemical Experiments.** All electrochemical measurements were undertaken at room temperature using an EG & G Princeton Applied Research 273 potentiostat/galvanostat under computer control. Measurements were carried using the same procedure as described in chapter 2 and Figure 2.1.

**ESI FT-ICR Mass Spectrometry.** Mass spectroscopy studies have been carried out by Dr. Touradj Souloki, Department of Chemistry, University of Maine. The ESI FT-ICR mass spectra were acquired with an IonSpec FT-ICR mass spectrometer equipped with a 7 T superconducting magnet (IonSpec Corp., Irvin, CA) and IonSpec99 software. A
stock solution of Auranofin or its cluster was prepared by dissolving 1 mg of the sample in 50:50 methanol: water solution (1 mg/ml, −0.5% acetic acid).

**Oxidation of Auranofin by [Cp₂Fe]PF₆ (one electron oxidation):** To 500 mg (0.73 mmol) of Auranofin dissolved in 100 ml CH₂Cl₂ under nitrogen was added 122 mg (0.36 mmol) of [Cp₂Fe]PF₆ (1:0.5). Stirring continued for 24 hr until the blue color of ferrocenium disappeared and a yellow color of ferrocene formed. The solvent was evaporated *in vacuo* and the residue was washed with ether (3X) to remove Cp₂Fe. The remaining off-white solid was recrystallized by dissolving in a small amount of CH₂Cl₂ (3 ml), followed by addition of ether or hexane.

**Independent Synthesis of the Digold µ-thiolato, [(R₃PAu)₂(TATG)]X (R = Et, Me; X = PF₆⁻, NO₂⁻, CF₃SO₃⁻, BF₄⁻).** 1 mmol of AgX was dissolved in 10 ml CH₃CN or C₂H₅OH and was added slowly to 1 mmol of Et₃PAuCl or Me₃PAuCl dissolved in 10 ml CH₂Cl₂ at 0°C. Stirring of the mixture at 0°C for 30 min continued in the dark and AgCl was then filtered on celite. The filtrate was reduced to 3 ml *in vacuo* and ether was added to form a white precipitate of Et₃PAuX which was filtered and washed with ether. To 1 mmol of (Et₃P)Au(TATG) or (Me₃P)Au(TATG) dissolved in 10 ml CH₂Cl₂ was added 1 mmol of Et₃PAuX or Me₃PAuX, respectively, dissolved in 10 ml CH₂Cl₂ and the mixture was stirred for 30 min at 0°C. The mixture was reduced to 5 ml *in vacuo* and ether was added to give an off-white precipitate. The sample was recrystallized by diffusion of ether into methylene chloride and dried over P₂O₅ *in vacuo* for 24 hrs.

Elemental analysis calculated for [(Et₃PAu)₂(TATG)]NO₃, C 29.57, H 4.64, Found, C 29.14, H 4.60. \(^1\)H NMR (300 MHz; CDCl₃) 1.2 (18H, dt, PCH₂CH₃), 1.85-2.1 (24, m, 4
OAc + 6 PCH₂CH₃), 4.0 (2H, m, H5), 4.25-4.30 (2H, dd, H6), 5.0-5.15 (2H, m, H2-H4), 5.50 (1H, d, H1); ³¹P {¹H} NMR (300 MHz, CDCl₃) 36.5 ppm. Elemental analysis calculated for [(Me₃PAu)₂(TATG)]NO₃.ether: C 26.17; H 4.16. Found, C 26.13; H 4.01.

¹H NMR (300 MHz; CDCl₃), 1.2 (18H, d, PCH₃), 2.0-2.1 (12, 4s, 4 OAc), 3.9 (2H, m, H5), 4.20-4.25 (2H, dd, H6), 5.0-5.2 (3H, m, H2-H4), 5.35 (1H, d, H1); ³¹P {¹H} NMR (300 MHz, CDCl₃) -0.17 ppm.

**Synthesis of Bis(tetraacetyltiohexose).** 0.5 ml of I₂ (0.93 M in acetonitrile) was added to 1.00 ml of HSATg (0.41 M in acetonitrile). After stirring for two minutes, the deep brown solution was titrated with 0.2 ml of double distilled water to a light yellow color, stirred for 10 min and then poured into 80 ml of cold aqueous KI solution (1.0 M). The solution was filtered and the precipitate was washed with water and dried.²¹

**Trials to Grow X-ray Quality Crystals.** The procedures involved in growing X-ray quality crystals of digold µ-thiolato cluster obtained by oxidation of Auranofin were meticulous and time consuming. Patience and persistence were the keys to success!. A variety of different solvent combinations, such as ether-methylene chloride, hexanes-methylene chloride, ether-chloroform, and cyclohexane-ethyl acetate (was used to obtain crystals of Auranofin) was used.’ In all-solvent mixtures the crystals were either very fine needles or no crystals formed even after two months. Another approach involving slow evaporation of methylene chloride, chloroform, or water yielded oily residues.
The other approach involved changing the counter anion; PF\textsuperscript{6}, NO\textsubscript{3}, BF\textsubscript{4}, CF\textsubscript{3}SO\textsubscript{3}, and Sn(Ph)\textsubscript{2}(NO)\textsubscript{3}\textsuperscript{2} were all tried. Using PF\textsuperscript{6} and BF\textsubscript{4} appeared to give oils or decomposition. Using CF\textsubscript{3}SO\textsubscript{3} yielded crystals that were yellowish-white and changed to orange-brown over time. The counter anion Sn(Ph)\textsubscript{2}(NO)\textsubscript{3}\textsuperscript{2} failed to replace the original nitrate counter ion as evidenced by the absence of aromatic resonances in the \textsuperscript{1}H NMR. The best counter anion was NO\textsubscript{3} in terms giving stable crystals, although they were small. The nitrate was promising also in terms of trials conducted previously by Dr. David Hill, who obtained acceptable crystals but the X-ray studies showed disorder in the final structure.\textsuperscript{22}

The magic bullet was changing the triethylphosphine to trimethylphosphine ligand in Auranofin. The crystals were dissolved in 3 ml and 20 ml of ether was added slowly without disturbing the solution. The crystals were grown by forming a colloidal state at room temperature first. The procedure involves sealing the test tube with a cork and inserting a needle to evaporate some of the solvent over a period of two days. The needle was then removed and the mixture was left for two days. The procedure was repeated for two months until a colloidal state formed and the mixture was left without disturbing. Finally X-ray quality crystals were obtained from the colloid as plates and needles.

For X-ray examination and data collection, a suitable crystal, approximate dimensions 0.36 x 0.08 x 0.07 mm, was mounted on the tip of a glass fiber. X-ray data was carried out by Dr. J. Krause Bauer, Department of Chemistry, University of Cincinnati. Intensity data were collected at 150K on a Siemens SMART 1K CCD.
differactometer (platform goniostat with $\chi$ fixed at 54.69°, sealed-tube generator, graphite-monochromated Mo $k\alpha$ radiation, $\lambda = 0.71073$ Å). The structure was solved by a combination of the Patterson method using SHELXTL v5.1 and the difference Fourier technique and refined by full-matrix least squares on $F^2$ for the reflections diffracting out to 0.75 Å. Non-hydrogen atoms were refined with anisotropic displacement parameters. Weights were assigned as $w^{-1} = \sigma^2(F_0^2) + (ap)^2 + bp$ where $a = 0.0487$, $b = 33.7775$ and $p = 0.33333F_0^2 + 0.66667F_e^2$. Hydrogen atoms were calculated based on geometric criteria and treated with a riding model. Hydrogen atom isotropic temperature factors were defined as $U(C) = U(H)$ where $a = 1.5$ for methyls and 1.2 for others. $[(\text{Me}_2\text{PAu})_2(\text{TATG})_2][\text{NO}_3]_2$ crystallizes with a badly disordered solvent which appears to be multiple H$_2$O molecules or highly disordered Et$_2$O. A suitable disorder model could not be resolved, thus the solvent contribution was subtracted from the reflection data using the program SQUEEZE. The refinement converged with crystallographic agreement factors of $R1 = 6.44\%$, $wR2 = 11.52\%$ for 6114 reflections with $I \geq 2\sigma(I)$ ($R1 = 9.58\%$, $wR2 = 13.02\%$ for all data) and 314 variable parameters.

**Results and Discussion**

**Chemical Oxidation Products.** Upon addition of $[\text{Cp}_2\text{Fe}]\text{PF}_6$ to Auranofin (0.5:1), the characteristic blue color of $[\text{Cp}_2\text{Fe}]\text{PF}_6$ changed slowly to yellow-orange due to formation of ferrocene. Stirring continued for 24 hr until the blue color of $[\text{Cp}_2\text{Fe}]\text{PF}_6$ disappeared and the solution was yellow. The solvent was evaporated in vacuo and the
residue was washed with ether \((3X)\) to remove \(\text{Cp}_2\text{Fe}\) and disulfide. The remaining off-white solid was recrystallized by dissolving in a small amount of \(\text{CH}_2\text{Cl}_2\) \((3 \text{ ml})\), followed by addition of ether or hexane. After work-up of the solution, the \(^1\text{H NMR}\) of the isolated product showed a larger chemical shift at \(\text{H1}\), relative to Auranofin, compared to other protons in the thioglucose unit.

\textbf{\(^1\text{H NMR Studies of Auranofin and the Oxidation Products.}\)} The resonances for the ring protons \((\text{H1}-\text{H6}, \text{Figure 3.2})\) on the thioglucose ligand in Auranofin and related structures have been unambiguously assigned.\(^{23}\) The thiolate resonances are a second-order pattern due to long-range virtual coupling.\(^{23}\) Monitoring the resonance shift of \(\text{H1}\) is an efficient approach for detecting coordination to gold(I). For example, replacing \(\text{H}^+\) of protonated tetraacetylthioglucose by \([\text{Au}(\text{PEt}_3)]^+\), to form Auranofin (Table 3.1), produces a coordination shift \((\Delta = \delta_{\text{Auranofin}} - \delta_{\text{Tetraacetylthioglucose}} \text{ at } \text{H1})\) of 0.60 ppm in CDCl\(_3\).\(^{23}\) The downfield chemical shift of \(\text{H1}\) is due to the electron density increase on the sulfur atom of the thioglucose ligand when it is coordinated to gold(I). Oxidation of the thiol to the corresponding disulfide is accompanied by the appearance of a doublet at 4.65 ppm in the disulfide and the disappearance of the \(\text{SH}\) resonance at 2.3 ppm (not shown in Table 3.1) and the triplet at 4.54 ppm in the thiol. \(^1\text{H NMR}\) data for Auranofin, thioglucose, disulfide, and digold \(\mu\)-thiolato cluster are reported in Table 3.1. The products of oxidation of Auranofin with \([\text{Cp}_2\text{Fe}]\text{PF}_6\) (Equation 3.1) were identified as \([\text{Et}_3\text{PAu})_2(\text{TATG})]\text{PF}_6, (\text{TATG})_2, and \text{Cp}_2\text{Fe} by comparison to authentic samples.
Table 3.1. $^1$H NMR data in the downfield region for Auranofin, TATG, (TATG)$_2$, and $[(Et_3PAu)_2(TATG)]X$, with various counter ions in CDCl$_3$.

<table>
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<th>Compound</th>
<th>H1</th>
<th>H2-H4</th>
<th>H5</th>
<th>H6</th>
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<tr>
<td>Auranofin</td>
<td>5.14(d)</td>
<td>4.94-5.09</td>
<td>3.71</td>
<td>4.07-4.28</td>
</tr>
<tr>
<td>TATG</td>
<td>4.54(t)</td>
<td>4.96-5.22</td>
<td>3.73</td>
<td>4.10-4.30</td>
</tr>
<tr>
<td>(TATG)$_2$</td>
<td>4.65(d)</td>
<td>4.96-5.40</td>
<td>3.80</td>
<td>4.20-4.38</td>
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<tr>
<td>$[(Et_3PAu)_2(TATG)]PF_6$</td>
<td>5.25(d)</td>
<td>5.00-5.14</td>
<td>3.96</td>
<td>4.10-4.25</td>
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<tr>
<td>$[(Et_3PAu)_2(TATG)]NO_3$</td>
<td>5.50(d)</td>
<td>5.00-5.15</td>
<td>4.00</td>
<td>4.25-4.30</td>
</tr>
<tr>
<td>$[(Et_3PAu)_2(TATG)]CF_3SO_3$</td>
<td>5.25(d)</td>
<td>4.95-5.15</td>
<td>3.80</td>
<td>4.10-4.30</td>
</tr>
</tbody>
</table>

2Et$_3$PAuTATG + [Cp$_2$Fe]PF$_6$ $\rightarrow$ $[(Et_3PAu)_2(TATG)]PF_6 + (TATG)_2 + Cp_2Fe$  \(3.1\)

The digold $\mu$-thiolato cluster was prepared according to Scheme 3.1, where $R =$ Me, Et. The disulfide, bis(tetraacetylthioglucose), was prepared by oxidation of tetraacetylthioglucose with I$_2$ (Equation 3.2).

2HTATG + I$_2$ $\rightarrow$ (TATG)$_2$ + 2I$^-$ + 2H$^+$  \(3.2\)
Scheme 3.1. Independent synthesis of [(R,R)AuCl(TATG)]

\[
\begin{align*}
\text{CH}_2\text{Cl}_2 & \quad \text{R}_3\text{Paux} \\
}(\text{CH}_2\text{SO})_2 & \quad \text{X} = \text{PF}_6, \text{NO}_3, \text{CF}_3\text{SO}_3, \text{BF}_4; \text{R} = \text{OH, CH}_2\text{CH}_3
\end{align*}
\]
The $^1$H NMR spectrum of [(Et$_3$PAu)$_2$(TATG)]PF$_6$ is shown in Figure 3.3 and the $^1$H NMR of bis(tetraacetylthioglucose) is shown in Figure 3.4.

The $^1$H NMR data for resonances in Auranofin, disulfide, and the digold p-thiolato cluster with different counter anions are reported in Table 3.1 and illustrated in Figures 3.2, 3.3, and 3.4. Generally, a downfield shift for the thiolate protons was noticed in the digold p-thiolato cluster spectrum. Comparing this spectrum (Figure 3.3) to Auranofin (Figure 3.2), the remote hydrogens (H2-H6) from the thiolate center shift downfield without a change in the splitting pattern. The appreciable shift at H1 ($\Delta \delta = 0.21-0.38$ ppm) in the digold p-thiolato cluster indicates the change in coordination of the thiolate center.

The spectrum of the crude oxidation product mixture contains an additional doublet at 4.65 ppm (H1), assigned as H1 in the disulfide (Figure 3.4). The spectrum of the crude mixture (Figure 3.5) is a combination of the disulfide and the digold p-thiolato cluster. Both of the multiplets at 3.85 (H5) and 4.2 (H6) are formed in the crude product and the disulfide. Assignment of the peaks due to disulfide or cluster was confirmed by mixing the disulfide and digold p-thiolato cluster in a 1:1 ratio and comparing the spectrum of this mixture product after chemical oxidation. The presence of a combined mixture from the cluster and the protonated thioglucose due to possible hydrolysis can be excluded due to the absence of the triplet (H1) at $\delta = 4.54$ ppm and the doublet (SH) at $\delta = 2.3$ ppm.
Figure 3.3: H NMR in CDCl₃ of [E₆PA₆TATQ]PF₆.
Figure 3.4: H NMR in CDCl$_3$ of bistetraacetyltetriethylene glycol.
Figure 3.5. 1H NMR in CDCl3 of Auranofin (1) + [Cp2Fe]PF6 (0.5)
Solvent dependence of the cluster is also apparent, similar to Auranofin.\textsuperscript{23} \textsuperscript{1}H NMR of the [(Et\textsubscript{3}PAu)\textsubscript{2}(TATG)]NO\textsubscript{3} in D\textsubscript{2}O showed an upfield shift of H1 to 5.6 ppm in addition to a small shift in other resonances. In DMSO the resonances showed a distinct feature not only downfield shifted but also showed a better resolving of overlapped resonances.

\textsuperscript{31}P \{\textsuperscript{1}H\}NMR of [(Et\textsubscript{3}PAu)\textsubscript{2}(TATG)]X. Previous studies showed that the \textsuperscript{31}P chemical shift is very dependent on the environment in gold compounds.\textsuperscript{21,23,24} Due to its sensitivity to a change in coordination and geometry in groups in the trans position, \textsuperscript{31}P NMR has been used efficiently in monitoring the interaction of gold drugs with biological systems. \textsuperscript{31}P NMR has been used to provide information concerning the behavior of red cells in D\textsubscript{2}O/saline in the presence of Auranofin and monitoring the interaction of Et\textsubscript{3}PAuCl with glutathione.\textsuperscript{25} The \textsuperscript{31}P NMR spectrum of AlbSAuP\textsubscript{3} in the presence of Et\textsubscript{3}PAuCl, in aqueous buffered solution at pH 7.9, contains a resonance at 36 ppm (Table 3.2) assigned to the reversibly formed species AlbS(AuPEt\textsubscript{3})\textsuperscript{2+}.\textsuperscript{21}

Figure 3.6 illustrates the \textsuperscript{31}P NMR spectra of Auranofin and [(Et\textsubscript{3}PAu)\textsubscript{2}(TATG)]X, X = PF\textsubscript{6}\textsuperscript{-} and NO\textsubscript{3}\textsuperscript{-}, in CDCl\textsubscript{3}. Both Auranofin and [(Et\textsubscript{3}PAu)\textsubscript{2}(TATG)]NO\textsubscript{3} gave rise to sharp \textsuperscript{31}P NMR resonances. The Auranofin spectrum shows a resonance at 38 ppm; however the gold cluster spectrum contains an upfield resonance at 37 ppm or 36 ppm depending on the counter anion and the solvent. The chemical shift (\Delta\delta) of 1 -2 ppm was also seen in the related clusters, [(PPh\textsubscript{3}Au)\textsubscript{2}(SC\textsubscript{6}H\textsubscript{4}CH\textsubscript{3})]\textsubscript{2}\textsuperscript{2+} and [dppeAu\textsubscript{2}(SC\textsubscript{6}H\textsubscript{4}CH\textsubscript{3})]\textsubscript{2}\textsuperscript{2+}, reported previously by our group.\textsuperscript{26} \textsuperscript{31}P NMR spectra of all clusters at room temperature showed
Figure 3.6. $^1$H NMR spectra in CDCl$_3$ of (a) Ammonium (b) [Et$_3$P(TMEDA)]Pf$_6$ and (c) [Et$_3$P(TMEDA)]Tf$_2$N.
Table 3.2. $^{31}$P NMR chemical shifts of Auranofin, [(Et$_3$PAu)$_2$(TATG)]$X$, and related complexes.

<table>
<thead>
<tr>
<th>Complex</th>
<th>$\delta$, ppm</th>
<th>Solvent</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Auranofin</td>
<td>38</td>
<td>CDCl$_3$</td>
<td>a</td>
</tr>
<tr>
<td>[(Et$_3$PAu)$_2$(TATG)]PF$_6$</td>
<td>37</td>
<td>CDCl$_3$</td>
<td>a</td>
</tr>
<tr>
<td>[(Et$_3$PAu)$_2$(TATG)]NO$_3$</td>
<td>36.5</td>
<td>CDCl$_3$</td>
<td>a</td>
</tr>
<tr>
<td>[(Et$_3$PAu)$_2$(TATG)]INO$_3$</td>
<td>36</td>
<td>D$_2$O</td>
<td>a</td>
</tr>
<tr>
<td>AlbSAuPEt$_3$</td>
<td>38.8</td>
<td>D$_2$O</td>
<td>21</td>
</tr>
<tr>
<td>[AlbS(AuPEt$_3$)$_2$]$^+$</td>
<td>36</td>
<td>D$_2$O$^b$</td>
<td>21</td>
</tr>
<tr>
<td>[Au(PEt$_3$)$_2$]$^+$</td>
<td>44</td>
<td>D$_2$O$^b$</td>
<td>21</td>
</tr>
</tbody>
</table>

a. Our data; relative to 85% H$_3$PO$_4$ in D$_2$O. The chemical shifts quoted are reproducible to ± 0.1 ppm. b. In aqueous buffered solution at pH = 7.9; relative to (MeO)$_3$PO.

The upfield chemical shift in [(Et$_3$PAu)$_2$(TATG)]$^+$ compared to Auranofin is an indication of the greater trans influence imposed by the $\mu$-thiolate groups, i.e., the greater the trans influence of the $\mu$-tetracetyl thioglucose units the weaker the trans Au-P bond and the more upfield the $^{31}$P chemical shift. It is noticeable that no resonance observed due to free Au(PEt$_3$)$_2$ ($\delta$ ppm) or any other phosphine species is observed at room temperature. Ab initio study of structures and energetics of sulfur-bridged copper clusters [Cu$_{20}$S$_n$(PR$_3$)$_m$] ($n = 1-4$, 6; $m = 0$, 2, 4, 6, 8; R = H, CH$_3$) predicted that the tertiary phosphine ligands are the reason for the stability of this class of clusters.
Titration of Et₃PAuNO₃ with Auranofin in CDCl₃ was followed by ³¹P{¹H}NMR (Figure 3.7). The results showed that when either Et₃PAuNO₃ or Auranofin is present in excess only a sharp single peak is observed due to rapid ligand exchange among the Et₃PAu⁺ species present. When the ratio of Auranofin/Et₃PAuNO₃ <1 the observed peak is broad. At the equivalence point, ([Et₃PAuNO₃] = [Auranofin]), the characteristic peak for the cluster is obtained at the same chemical shift as the pure sample.

**Effect of Counter Ions on Chemical Shifts.** ¹H NMR. It is noteworthy that the H1 resonance shifts upon changing the counter anion, which supports to a limited extent, the possibility of counter anion interaction with the digold µ-thiolato cluster. In the case of X = NO₃⁻ (Figure 3.8), H1 shifts to 5.5 ppm in comparison to 5.25 ppm when X = PF₆⁻, CF₃SO₃⁻, or BF₄⁻. Generally the peaks shifted and broadened on going from Auranofin to the cluster, especially when X = NO. The region of 5.0 to 5.5 ppm, which contains H1-H4 splits into three groups in the cluster. For example when X = PF₆⁻ or CF₃SO₃⁻, H4 is centered at 5.02 ppm (Figures 3.3 and 3.9). In the isolated product, X = PF₆⁻, NO₃⁻, or CF₃SO₃⁻, the first and second groups did not show further splitting; however, the third group appears as a doublet in the range of 5.25-5.50 ppm as shown in Table 3.1 and Figures 3.3, 3.8, and 3.9.

The largest shift was noticed in H1 in case X = NO₃⁻. The simple explanation for this noticeable shift, compared to other counter anions, is due to the interaction of NO₃⁻ with H1 through hydrogen bond.
Figure 3.7. $^{31}$P NMR spectra of Auranofin, Et$_3$PAuNO$_3$, and their mixtures in CDCl$_3$ solutions. The mole ratios of Auranofin:Et$_3$PAuNO$_3$ are (A) 1:0, (B) 0.66:0.34, (C) 0.5:0.5, (D) 0.39:0.61, (E) 0.20:0.80, and (F) 0:1.
Figure 3.8. H NMR in CDCl$_3$ of [Et$_2$P$_2$(TMS)]$_2$NO$_2$. 
b) $^{31}$P NMR. Both Auranofin and the digold p-thiolato cluster with PF$_6^-$ counter anion gave sharp $^{31}$P NMR resonances at 38 and 37 ppm, respectively (Figure 3.6). A broad peak at 36.5 ppm was noticed in [(Et$_3$PAu)$_2$(TATG)]NO$_3^-$. In X = CF$_3$SO$_3^-$, $^{31}$P NMR showed a sharp peak at 37 ppm as in X = PF$_6^-$. The higher shift and broadness in $^{31}$P NMR, X = NO$_3^-$, supports to a limited extent, the possibility of counter anion interaction with the digold p-thiolato cluster, which was noticed also in $^1$H NMR studies.

**Electrochemical Oxidation Studies.** As previously discussed, Auranofin irreversibly oxidizes at potentials of 1.1 and 1.6 V vs. Ag/AgCl in 0.1 M Bu$_4$NBF$_4$/CH$_2$Cl$_2$ solutions (Chapter 2 and Figure 2.3). The CV wave-shapes of phosphine gold thiolate complexes are sensitive to the type of electrode and solvent due to adsorption effects at the electrode.$^{15,19}$ The electrochemical response of Auranofin at 1.1 V vs. Ag/AgCl is sensitive to the nature of the supporting electrolyte.$^{15}$

The electrochemical oxidative behavior of [(Et$_3$PAu)$_2$(TATG)]NO$_3^-$ was investigated by using cyclic voltammetry (CV) in 0.1 M Bu$_4$NBF$_4$/CH$_2$Cl$_2$ solutions using Pt working and auxiliary electrodes and Ag/AgCl reference. Cyclic voltammograms of [(Et$_3$PAu)$_2$(TATG)]NO$_3$ as a function of scan rate and concentration are shown in Figures 3.10 and 3.11.

It is of interest to compare the oxidation potentials of Auranofin with that of the cluster. The isolated cluster showed only the second irreversible peak with a small shift to 1.65 V vs. Ag/AgCl. However, at similar concentration and scan rate, the current decreased from Auranofin to the cluster. The peak at 1.65 V showed dependence on
Figure 3.10. Cyclic voltammogram of 1.0 M \( \text{ETPAN}^2 \) and 0.1 M Bu4NBF4/CH2Cl2 as scan rate: (a) 20 mV s\(^{-1}\), (b) 100 mV s\(^{-1}\), and (c) 200 mV s\(^{-1}\).

Potential (V) vs. Ag/AgCl
Figure 3.11. Cyclic voltammograms of [(E)Py]2(TATC)NO3 in 0.1 M Bu4NB4Cl.2 at scan rate 100 mV/s.

Potential (V) vs Ag/AgCl

Current (µA)
concentration and scan rate (Figure 3.10 and 3.11). Cyclic voltammetry of the crude product following the complete oxidation of Auranofin using [Cp₂Fe]PF₆ showed a reversible peak at 0.35 V, assigned for ferrocene, in addition to a peak at 1.65 V assigned for the cluster.

Mass Spectroscopy Studies.

Mass spectroscopy studies have been carried out by Professor Touradj Solouki, Department of Chemistry, University of Maine. Mass spectroscopy studies on Auranofin and its digold p-thiolato cluster (Figure 3.12 and 3.13) were carried out in 50:50 methanol: water, with 0.5% acetic acid by using ESI –1.7 keV, soft ionization, and positive ion Mo. The digold p-thiolato cluster, [(Et₃PAu)₂(TATG)]NO₃, showed a peak at m/e 993 as the parent peak in addition to another peak at m/e 994 assigned to the cluster + H⁺ species (Figure 3.12). The ESI studies showed that the cluster is stable and no peaks due to decomposition products have been noticed. Specifically a peak at m/e 679, which would correspond to Auranofin was not observed.

Mass spectroscopy studies on Auranofin were carried out by using ESI –1.7 keV, soft ionization, and positive ion Mo in 50:50 methanol: water with 0.5% acetic acid. The spectrum showed peaks at m/e 679, 1553, and 1671 (Figure 3.13). Unexpectedly, the Auranofin peak at m/e 679 is not the major peak in the spectrum rather the peak at m/e 993 for the digold p-thiolato cluster is the major peak. The peaks at m/e 1553 and 1671 are assigned to [(Et₃P)₂(Au)₃(TATG)]⁺ and [(Et₃PAu)₃(TATG)]²⁺, respectively. A simple explanation for these unexpected results
Figure 3.12: ESI of [(EthPAU)_{2}(TATG)]NO₃ in 50:50 methanol: water, 0.5% acetic acid
in the ESI studies of Auranofin is probably due to the acetic acid used which may have protonated the thiolate, allowing for formation of the digold p-thiolato cluster according to Equation 3.3.\textsuperscript{16}

\[
2 \text{Et}_3\text{PAu}(\text{TATG}) + \text{H}^+ \rightarrow [(\text{Et}_3\text{PAu})_2(\text{TATG})]^+ + \text{HTATG}
\]

\textbf{Disulfide Exchange Studies.} Previous studies in our group on the disulfide exchange reaction between gold(1) thiolates and disulfides showed dinuclear gold(1) thiolates reacted with disulfides faster than mononuclear gold(1) thiolates.\textsuperscript{19}

The tetranuclear gold(I) cluster, $[(\text{PPh}_3\text{Au})_4(\text{SC}_6\text{H}_4\text{CH}_3)_2][\text{PF}_6]$, formed after chemical oxidation of $\text{PPh}_3\text{Au}(\text{SC}_6\text{H}_4\text{CH}_3)$ was allowed to react with $(\text{SC}_6\text{H}_4\text{Cl})_2$ and the unsymmetrical disulfide, $\text{ClC}_6\text{H}_4\text{SSC}_6\text{H}_4\text{CH}_3$, appears to form first followed by the symmetrical disulfide, $(\text{SC}_6\text{H}_4\text{CH}_3)_2$. Interestingly, the disulfide exchange reaction between the cluster and disulfide was found to be faster than the neutral gold(I) thiolate complexes.\textsuperscript{26}

Auranofin cluster was allowed to react with glutathione disulfide, in D\textsubscript{2}O and the reaction was monitored for 7 days. Figure 3.14 and 3.15 show the \textsuperscript{1}H NMR of glutathione and digold p-thiolato, $[(\text{Et}_3\text{PAu})_2(\text{TATG})]\text{NO}_3$ in D\textsubscript{2}O, respectively. The spectra of the reaction mixture are complex. Therefore I chose to compare

![Glutathione disulfide](image)
Figure 3.14. 1H NMR of glutathione disulfide in D2O.
the shift in H1 in [(Et3PAu)2(TATG)]NO3 at 5.6 ppm and H5 in glutathione disulfide at 3.3 ppm. The reason for this choice is that these hydrogens are both close to the sulfur atoms, i.e. the disulfide exchange centers. The doublet of doublet at 3.3 ppm in glutathione disulfide showed a slight upfield shift after 16 hrs and a new multiple appeared at 3.4 ppm (Figure 3.16). After about 7 days the peak at 3.3 ppm had decreased and the peak at 3.4 ppm had increased. There was no further change after 7 days. The peak at 5.6 ppm in [(Et3PAu)2(TATG)]NO3 broadened and showed a negligible shift after 7 days. That the reaction was very slow and further studies are needed to clarify the nature of the reaction.

**X-ray Studies of [(Et3PAu)2(TATG)]NO3 and Related Structures.** The mononuclear gold thiolate complex PPh3Au-p-tc, similar to Auranofin, forms a tetranuclear gold cluster and disulfide upon oxidation by [Cp2Fe]PF6.19 X-ray data shows equi-distant gold atoms with a bridging thiolate bisecting the gold atoms in each unit. The four gold atoms form a square with Au...Au distances of 3.15 Å and 3.17 Å.19 Fackler et al. reported the X-ray structure of [(Ph3PAu)2SCH2Ph]2(NO3)2 as a dimeric structure with a strong gold-gold interactions of 3.07 and 3.12 Å.28

Hill et al. obtained preliminary data on the solid state structure of [(Et3PAu)2(TATG)]2(NO3)2 in which two gold atoms coordinate to one sulfur (Figure 3.17). In addition, the structure shows the two ionic units arranged in a square dimer composed of four gold atoms all approximately equidistant. The sulfur atoms are on opposite sides (trans) of the gold square bisecting the two phosphorous atoms above them.
Figure 3.16. 1H NMR of glutathione disulfide after mixing with (Et3P)2TATC[(NO3)2]
Figure 3.17. Crystal structure of product of reaction of Auranofin and \( \text{Et}_3\text{PAuNO}_3 \).\textsuperscript{22}
The Au-S-Au angles are approximately $88^0$ and are somewhat compressed. This compression may be due to the gold-gold interaction. The Au...Au distance was found to be 3.2 Å with Au-S and Au-P bond lengths ranging from 3.34 to 2.39 Å and 2.19 to 2.35 Å, respectively. Unfortunately, the quality of the data was not high enough to completely solve the structure, so it was never published.22

Crystal Structure Analysis of $[(\text{Me}_3\text{PAu})_2(\text{TATG})]_2(\text{NO}_3)_2$. As discussed in the experimental part, multiple attempts to grow X-ray quality crystals for $[(\text{Et}_3\text{PAu})_2(\text{TATG})]_2(\text{NO}_3)_2$ showed a very limited success. Changing the counter anions from PF$_6^-$ to NO$_3^-$, BF$_4^-$, CF$_3$SO$_3^-$, or Sn(Ph)$_2$(NO$_3$)$_3^-$ failed to produce X-ray quality crystals. A variety of different solvent combinations yielded very fine needles or no crystals. Trials to grow crystals by slow evaporation of CHCl$_3$, CH$_2$Cl$_2$, or H$_2$O yielded oily residues.

$^1$H NMR and elemental analysis showed that both $[(\text{Et}_3\text{PAu})_2(\text{TATG})]_2(\text{NO}_3)_2$ and $[(\text{Me}_3\text{PAu})_2(\text{TATG})]_2(\text{NO}_3)_2$ contain 2 PR$_3$, R = Et or Me, per TATG. Synthesis of both derivatives was achieved as shown in Scheme 3.1. Comparing $^1$H NMR of $[(\text{Et}_3\text{PAu})_2(\text{TATG})]_2(\text{NO}_3)_2$ (Figure 3.3) with $[(\text{Me}_3\text{PAu})_2(\text{TATG})]_2(\text{NO}_3)_2$ (Figure 3.18), the former showed H1 at 5.35 vs. 5.5 ppm for the later.

Good quality X-ray crystals were achieved by replacing triethylphosphine by trimethylphosphine and crystals were grown from CH$_2$Cl$_2$-ether as described in the experimental part.
Crystals of [(Me3PAu)2(TATG)]2(NO3)2 were obtained as colorless plates and needles from CH2Cl2-Et2O. Crystal data, data collection and processing parameters are reported in Table 3.3. Selected bond lengths and angles are listed in Table 3.4.

The molecular structure of [(Me3PAu)2(TATG)]2(NO3)2, is shown in Figure 3.19 and 3.20. The molecular and crystallographic symmetries coincide running through the center of the cation and anions (N1 and N2 of the nitrate ions lie on special positions). The gold-gold distances are Au1-Au2 = 3.1062(7), Au1-Au1A = 3.1713 (11) and Au2-Au2A = 3.1446(12) Å.
Table 3.3. Crystal data and structure refinement for [(Me$_3$PAu)$_2$(TATG)]$_2$(NO$_3$)$_2$.

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<th>Value</th>
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</tr>
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<td>150(2) K</td>
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<td>Wavelength</td>
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<td>3712</td>
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<tr>
<td>Crystal size</td>
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<tr>
<td>$\theta$ range for data collection</td>
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<td>Limiting indices</td>
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<tr>
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<td>Independent reflections</td>
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</tr>
<tr>
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<td>Full-matrix least-squares on $F^2$</td>
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<tr>
<td>Data/restraints / parameters</td>
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<tr>
<td>Goodness-of-fit on $F^2$</td>
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<tr>
<td>Final R indices [I &gt; 2$\sigma$(I)]</td>
<td>R1 = 0.0644, wr2 = 0.1152</td>
</tr>
<tr>
<td>R indices (all data)</td>
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</tr>
<tr>
<td>Largest diff. Peak and hole</td>
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</tr>
</tbody>
</table>
Table 3.4. Selected bond lengths (Å) and angles (°) for

$[(\text{Me}_3\text{PAu})_2(\text{TATG})_2(\text{NO}_3)_2].$

<table>
<thead>
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<th>Length (Å)</th>
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<td>Au(1)-S(1)</td>
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<tr>
<td>Au(1)-Au(2)</td>
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<td>Au(1)-Au(1)#1</td>
</tr>
<tr>
<td>Au(2)-P(2)</td>
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<td>1.76(2)</td>
<td>P(2)-C(17)</td>
</tr>
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<td>48.8(8)</td>
<td>P(1)-Au(1)-Au(1)</td>
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<td>O(13)-N(2)-O(14)</td>
</tr>
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</table>
Figure 3.20. Another view of [(MesPPh2TATOF)2(CN)]2.
Conclusions

The present study clearly demonstrates that Auranofin can be oxidized chemically and electrochemically at the thiolate center forming a disulfide and a bridging thiolate cluster $[(\text{Et}_3\text{PAu})_2(\text{TATG})]_2(\text{NO}_3)_2$. Such redox behavior provides an insight into the possible biological reactions that occur upon administration of Auranofin. The prediction of the fate of Auranofin \textit{in vivo} is complicated by a variety of reactions occurring at the gold center. In addition the circulating form may be different from that of the initial drug.$^{1,2,5,16}$

Toxicity of anti-rheumatoid arthritis drugs is believed to be due to the formation of disulfides which lead to oxidative stress in the cell.$^{18}$ The formation of disulfide and cluster by mild oxidation of Auranofin is directly related to the oxidative stress effect.

One-electron oxidation of Auranofin results in homolytic cleavage of the Au-S bond and formation of $\text{Et}_3\text{PAu}^+$ and thiol radical, SR, which rapidly dimerizes to produce disulfide (see Scheme 3.2). Previous studies in our lab on the electronic structure of gold(I) thiolate complexes have assigned the HOMO orbitals of these complexes as having significant sulfur character.$^{19}$ The cation, $\text{Et}_3\text{PAu}^+$, reacts with a molecule of the starting mononuclear complex to form a digold complex with thiolate bridging two gold centers, which dimerizes via Au...Au bonds to form the observed tetragold cluster.
Scheme 3.2. Mechanism of Auranofin oxidation (L = Et₃P, R = Tetraacetylthioglucose).

The mechanism of Auranofin oxidation is supported by the independent synthesis of the tetragold cluster (see Scheme 3.1) and is consistent with the n value (0.5) determined by bulk electrolysis.
References


15. Mohamed, A. A.; Bruce, A. E.; Bruce, R. M. Metal-Based Drugs, 1999, 6, 233-238, Mohamed, A. A.; Bruce, A.; Bruce, M. 216th National Meeting of the American Chemical Society, Boston, MA, August 1998.


CHAPTER 4

Electron-Transfer Studies between Ferrocene and Gold Thiolates.

Determination of the Standard Potential of Gold(I) Thiolate Oxidation

Introduction

The medicinal effects of gold(I) thiolate drugs have been extensively investigated during the last two decades. Redox reactivity of gold(I) thiolate drugs, especially oxidation, has been invoked in partial explanation of both therapeutic and toxic side effects. Oxidation of Auranofin with hypochlorite, a strong oxidant released by phagocytic cells, has also been studied by Shaw and coworkers. Sulfonate and Et₃PO formed first followed by oxidation of gold(I) and gold(III).

The electrochemistry of a series of neutral phosphine gold(I) thiolate complexes has been investigated in our laboratory. The series includes cyclic dinuclear gold(I) complexes formed from 1,2-propanedithiolate (pdt) and bis-chelating phosphines, Au₂(LL)(pdt) (LL = dppe and dpppn), open dinuclear gold(I) complexes formed Gom para-thiocresolate (p-tc) and bis-chelating phosphines, Au₂(LL(p-tc))(LL = dppe, dppe, dppp, dppb, or dpppn), and mononuclear complexes, Auranofin and Au(PPh₃)(p-tc). Oxidative cyclic voltammetry experiments were performed at Pt and glassy carbon electrodes in 0.1 M Bu₄NPF₆/CH₃CN or 0.1 M Bu₄NBF₄/CH₂Cl₂ solutions.

Cyclic voltammetry studies on PPh₃Au(p-tc) showed two irreversible peaks at +0.82 and +1.50 V vs. Ag/AgCl. However, Auranofin showed two irreversible peaks at
higher potentials of +1.1 and +1.6 V vs. Ag/AgCl. The first irreversible peaks in PPh₃Au(SC₆H₄CH₃) and Auranofin were assigned as thiolate oxidation to the corresponding disulfide.⁴

Our group has also studied the chemical oxidation of a series of mononuclear and dinuclear gold(I) thiolates using [Cp₂Fe]PF₆ in CH₂Cl₂.⁵ The results of the oxidation showed the formation of gold(I) clusters and disulfide. The chemical oxidation process is complete within 2-24 hours. For example, PPh₃Au(p-tc) is oxidized by [Cp₂Fe]PF₆ more quickly than Auranofin. The simple explanation of this time variation is based on the accessibility of the thiolate oxidation potential to Fc/Fc⁺ couple.

Our goal of this study is to report the standard potential of the irreversible thiolate oxidation in gold(I) thiolate complexes, such as PPh₃Au(p-tc) using [Cp₂Fe]PF₆ and cyclic voltammetry. Quantitative measurements of Cp₂Fe and [Cp₂Fe]PF₆ will be measured by using W-vis spectroscopy.

**Experimental Section**

**Reagents.** Methylene chloride and acetonitrile were purchased from Aldrich. Supporting electrolyte, tetra-N-butylammonium teterafluoroborate (Bu₄NBF₄) was purchased from Aldrich and recrystallized (2X) from CH₂Cl₂/ether. Auranofin was purchased from Pfanstiehl Laboratories, Inc. PPh₃Au(p-tc) was prepared according to previously published methods. [Cp₂Fe]PF₆ and Cp₂Fe were purchased from Aldrich; Cp₂Fe was purified by sublimation.
Cyclic Voltammetry (CV) Experiments. CV experiments were conducted using an EG & G Princeton Applied Research 273 potentiostat/gavonostat under computer control. CV measurements were performed in CH₂Cl₂ or CH₃CN with 0.15 M Bu₄NBF₄ as supporting electrolyte using the same setup as shown in Figure 2.1. Cyclic voltammograms were recorded in the potential range 0 to 1.9 V.

UV-vis Measurements. W-visible spectra were obtained by using a Hewlett Packard 8452 diode array spectrometer in 1-cm quartz cuvettes.

Chemical Equilibrium Studies. All manipulations were carried out in the dry box. Solutions containing the components were allowed to react in the dry box for 24, 48, and 72 hrs and samples were taken to check the completeness of the reaction by using UV-vis. The quartz cuvettes for W-vis measurements were sealed with rubber septa. The reaction was found to be complete after the first 24 hrs. Chemical equilibrium constants and standard oxidation potentials were calculated using equations shown in the results section.

Results and Discussion.

Recently, we reported on the electrochemical and chemical oxidation of gold thiolates such as PPh₃Au(SC₆H₄CH₃) and Auranofin.⁴ Electrochemical oxidation of Auranofin in 0.1 M Bu₄NBF₄/CH₂Cl₂ showed two irreversible peaks at +1.1 and +1.6 V vs. Ag/AgCl. The first irreversible oxidation potential at +1.1 V was assigned as thiolate oxidation to disulfide based on bulk electrolysis studies. The chemical oxidation of gold(I) thiolates, using [Cp₂Fe]PF₆, formed a tetragold(I) cluster and disulfide.⁵
Our goal is to measure the standard potential of gold(I) thiolate oxidation by using a reversible couple such as Fe/Fc$.^+$ The oxidation of gold(I) thiolates using [Cp$_2$Fe]PF$_6$ in acetonitrile under nitrogen produced disulfide, cluster, and ferrocene. The cluster was formed by dimerization of the first formed dinuclear species to form a tetranuclear gold(I) cluster.

**Electrochemical Studies.**

The cyclic voltammetry of a 10 mM solution of Cp$_2$Fe in 0.15 M Bu$_4$NBF$_4$/CH$_3$CN solution at a scan rate of 100 mVs$^{-1}$ in the potential range 0 to 0.75 V is shown in Figure 4.1. The reversible couple for 10 mM Fe/Fe$^+$ is seen at $E_{1/2} = 0.50$ V; however the thiolate oxidation of a 10 mM solution of PPh$_3$Au(SC$_6$H$_4$CH$_3$) obtained at 0.9 V vs. Ag/AgCl. A mixture of 10 mM Cp$_2$Fe and 10 mM PPh$_3$Au(SC$_6$H$_4$CH$_3$) showed an enhancement in current under the ferrocene peak. The enhancement in current showed that ferrocene is an electron-transfer catalyst.$^6$,$^7$

**UV-vis studies.** Reaction of PPh$_3$Au(SC$_6$H$_4$CH$_3$) with [Cp$_2$Fe]$^+$ in acetonitrile was followed by UV-vis for several days (Equations 4.1 and 4.2). The peaks at 440 nm ($\varepsilon = 98$) and 630 nm ($\varepsilon = 395$) for ferrocene and ferrocenium, respectively, were monitored for 3 days and the reaction was found to be complete in the first 24 hrs. Figure 4.2 shows the UV-vis spectra of $-5.12$ mM [Cp$_2$Fe]PF$_6$ in CH$_3$CN and its UV-vis spectrum after reaction with $-10$ mM PPh$_3$Au(C$_6$H$_4$CH$_3$) after equilibration. The quantities of [Cp$_2$Fe] and [Cp$_2$Fe]$^+$ at equilibrium were measured by Beer’s law plots for each compound.
Figure 4.1. Cyclic voltammetry of ferrocene (10 mM), PPh₃Au(SC₆H₄CH₃) (10 mM), and their mixture (10 mM) in 0.15 M Bu₄NBF₄/CH₃CN using Pt working electrode.
Figure 4.2. UV-vis spectrum of 100 mM PPh₃Au(SC₆H₄CH₃)_2 after mixing with 5 mM [CP₂Fe]²⁺.

Absorbance
(Figure 4.3 and 4.4). Reduction of [Cp₂Fe]⁺ to [Cp₂Fe] referencing was 86% complete in the first 24 hrs. At 86% of the reaction completion, the equilibrium constant (Equations 4.3, 4.4, and 4.5), $K_{eq}$, was found to be $14.54 \times 10^{-3}$ M⁻¹. Figure 4.5 shows the effect of completion of the first reaction (Equations 4.1 and 4.2), i.e. Fe⁺/Fc, on the standard potential of gold thiolate. In a broad sense, the standard potential decreases as the reaction goes to completion. From Figure 4.5, at 86% completion of the Fe⁺/Fc process the standard potential of thiolate oxidation is 0.25 V vs. Ag/AgCl; at 40% completion the potential is 0.37 V (Equation 4.6).

$$\text{PPh}_3\text{AuSR} + \text{Fc}^+ = \text{PPh}_3\text{AuSR}^+ + \text{Cp}_2\text{Fe} \quad \text{4.1}$$

$$\text{PPh}_3\text{AuSR}^+ + \text{PPh}_3\text{AuSR} = [(\text{PPh}_3\text{Au})_4(\text{SR})_2]^{1/2} + [\text{RSSR}]^{1/2} \quad \text{4.2}$$

$$K_1 = [\text{PPh}_3\text{AuSR}]^+ [\text{Cp}_2\text{Fe}]/[\text{PPh}_3\text{AuSR}][\text{Cp}_2\text{Fe}]^+ \quad \text{4.3}$$

$$K_2 = [(\text{PPh}_3\text{Au})_4(\text{SR})_2]^{1/2} [\text{RSSR}]^{1/2}/[\text{PPh}_3\text{AuSR}]^+ [\text{PPh}_3\text{AuSR}] \quad \text{4.4}$$

$$K_{eq} = K_1.K_2 = [(\text{PPh}_3\text{Au})_4(\text{SR})_2]^{1/2} [\text{RSSR}]^{1/2} [\text{Cp}_2\text{Fe}]/[\text{Cp}_2\text{Fe}]^+ [\text{PPh}_3\text{AuSR}]^2 \quad \text{4.5}$$

$$E = E_{1/2(\text{Au/Aur}^+)}^0 - RT/nF \log [\text{PPh}_3\text{AuSR}]^+ /[\text{PPh}_3\text{AuSR}]$$

$$E = E_{1/2(\text{Fc/Fc}^+)}^0 - RT/nF \log [\text{Cp}_2\text{Fe}]/[\text{Cp}_2\text{Fe}]^+$$

$$R = C_6H_4CH_3$$

The symbol $E$ represents the potential and $E^0(\text{Fc/Fc}^+)$ is a constant (0.35 V), called the standard potential. The gas constant $R$ is expressed in joules K⁻¹ mol⁻¹, $T$ is the
Figure 4.3. Beer's law plot of Phosphine in CHClCN at 440 nm.

Concentration of PC (mM)

Absorbance

\[ 0.0983x = y \]
Figure 4.4. Beer’s Plot of Ferrocenium in CH$_3$CN/N$_2$ at 630 nm.
Figure 4.5. Prediction based on simulation for change in $E^{1/2}_0 (V)$ for $\text{PPH}_{3} \text{Au(SC}_{6} \text{H}_{4} \text{CH}_{3})$ with change in $[\text{Fe}^3]/[\text{Fe}^2]^%$. 

$0 10 20 30 40 50 60 70 80 90 100$

$E_{1/2}^0 (V)$
temperature (in kelvin); $n$ is the number of electrons appearing in the balanced equation for the half-reaction, and $F$ is the number of coulombs per mole (965,485 coulombs).\(^6\)

\[
E^{0}_{1/2(Au/Au^{+})} = \frac{RT}{nF} \log \left[ \frac{[PPh_3AuSR]^+/[PPh_3AuSR]}{[PPh_3Au^+/[PPh_3AuSR]^+] \left[ Cp_2Fe \right]} \right]
\]

\[
E^{0}_{1/2(Fe/Fe^{+})} = \frac{RT}{nF} \log \left[ \frac{[Cp_2Fe]^+/[Cp_2Fe]}{[PPh_3Au^+/[PPh_3AuSR]^+] \left[ Cp_2Fe \right]} \right]
\]

Where $n = 1$ and $E^{0}_{1/2(Fe/Fe^{+})} = 0.35$ V

\[
[PPh_3AuSR] = [Cp_2Fe]^+
\]

\[
[PPh_3AuSR]^+ = [Cp_2Fe]
\]

As shown in Equation 4.2, one molecule of $PPh_3Au(SC_6H_4CH_3)$ is depleted by reaction with another molecule of $PPh_3Au(SC_6H_4CH_3)^+$ to form a gold(I) cluster and disulfide. Figure 4.6 shows the effect of $[PPh_3Au(SC_6H_4CH_3)]$ or $[PPh_3Au(SC_6H_4CH_3)]^+$ depletion on the standard potential of gold(I) thiolate oxidation. As expected, as the species is depleted the standard potential decreases gradually. Assuming the chemical reaction in Equation 4.2 is not considered, the standard potential would be 0.25 V vs. Ag/AgCl (Figure 4.6).
Figure 4.6: Prediction based on simulation for change in $\frac{\Delta}{2}$ with depletion of [PPh$_3$AuSR]$^-$.
Conclusion

The irreversible oxidation of gold(I) thiolates was explained by an EC mechanism, i.e. thiolate oxidation followed by formation of disulfide. The standard potential of thiolate oxidation was determined using the reversible couple Fc/Fc⁺. The standard potential of the gold(I) thiolate complex, \textit{PPh₃Au(SC₆H₄CH₃)}, was estimated, based on simulation, to be 0.25 V vs. Ag/AgCl. Ferrocene, an electron-transfer catalyst, enhances the current of the thiolate oxidation.

Further estimation of the potential may be found by trying other oxidants that have potentials more positive than \([\text{Cp}_2\text{Fe}]PF_6\) such as \([\text{Cp}^*\text{Fe}]PF_6\).
References


CHAPTER 5

Oxidation Chemistry of Solganol: Anti-Arthritic Gold-Sulfur Drug

Introduction

That gold complexes are effective as anti-rheumatoid arthritis is well documented. Gold(I) thiolates, administered parenterally (by injection), have been used for many years in the treatment of rheumatoid arthritis. Solganol (Figure 5.1), a water soluble but not lipid soluble gold(I)-thioglucose drug, has been used for the treatment of rheumatoid arthritis for over half a century.

![Figure 5.1. Structure of Solganol.](image)

Solganol

While there is no available x-ray crystal structure for Solganol; recently Bau reported the x-ray crystal structure of Myochrysine, gold(I)-thiomalate, as a polymeric
structure with two interpenetrating spirals.¹ The unit cell contains two independent gold atoms, one of which has an essentially linear S-Au-S arrangement (178.9°) and the other is distorted from linearity to 169.4.²

The polymeric yellow solution of Solganol is characterized by two broad bands in the UV-vis spectrum; the first band occurs at 250 nm and the second at 270 nm with a tail beyond 400 nm.³ The ¹⁹⁷Au Mossbauer spectroscopy shows gold atoms coordinated to two thioglucose units (IS = 1.40, QS = 6.20 mm s⁻¹) and extensive polymerization is possible.⁴

The chemical oxidation of Solganol in aqueous medium occurs upon addition of hypochlorite, a strong oxidant released by phagocytic cells.⁵ The oxidation process involved thioglucose ligand followed by Au⁺⁺ oxidation. The oxidation to Au(III) was confirmed by UV-vis and Ion-Chromatography after treating the oxidation product with HCl. Hypochlorite oxidation of Solganol occurred slightly slower than for Myochrysine (gold(I)-thiomalate) near the end point.⁵ Aqueous solutions of Solganol undergo redox reactions to form Au(0) and the disulfide, TgSSTg, which subsequently undergoes hydrolytic redox disproportionation to TgSO₂H and TgSH.⁶

\[
2\text{H}_2\text{O} + 4\text{AuSTg} \longrightarrow 4\text{Au}^0 + \text{TgSO}_2\text{H} + 3\text{TgSH}\quad 5.1
\]

While there is great interest in the biological study of gold drugs; little is known about their redox behavior.⁷ Studying the redox behavior of gold(I)-drugs is directly related to their toxicity and therapeutic effects in vivo. As an extension of our work on the
chemical and electrochemical oxidation of gold(I)-drugs we decided to investigate the oxidation of Solganol, in aqueous medium, using cyclic voltammetry and the chemical oxidizing agent such as \([\text{Cp}_2\text{Fe}]\text{PF}_6\).

**Experimental Section**

**Reagents.** Water, \(\text{D}_2\text{O}\), HCl, \([\text{Cp}_2\text{Fe}]\text{PF}_6\), and sodium perchlorate (NaClO\(_4\)) were purchased from Aldrich and were used as received. Solganol was purchased from Fluka and was used as received.

**Cyclic Voltammetry (CV) Experiments.** CV experiments were performed using an EG&G Princeton Applied Research 273 potentiostat/galvanostat under computer control. CV measurements were performed in 0.5 M NaClO\(_4\)/\(\text{H}_2\text{O}\) using the same setup shown in Figure 2.1. Cyclic voltammograms were recorded in the potential range 0 to 1.7 V in \(\text{H}_2\text{O}\) under nitrogen with 0.5 M NaClO\(_4\) as supporting electrolyte. All potentials were referred to a silver-silver chloride electrode (Ag/AgCl) at room temperature. pH values were adjusted by Analar grade HCl.

**Bulk Electrolysis.** Bulk electrolysis experiments were performed as described in chapter 2 and Figure 2.2. The electrolytic cell was assembled after oven drying at 110\(^0\) C. A 0.5 M NaClO\(_4\)/\(\text{H}_2\text{O}\) solution was introduced into the cell, stirred, and degassed with nitrogen for 10 minutes. Solganol was added (10 to 20 mg) and the solution was stirred for 10 minutes. The total number of electron equivalencies (n) and coulombs (Q) passed were calculated as shown in chapter 2.
'H NMR measurements. 'H NMR spectra, recorded in D\textsubscript{2}O, by using a Gemini 300 NMR spectrometer. Chemical shifts were measured relative to the HDO resonance.

Chemical Oxidation. To 7.0 mg (1 mmol) of Solganol dissolved in 5 ml D\textsubscript{2}O was added 3 mg (0.5 mmol) of finely grounded [Cp\textsubscript{2}Fe]PF\textsubscript{6}. The mixture was stirred and a sample was taken after 24 hr for 'H NMR. The yellowish-green color due to [Cp\textsubscript{2}Fe]PF\textsubscript{6} did not change even after 72 hrs of mixing.

Results and Discussion

Cyclic voltammograms of degassed 6 mM Solganol were investigated in 0.5 M NaClO\textsubscript{4}/H\textsubscript{2}O solutions at a Pt wire counter electrode, an Ag/AgCl reference electrode, and a Pt working electrode. Solganol solutions showed a well-defined irreversible oxidation peak at +1.2 V \textit{vs.} Ag/AgCl dependent of the scan rate, concentration, and pH values. The oxidative response of Solganol solutions investigated in the potential range 0 to +1.7 V is irreversible even at slow scan rates of 20-100 mV/s.

The oxidative cyclic voltammogram of degassed 6 mM Solganol at 20, 50, and 100 mV/s is shown in Figure 5.2. The position of the peak shifted to higher potentials with increasing scan rate from 20 to 100 mV/s. At higher scan rates (>100 mV/s) a reduction peak at +0.5 V (return scan) started to grow in and the peak at +1.2 V increased in current (see Figure 5.3).

Multiple scan cyclic voltammograms obtained for degassed 6 mM Solganol in the potential range 0 to +1.5 V and at a scan rate of 100 mV/s are shown in Figure 5.4, the first and fifth scans are shown only in the figure. The first scan was taken after cleaning
Figure 5.2: Cyclic voltammery of 6.0 mM solution in 0.5 M NaClO$_4$/H$_2$O at scan rates: (a) 20 mV/s, (b) 50 mV/s, (c) 100 mV/s.
Figure 5.2. Cyclic voltammetry of 6.0 mM NaClO in 0.5 M NaClO/HClO at scan rates (a) 400 mVs⁻¹.
Figure 5.4. Multiple scan cyclic voltammogram of 6.0 mM Spinone in 0.5 M NaClO₄/H₂O at 100 mV/s.

Voltage vs. Ag/AgCl [V]

First Cycle

Fifth Cycle

Current (μA)
the electrode while the other scans were taken continuously. The feature of the slightly asymmetric broad peak at +1.2 V changed to a symmetrical sharp response by the fifth cycle. This behavior is due to a possible filming of the redox products on the electrode. The newly formed peak at +0.2 V assigned to the reduction of the hydrolyzed Au(III) formed after the oxidation of Au(I).8

**pH Studies.** The pH dependence of the cyclic voltammograms of 6 M Solganol was studied by gradually decreasing the pH by the stepwise addition of HCl. Solganol showed similar cyclic voltammetry behavior, i.e. no additional peaks, at different pH values by using HCl (Figure 5.5). Generally, the redox peaks shifted to lower potentials upon lowering the pH values.

Electrochemical reduction of 6 mM HAuCl4 in 0.5 M NaClO4/H2O at a scan rate of 100 mV/s is shown in Figure 5.5c. The reduction peak at 0.55 V is coupled with an oxidation peak at 1.10 V vs. Ag/AgCl. The reduction of HAuCl4 at 0.55 V is due to the AuCl4⁻/AuCl2⁻ process and the peak at 1.10 originates from the oxidation of the generated AuCl2⁻ to Au(III).9

At pH = 2, 6 mM Solganol solution showed an oxidation peak at 1.18 V vs. Ag/AgCl (compare Figure 5.5a vs. 5.5b). At this low pH value Solganol is expected to transform to AuCl2⁻ which in turn oxidizes to Au(III) at 1.18 V.

**Bulk Electrolysis and Chemical Oxidation.** Bulk electrolysis of Solganol at +1.3 V vs. Ag/AgCl in 0.5 M NaClO4/H2O showed that n = 2 (2.2, 2.1, and 1.8), consistent with a Au(I) oxidation. Bulk electrolysis of Auranofin at +1 V vs. Ag/AgCl in 0.1 M
Figure 5.2: (a) Cyclic voltammogram of 6 mM Solganol at pH = 2. (b) Cyclic voltammogram of 6 mM Solganol in 0.5 M NaClO₄/H₂O at 100 mV/s and pH = 6.7. (c) Cyclic voltammogram of 6 mM HAuCl₄ in 0.5 M NaClO₄/H₂O at 100 mV/s.
Bu₄NBF₄/CH₂Cl₂ showed that the oxidation is a 0.5 electron process, i.e. sulfur-based oxidation.¹⁰

Chemical oxidation using [Cp₂Fe]PF₆ in D2O was followed by ¹H NMR. The characteristic peaks of the thioglucose unit did not shift and the characteristic color of [Cp₂Fe]PF₆ persisted in the solution. This shows the high stability of the thiolate in the polymeric Solganol to oxidation. Oxidation of Auranofin using [Cp₂Fe]PF₆ resulted in formation of disulfide and tetrargold(I) cluster (chapter 3).

Conclusion

Previously, we reported on the oxidative cyclic voltammetry of Auranofin, 2,3,4,6-tetra-O-β-D-glucopyranosato-S(triethylphosphine)gold(I), in 0.1 M Bu₄NPF₆/CH₂Cl₂ or 0.1 M Bu₄NBF₄/CH₂Cl₂ solutions at a Pt working electrode vs. a Ag/AgCl reference electrode, Table 5.1." Two irreversible anodic peaks at +1.1 and +1.6 V vs. Ag/AgCl were obtained and assigned as thiolate and Au(I) responses, respectively."

Anderson and Sawtelle have investigated the aqueous redox processes for the electrogenerated gold(I) species, [AuCl₂]⁻, complexed by biologically relevant ligands such as cysteine and penicillamine.⁹ They propose an aqueous reduction mechanism that begins with [AuCl₄]⁻ as illustrated in equations 5.2-5.4. The progress of these electron transfer and coupled chemical reactions can be followed by cyclic voltammetry and UV-vis spectroelectrochemistry. Upon formation of [AuCl₂]⁻, addition of cysteine or penicillamine leads to complexation and changes in the electrochemistry, which allows an
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<td>SCE</td>
<td>H_2O/HNO_3</td>
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<td>+1.19 (m)</td>
<td>+1.20 (m)</td>
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<td>Complex</td>
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<tr>
<td>6</td>
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<td>H_2O/HNO_3</td>
<td>1.6 (m)</td>
<td>1.6 (m)</td>
<td>1.2 (m)</td>
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**Table S.1** Cyclic Voltammetry data for Solution and Related Complexes.
estimation of the oxidation potentials (see Table 5.1) of the Au[cysteine] and Au[penicillamine] complexes. Cyclic voltammetry control experiments with cysteine and penicillamine indicate that the observed electrochemical responses do not originate from these free species in solution (see Table 5.1).9

\[
[AuCl_4]^- \quad = \quad [AuCl_2]^+ + 2 Cl^- \quad \text{(5.2)}
\]

\[
[AuCl_2]^+ + 2 e^- \quad = \quad [AuCl_2]^2- \quad \text{(5.3)}
\]

\[
[AuCl_2]^2- + e^- \quad = \quad \text{Au} + 2 Cl^- \quad \text{(5.4)}
\]

Comparing the oxidative study of Auranofin vs. Solganol, the former studied in a non-aqueous medium (CH₂Cl₂) and showed two anodic peaks at 1.1 V (sulfur based oxidation) and 1.6 V (gold based oxidation) vs. Ag/AgCl while the latter showed only one anodic response at 1.2 V vs. Ag/AgCl. The second anodic peak (irreversible) in Auranofin at 1.6 V which was assigned as gold based-oxidation (Au⁰) corresponds to the oxidation peak at 1.2 V in Solganol.

Recent results from our laboratory indicate that mononuclear and binuclear phosphine gold(I) thiolate complexes undergo one-electron oxidation to form tetranuclear gold(I) clusters and disulfide.¹¹ Our study proved that Solganol behaved differently from other complexes, perhaps due in part to the polymeric nature of Solganol. Cyclic voltammetry of linear phosphine gold(I) thiolate complexes showed an irreversible sulfur-based oxidation process above +0.5 V (vs SCE); however, magnesium complex
with bridging thiolates, Mg(Py)$_3$(μ-SPh)$_3$·Mg(μSPh)$_3$·Mg(Py)$_3$, shows only an irreversible oxidation at +0.975 mV (vs SCE).\textsuperscript{12}

To summarize, the irreversible peak at +1.2 V vs. Ag/AgCl was assigned as Au$^{III}$ based on the following facts:

1. Bulk electrolysis at +1.3 V showed $n = 2$.

2. Chemical oxidation of Solganol showed no change in the $^1$H NMR or the color of FcPF$_6$, which indicates no thiolate oxidation.

3. At pH = 2 (HCl), the oxidation peak for a Solganol solution is similar to the reduced form of HAuCl$_4$, i.e. AuCl$_2^-$.
References


(c) Abdou, H; Bruce, A. E.; Bruce, M. R. M., Unpublished results. (d) Mohamed, A. A.; Bruce, A. E.; Bruce, M. R. M. Unpublished results.

CHAPTER 6

Synthesis, Characterization, and Photophysical Studies of Dinuclear Gold (I) Halide and Thiolate Complexes of Bis(diphenylphosphine)benzene. X-ray Crystal Structure of (AuCl)$_2$dpbz

Introduction

Phosphine gold (I) thiolates have a long history of medicinal activity as anti-rheumaoid arthritis drugs. Auranofin, 2,3,4,6-tetra-O-acetyl-1-β-D-glucopyranosato-S)(triethylphosphine) gold(I) is an orally effective antiarthritis agent in experimental animals and men. A number of dinuclear phosphine gold(I) thiolates have been evaluated for antitumor activity.‘,’

The antitumor activity of phosphine ligands has been reported after isolating bis(diphenylphosphine)ethane, dppe, as a by-product from the synthesis of Ph$_2$P(CH$_2$)$_2$Cl.$^1$ Complexation of the phosphine ligands as dppe with gold(I) protects the ligand from air oxidation and increase its cytotoxicity which is evident in the (AuCl)$_2$dppe with more cytotoxicity than dppe alone.’ Bisphosphines e.g. R$_2$P(CH$_2$)$_n$PR$_2$ (n = 1-4, R = Ph or Et) and Ph$_2$PCH=CHPPh$_2$ have been shown to posses a broad spectrum of antitumor effects in p388 leukemia models.$^2$ Linear digold(I) bisphosphine molecules are the subjects of many clinical studies in order to establish their promised antitumor activity.’ Our group has been investigating dinuclear gold(I) complexes such as
$\text{Au}_2(p-\text{SC}_6\text{H}_4\text{CH}_3)_2(\text{LL})$ and $\text{Au}_2(\text{SCH}_2\text{CH}_2\text{CH}_2\text{S})(\text{LL})$ where LL is a flexible, bisphosphine ligand varying from 1,1-bis(diphenylphosphino)methane to 1,5-bis(diphenylphosphino)pentane.\textsuperscript{3} These complexes exhibit $S \rightarrow \text{Au}$ charge transfer transitions in the UV-visible (330-360 nm) that appear to be perturbed by gold(I)-gold(I) interactions.\textsuperscript{3b} Recently our group investigated the dinuclear, gold(I) complexes employing cis- and trans-dppee ligands, $\text{Au}_2X_2(\text{cis-}\text{dppee})$ and $\text{Au}_2X_2(\text{trans-}\text{dppee})$ ($X = \text{Cl, Br, I, } p-\text{SC}_6\text{H}_4\text{CH}_3$).\textsuperscript{4} These two series offer the opportunity to examine and compare electronic structure and reactivity of conformations in which the two gold atoms are constrained to be within bonding distance vs. where intramolecular approach of the two gold atoms is precluded.

\[ \begin{array}{c}
\text{A} \\
\begin{array}{c}
\text{Ph} \\
\text{H} \\
\text{C} \\
\text{P} \\
\text{Au} \\
\text{X} \\
\text{Ph} \\
\text{Ph} \\
\text{Ph} \\
\text{H} \\
\text{C} \\
\text{P} \\
\text{Au} \\
\text{X} \\
\text{Ph} \\
\text{Ph} \\
\text{Ph}
\end{array}
\end{array}
\begin{array}{c}
\text{B} \\
\begin{array}{c}
\text{Ph} \\
\text{H} \\
\text{C} \\
\text{P} \\
\text{Au} \\
\text{X} \\
\text{Ph} \\
\text{Ph} \\
\text{Ph} \\
\text{Ph} \\
\text{H} \\
\text{C} \\
\text{P} \\
\text{Au} \\
\text{X} \\
\text{Ph} \\
\text{Ph} \\
\text{Ph}
\end{array}
\end{array}
\begin{array}{c}
\xrightarrow{h \nu} \\
\text{X = Cl, Br, I, } p-\text{SC}_6\text{H}_4\text{CH}_3
\end{array}
\]
In this study the backbone is the phenyl ring in bis(diphenylphosphine)benzene is more rigid than the ethylene group in bis(diphenylphosphine)ethylene. Hence the cis-trans isomerization is precluded. Our goal is the synthesis, characterization, and investigation of the photophysical behavior of a new class of halo and thiolato gold (I) complexes of the formula \((\text{Au}X)_2\text{dppbz}, X = \text{Cl, Br, I, } p-\text{SC}_6\text{H}_4\text{CH}_3\). The x-ray of \((\text{AuCl})_2\text{dppbz}\) as an example of the linear geometry of the dinuclear gold(I) complexes will be discussed.

\[ X = \text{Cl, Br, I, } p-\text{tc} \]

**Experimental Section**

**Reagents.** Solvents were purchased from Aldrich and used as received without further purification. \(\text{HAuCl}_4\cdot 3\text{H}_2\text{O}\) was purchased from Aithaca or was obtained as a loan from Alfa Aesar/Johnson Matthey. The ligand dppbz, \(\text{HAuBr}_4\cdot 3\text{H}_2\text{O}, \text{Et}_4\text{NBr, Et}_4\text{NI}\), and \(p\)-thiocresol were purchased from Aldrich.

**Measurements.** Microanalyses were performed by Dessert Analytics, Az. Melting points were determined by using a Thomas Hoover melting point apparatus and reported without
correction. $^1$H NMR spectra, recorded in CDCl$_3$ or CD$_2$Cl$_2$, by using a Gemini 300 NMR spectrometer. Chemical shifts were measured relative to the solvent resonance.$^{31}$P NMR resonances were recorded in CDCl$_3$ and referenced to an external sample of 85% H$_3$PO$_4$. Luminescence experiments were made by using a Perkin-Elmer LS-50 Luminescence Spectrometer. A 40-50 $\mu$s time delay between excitation pulse and emission detection was used to eliminate light scattering and to observe phosphorescence. Slit widths for excitation and emission monochromators were typically set at 10 nm. UV-visible spectra were obtained using a Hewlett Packard 8452 diode array spectrometer in 1 cm quartz cuvettes.

**Synthesis of [µ-1,2-Bis(diphenylphosphino)benzene]bis[Chlorogold(I)] (1).** In a round bottomed flask, thiodiethanol (0.45 ml, 2.22 mmol) in MeOH (3 ml) was added over 15 min to a solution of HAuCl$_4$·3H$_2$O (0.40 g, 1.11 mmol) in H$_2$O (5 ml)/MeOH (8 ml) kept at 0°C. After stirring for an additional 15 min, dppbz (0.25 g, 0.56 mmol) in a mixture of CHCl$_3$ (15 ml)/MeOH (10 ml) was added to the colorless gold solution yielding an immediate white precipitate. The mixture was warmed to room temperature (1 h) and MeOH (30 ml) was added to enhance the formation of precipitate. The white precipitate was filtered after stirring for additional 1 h and washed with MeOH and air dried to give 0.38 g. Recrystallization of the white powder from CH$_2$Cl$_2$-Et$_2$O gave 0.25 g. Crystals for x-ray analysis were grown by a slow diffusion in methylene dichloride/Et$_2$O.

**Synthesis of [µ-1,2-Bis(diphenylphosphino)benzene]bis[Bromogold (I)] (2).** Method A. To 0.25 g of 1 in a round-bottomed flask, dissolved in 15 ml CH$_2$Cl$_2$, was added slowly 0.28 g of Bu$_4$NBr, dissolved in 5 ml CH$_2$Cl$_2$, and the solution mixture was stirred
for 15 min. A cloudy white precipitate formed and stirring continued for 30 min. The solvent was reduced in vacuo to 5 ml. Excess methanol (20-30 ml) was added to facilitate the precipitation process. The white precipitate was filtered, recrystallized from CH₂Cl₂/Et₂O, and air-dried to yield 0.26 g. **Method B.** In a round bottomed flask, thiodiethanol (0.50 ml, 5.0 mmol) in MeOH (3 ml) was added over 15 min to a solution of HAuBr₄.2H₂O (0.50 g, 0.84 mmol) in H₂O (5 ml)/MeOH (8 ml) kept at 0°C. After stirring for an additional 15 min, dpbb (0.166 g, 0.37 mmol) in CHCl₃ (15 ml)/MeOH (10 ml) was added to the colorless gold solution yielding an immediate white precipitate. The mixture was warmed to the room temperature (1h) and MeOH (30 ml) was added to complete the precipitation process. The white precipitate was filtered after stirring for an additional 1h, washed with MeOH, and air dried to give 0.25 g. Recrystallization of the white powder from CH₂Cl₂/ether gave 0.20 g.

**Synthesis of [µ-1,2-Bis(diphenylphosphino)benzene]bis[Iodogold (I)] (3).** The same procedure was used as for 2, method A. Using Bu₄NI as the source of iodide. The sample was recrystallized from CH₂Cl₂/Et₂O to form an off-white solid.

**Synthesis of [µ-1,2-Bis(diphenylphosphino)benzene]bis[p-thiocresolatogold (I)] (4).** 0.05 g (0.05 mmol) of 1 was dissolved in 7 ml of CH₂Cl₂. 0.02 g (0.10 mmol) p-thiocresol was dissolved in 5 ml ethanol. 25 ml of 0.1 M NaOH was added slowly and the solution was stirred for 30 min. The thiolate solution was slowly added to the methylene dichloride solution of 1 and a yellow color formed immediately. Stirring was continued for 30 min and a yellow precipitate formed gradually. The volume was reduced to 5 ml in vacuo and more precipitate formed. The yellow precipitate was filtered and washed with
hexanes and ethanol. In order to get rid from the tetrahedral structure which formed I did the solvent extraction by water of \((\text{Au-p-tc})_2\text{dppbz}\) solution in methylene dichloride. The product was recrystallized from \(\text{CH}_2\text{Cl}_2/\text{hexanes}\) to yield 0.021 g.\(^5\) Table 6.1 shows the characterization data for \((\text{AuX})_2\text{dppbz}, \text{X} = \text{Cl}, \text{Br}, \text{I}, \text{and} \ p-C\text{H}_3\text{C}_6\text{H}_4\text{S}\). Figures 6.1, 6.2, and 6.3 show \(^1\text{H}\) NMR of dppbz ligand and its complexes.

**Abbreviations:** The following abbreviations are used: p-tc = p-thiocresol; pdt = 1,3-propanedithiol; dppe = 1,2-bis(diphenylphosphine)ethane; dppp = 1,2-bis(diphenylphosphine)propane; dppb = 1,2-bis(diphenylphosphine)butane; dpppn = 1,2-bis(diphenylphosphine)pentane.
Table 6.1. Summary of synthesis and characterization data for (AuX)₂dppbz, X = Cl, Br, I, or p-CH₃C₆H₄S:

<table>
<thead>
<tr>
<th>Complex</th>
<th>Yield (%) Unrec.</th>
<th>Analysis (%) Found (Calc) C</th>
<th>Analysis (%) Found (Calc) H</th>
<th>'H NMR Signals in CD₂Cl₂</th>
<th>³¹P ('H)NMR in CDCl₂&lt;sup&gt;a&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>(AuCl)₂dppbz, 1 White</td>
<td>75%</td>
<td>39.17 (39.54)</td>
<td>2.73 (2.65)</td>
<td>7.12-7.55 (m, 24H)</td>
<td>25.7 ppm(S)</td>
</tr>
<tr>
<td>(AuBr)₂dppbz.0.5Et₂O, 2 White</td>
<td>97%</td>
<td>37.90 (38.01)</td>
<td>3.14 (3.19)</td>
<td>7.16-7.55 (m, 24H)</td>
<td>26.0 ppm(S)</td>
</tr>
<tr>
<td>(AuI)₂dppbz, 3 Off-White</td>
<td>66%</td>
<td>33.10 (32.93)</td>
<td>2.19 (2.21)</td>
<td>7.20-7.60 (m, 24H)</td>
<td>26.9 ppm(S)</td>
</tr>
<tr>
<td>(Au-p-tc)₂dppbz, 4 Yellow</td>
<td>35%</td>
<td>48.52 (48.63)</td>
<td>3.40 (3.52)</td>
<td>2.24 (s, 6H, p-CH₃)</td>
<td>30.8 ppm(S)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>6.80(d,4H, m-H in p-tc)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>7.0-7.6 (m, 28H)</td>
<td></td>
</tr>
</tbody>
</table>

---

<sup>a</sup> dppbz ligand at -13.0(s)
Figure 6.1. $^1$H NMR spectrum in CDCl$_3$ of bis(diphenylphosphino)benzene.
Figure 6.2. $^1$H NMR spectrum in CD$_2$Cl$_2$ of (AuX)$_2$dpdz (a) $X =$ Cl; (b) $X =$ Br; (c) $X =$ I.
Figure 6.3. $^1$H NMR spectrum in CDCl$_3$ of (Au-p-$SC_{6}H_{4}$CH$_{3}$)$_2$dpdz (a) whole spectrum; (b) enlarged phenyl area.
Crystal Structure Analysis of [\(\mu-1,2\text{Bis(diphenylphosphino)benzene}\)]

\(\text{bis[Chlorogold(I)](I)}\). Crystals of \((\text{AuCl})_2\text{dppbz}\) were obtained as colorless needles from \(\text{CH}_2\text{Cl}_2\)-Et\(_2\)O. Crystal data, data collection and processing parameters are reported in Table 6.2. Selected bond lengths and angles are listed in Table 6.3. Atomic coordinates \([x 10^4]\) and equivalent isotropic displacement parameters \([\AA^2 x 10^3]\) for \((\text{AuCl})_2\text{dppbz}\) are given in Table 6.4. For x-ray examination and data collection, a suitable crystal, approximate dimensions \(0.45 \times 0.12 \times 0.08\) mm, was mounted on the tip of a glass fiber. X-ray data was carried out by Dr. J. Krause Bauer, Department of Chemistry, University of Cincinnati. Intensity data were collected at 293K on a Siemens SMART 1K CCD diffractometer (platform goniostat with \(\chi\) fixed at 54.69\(^\circ\), sealed-tube generator, graphite-monochromated Mo \(k\alpha\) radiation, \(\lambda = 0.71073\) Å). The structure was solved by a combination of the Patterson method using SHELXTL v5.1 and the difference Fourier technique and refined by full-matrix least squares on \(F^2\) for the reflections diffracting out to 0.75 Å. Non-hydrogen atoms were refined with anisotropic displacement parameters. Weights were assigned as \(w^{-1} = \sigma^2(F_0^2) + (a)p^2 + bp\) where \(a = 0.0299, b = 0.000\) and \(p = 0.33333F_0^2 + 0.66667F_0^2\). Hydrogen atoms were calculated based on geometric criteria and treated with a riding model. Hydrogen atom isotropic temperature factors were defined as \(U(C)\ast a = U(H)\) where \(a = 1.5\) for methyls and 1.2 for aromatics. \((\text{AuCl})_2\text{dppbz}\) crystallizes with a badly disordered solvent which appears to be Et\(_2\)O. A suitable disorder model could not be resolved, thus the solvent contribution was subtracted from the reflection data using the program SQUEEZE. The refinement converged with
crystallographic agreement factors of R1 = 4.29 %, wR = 6.60 % for 5769 reflections with I ≥ 2σ (I) (R1 = 8.86 %, wR2 7.64 % for all data) and 325 variable parameters.
Table 6.2. Crystal data and structure refinement for (AuCl)$_2$dpbb (1)

<table>
<thead>
<tr>
<th>Property</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Empirical formula</td>
<td>C$<em>{30}$H$</em>{24}$Au$_2$Cl$_2$P$_2$</td>
</tr>
<tr>
<td>Formula weight</td>
<td>911.27</td>
</tr>
<tr>
<td>Temperature</td>
<td>293(2) K</td>
</tr>
<tr>
<td>Wavelength</td>
<td>0.71073 Å</td>
</tr>
<tr>
<td>Crystal system, Space group</td>
<td>Orthorombic, Pbc</td>
</tr>
<tr>
<td>Unit cell dimensions</td>
<td>a = 16.955(3) Å, b = 18.160(2) Å, c = 22.225(1) Å</td>
</tr>
<tr>
<td>Volume, Z</td>
<td>6843.7(2) Å$^3$, 8</td>
</tr>
<tr>
<td>Density (calculated)</td>
<td>1.769 Mg/m$^3$</td>
</tr>
<tr>
<td>Absorption coefficient</td>
<td>8.830 mm$^{-1}$</td>
</tr>
<tr>
<td>F(000)</td>
<td>3408</td>
</tr>
<tr>
<td>Crystal size</td>
<td>0.45 x 0.12 x 0.08 mm</td>
</tr>
<tr>
<td>$\theta$ range for data collection</td>
<td>2.40 to 28.30$^0$</td>
</tr>
<tr>
<td>Limiting indices</td>
<td>-18 &lt; h &lt; 22, -23 &lt; k &lt; 24, -29 &lt; l &lt; 24</td>
</tr>
<tr>
<td>Reflections collected</td>
<td>45724</td>
</tr>
<tr>
<td>Independent reflections</td>
<td>8478 ($R_{int} = 0.0605$)</td>
</tr>
<tr>
<td>Max. and min. transmission</td>
<td>0.5385 and 0.1093</td>
</tr>
<tr>
<td>Refinement method</td>
<td>Full-matrix least-squares on F$^2$</td>
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<tr>
<td>Data/restraints / parameters</td>
<td>8478 / 0 / 325</td>
</tr>
<tr>
<td>Goodness-of-fit on F$^2$</td>
<td>1.048</td>
</tr>
<tr>
<td>Final R indices [I &gt; 2\sigma(I)]</td>
<td>R1 = 0.0429, wr2 = 0.0660</td>
</tr>
<tr>
<td>R indices (all data)</td>
<td>R1 = 0.0886, wR2 = 0.0764</td>
</tr>
<tr>
<td>Largest diff. Peak and hole</td>
<td>0.573 and −0.576 eÅ$^{-3}$</td>
</tr>
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Table 6.3. Selected bond lengths (Å) and angles (°) for (AuCl)$_2$dpbzt (1)

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<th>Bond/Angle</th>
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<th>Value 2</th>
</tr>
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<tr>
<td>Au(1)-P(1)</td>
<td>2.241(2)</td>
<td>Au(I)-Cl(1)</td>
</tr>
<tr>
<td>Au(1)-Au(2)</td>
<td>2.996(1)</td>
<td>Au(2)-P(2)</td>
</tr>
<tr>
<td>Au(2)-Cl(2)</td>
<td>2.293(2)</td>
<td>P(1)-C(7)</td>
</tr>
<tr>
<td>P(1)-C(1)</td>
<td>1.817(6)</td>
<td>P(1)-C(13)</td>
</tr>
<tr>
<td>P(2)-C(19)</td>
<td>1.821(6)</td>
<td>P(2)-C(14)</td>
</tr>
<tr>
<td>P(2)-C(25)</td>
<td>1.828(6)</td>
<td>C(13)-C(14)</td>
</tr>
<tr>
<td>P(1)-Au(1)-Cl(1)</td>
<td>173.07(6)</td>
<td>P(1)-Au(1)-Au(2)</td>
</tr>
<tr>
<td>Cl(1)-Au(1)-Au(2)</td>
<td>102.99(5)</td>
<td>P(2)-Au(2)-Cl(2)</td>
</tr>
<tr>
<td>P(2)-Au(2)-Au(1)</td>
<td>95.71(4)</td>
<td>Cl(2)-Au(2)-Au(1)</td>
</tr>
<tr>
<td>C(7)-P(1)-C(1)</td>
<td>104.1(3)</td>
<td>C(7)-P(1)-C(13)</td>
</tr>
<tr>
<td>C(1)-P(1)-C(13)</td>
<td>106.0(3)</td>
<td>C(7)-P(1)-Au(1)</td>
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<td>C(1)-P(1)-Au(1)</td>
<td>113.6(2)</td>
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<td>C(14)-C(13)-P(1)</td>
<td>123.4(4)</td>
<td>C(13)-C(14)-P(2)</td>
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Table 6.4. Atomic coordinates \([x \times 10^4]\) and equivalent isotropic displacement parameters \([\AA^2 \times 10^3]\) for \((\text{AuCl})_2\text{dppbz}\) (1).

<table>
<thead>
<tr>
<th></th>
<th>(x)</th>
<th>(y)</th>
<th>(z)</th>
<th>(U(\text{eq}))</th>
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<tr>
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<td>7635(1)</td>
<td>3973(1)</td>
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<td>4370(1)</td>
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<td>63(2)</td>
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<td>7298(3)</td>
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<td>8259(5)</td>
<td>7405(9)</td>
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<td>6204(3)</td>
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</table>
Results and Discussion

The reaction of \([\text{AuCl (thiodiethanol)}]\), generated \textit{in situ} by reduction of H\text{AuCl}_4 with thiodiethanol, with dppbz (2:1) leads to a linear two-coordination complex, (\text{AuCl})_2dppbz (1). Reacting 1 with Et_4NBr or Et_4NI leads to the formation of (\text{AuX})_2dppbz, X = Br (2), or I (3), respectively. The thiolato derivative, 4 is obtained by reacting 1 with deprotonated \(p\)-thiocresol. The thiolato substituent is prepared \textit{in situ} by deprotonation of \(p\)-thiocresol with an ethanol solution of NaOH. Isolated products were assigned on the basis of NMR spectroscopy and analytical data (Table 6.1).

The \(1^H\) NMR of dppbz in CDCl_3 shows a complex multiplet at 7.0-7.4 ppm (Figure 6.1). Coordination to gold derivatives shifts the peaks slightly downfield to 7.17-7.6 ppm with a noticeable splitting in the peaks (Figure 6.2-6.4). A singlet resonance is observed in all complexes in the \(31^P\{1^H\}\) NMR study, which indicates the presence of two equivalent phosphorous atoms at room temperature. The resonance of the free ligand is recorded at \(-13.0\) ppm and a downfield shift is observed upon coordination to gold(I). The chemical shift of 30.8 ppm for 4 is characteristic of phosphine gold \textit{thiolates}.\(^{3b}\)

Molecular Structure of (\text{AuCl})_2dppbz (1). The molecular structure of (\text{AuCl})_2dppbz (1) is shown in Figure 6.4; bond lengths and bond angles are reported in Table 6.3. The Au-Au distance of 3.0(1)Å is comparable to those observed for \text{Au}_4(tppb)(C≡CPh)$_4$, tppb = tetraphenylphosphinobenzene
Figure 6.4. Thermal probability ellipsoids of (AuCl)$_2$dppbz.
3.1541(4) Å,\(^7\) Au$_2$(μ-S$_2$C$_2$B$_{10}$H$_{10}$)(PPh$_3$)$_2$, 3.0746(9) Å,\(^8\) Au$_2$(μ-S$_2$C$_2$B$_{10}$H$_{10}$)(μ-dppee), 3.0195(5) Å,\(^8\) and Au$_2$(μ-S$_2$C$_2$B$_{10}$H$_{10}$)(μ-dppph), 2.9771(10) Å.\(^7\) The P-Au-Cl moieties are linear (−173') with a dihedral angle of 105.9'.

(AuCl)$_2$dppbz crystallizes in S-shaped layers with what appears to be badly distorted Et$_2$O solvent molecules. The solvent resides in the channels created by the S-shaped nature of the layers. Since the identity of the solvent is not exactly known, the crystallographic refinement was completed with the solvent contribution subtracted from the data.

The bond lengths of Au-Cl and Au-P, bond angle of P-Au-Cl, and Au...Au distance in (AuCl)$_2$dppbz (1), a benzene-bridged complex, are of similar values to cis-(AuCl)$_2$dppee, an ethylene-bridged complex.\(^9\) In cis-(AuCl)$_2$dppee, the Au-P and Au-Cl lengths are 2.239(5) and 2.299(5) Å, respectively, which are similar to those of 2.236(2) and 2.293(2) in 1. The P-Au-Cl angle in 1 of 173.21' is comparable to 173.2' in cis-(AuCl)$_2$dppee. The gold-gold interaction did not change greatly by replacing ethylene by phenyl; in cis-(AuCl)$_2$dppee the Au...Au distance is 3.05 Å, which is slightly greater than that in 1 3.0 Å.

**UV-vis and Photophysical Studies.** The W-vis spectra of (AuX)$_2$dppbz, X = Cl, Br, I, p-tol in methylene chloride at room temperature all show a broad UV absorption band ($\lambda_{max} = 280$ nm) that tails into the near visible. The UV-vis spectra for 1-4 in Figure 6.5 show a red shift in the onset of the manifold of low energy transitions going from X = Cl
to $X = SR$, which correlates to the softness of $X$. This trend indicates a significant contribution of the ligand, $X$ in the lowest energy transitions.

Luminescence studies on $(AuX)_2dppbz$ in degassed methylene chloride at room and low temperatures resulted in peaks indistinguishable from the solvent. Similar results were obtained for $(AuX)_2dppee$ under the same conditions.$^4$
Figure 6.5 UV-Visible spectra in CH₂Cl₂ solution of 4νX(4νX)²dppqz (X = C₄H₆, Y = Br, X = C₆H₅)
References


5. It has been noticed that [Au(dppbz)_2]^+ can be formed if the linear gold(I) complex, (Au-p-tc)_2dppbz, is left in methylene dichloride or chloroform for a few minutes. ^31P NMR for a pure sample of (Au-p-tc)_2dppbz (with a good elemental ananlysis) in CD_2Cl_2 or CDCl_3 showed a single peak at 30.82 ppm and after a few minutes another peak at 21.0 ppm started to appear due to [Au(dppbz)]^+. Independent synthesis of this complex showed a ^31P NMR peak at 21.0 ppm.


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65. Mohamed, A. A.; Bruce, A.; Bruce, M. 216th National Meeting of the American Chemical Society, Boston, MA, August 1998.


APPENDIX

CHAPTER 9

The electrochemistry of gold and silver complexes

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I. INTRODUCTION

Gold and silver belong to the group known as coinage metals. They occupy positions near
the bottom of the electrochemical series and so they are difficult to oxidize. Silver oxidizes
to Ag⁺ at +0.7996 V vs NHE while Au⁰ → Au⁺ oxidation takes place at +1.692 V and
Au⁺ → Au⁺² occurs at +1.498 V (Table 1). In contrast, metals near the top of the electro-
chemical series, such as Na, are very active, i.e. Na oxidizes to Na⁺ at −2.71 V vs NHE'.

The reactivity of Cu, Ag and Au decreases down the group². Although gold and silver are
often grouped together, their chemical and physical properties differ significantly, partly
as a result of increased relativistic effects for gold³. The effects of solvent interaction

---

The chemistry of organic derivatives of gold and silver
Edited by S. Patai and Z. Rappoport © 1999 John Wiley & Sons Ltd
The electrochemical investigations of gold and silver have employed a range of electrochemical techniques, working electrodes, solvents and reference electrodes. In compiling the tables that appear in this chapter, a decision was made to report all potentials as

<table>
<thead>
<tr>
<th>Reaction</th>
<th>Standard reduction potential</th>
<th>$E^0$, V vs NHE$^0$</th>
</tr>
</thead>
<tbody>
<tr>
<td>$\text{AgI} + e^- = \text{Ag} + I^-$</td>
<td>-0.15224</td>
<td></td>
</tr>
<tr>
<td>$\text{Ag}_2\text{CO}_3 + 2e^- = 2\text{Ag} + \text{CO}_3^{2-}$</td>
<td>-0.017</td>
<td></td>
</tr>
<tr>
<td>$\text{AgBr} + e^- = \text{Ag} + \text{Br}^-$</td>
<td>+0.07133</td>
<td></td>
</tr>
<tr>
<td>$\text{AgCl} + e^- = \text{Ag} + \text{Cl}^-$</td>
<td>+10.22233</td>
<td></td>
</tr>
<tr>
<td>$\text{AgNO}_3 + e^- = \text{Ag} + \text{NO}_3^-$</td>
<td>+0.564</td>
<td></td>
</tr>
<tr>
<td>$\text{AgF} + 2e^- = \text{Ag}+2\text{F}^-$</td>
<td>+0.779</td>
<td></td>
</tr>
<tr>
<td>$\text{Ag}^+ + e^- = \text{Ag}$</td>
<td>+0.7996</td>
<td></td>
</tr>
<tr>
<td>$\text{AuBr}_4^- + 3e^- = \text{Au} + 4\text{Br}^-$</td>
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</tr>
<tr>
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<tr>
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<td></td>
</tr>
<tr>
<td>$\text{Au}^+$</td>
<td>+1.692</td>
<td></td>
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<td>$\text{Ag}^{2+} + e^- = \text{Ag}^+$</td>
<td>+1.980</td>
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$^a$At 25°C and 1 atm
9. The electrochemistry of gold and silver complexes

<table>
<thead>
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<th>Reference Electrode</th>
<th>redox couples</th>
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<tbody>
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<td>SCE</td>
<td>Ag/AgCl'</td>
</tr>
<tr>
<td></td>
<td>+0.045 V</td>
</tr>
<tr>
<td></td>
<td>-0.307 V</td>
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<td></td>
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<td>-0.559 V</td>
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<tr>
<td>Ag/AgCl'</td>
<td>+0.307 V</td>
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<td></td>
<td>+0.241 V</td>
</tr>
<tr>
<td></td>
<td>+0.559 V</td>
</tr>
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<td>+0.604 V</td>
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<tr>
<td>Fe/Fc'</td>
<td>+0.307 V</td>
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<td>+0.352 V</td>
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<td>+0.197 V</td>
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<td>+0.252 V</td>
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<tr>
<td></td>
<td>+0.800 V</td>
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<tr>
<td>NHE</td>
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<tr>
<td></td>
<td>-0.197 V</td>
</tr>
<tr>
<td></td>
<td>-0.549 V</td>
</tr>
<tr>
<td></td>
<td>-0.800 V</td>
</tr>
</tbody>
</table>

*Read across table and add voltage factor to convert from one reference electrode or couple to another. All data taken from Reference 4.

Table 2 presents the conversion factors employed in discussions in the chapter. A survey of the electrochemical literature reveals that differences in conversion factors exist. Thus, Table 2 is provided only for the purpose of approximating potentials in different reference systems. The reader is referred to a number of excellent reference which discuss the complications involved in rigorously converting reference systems.

In compiling the redox couples for tables that appear in this chapter, we have routinely rounded peak potentials to the nearest 10 mV. Redox potential values that appear to occur outside the normal useful working range of a solvent at a particular electrode were not, in general, included in the tables. For ligands that have common or easily recognized abbreviations, these are also provided in the tables and may also be used in the text and equations. For many of the entries in the tables, notations have been made about reversible (rev), quasi-reversible (qr) or irreversible (ir) processes.

II. DITHIOLENES AND DISELENOLENES

In 1,2-dithiolene complexes (or the selenium analogs), there is extensive delocalization of the electrons through the \( \pi \) system of the ligand as well as with metal \( d_{\pi} \) orbitals of the corresponding symmetry. This extensive delocalization makes it possible for dithiolene complexes to exist with a range of electron populations. It also makes assignment of the metal oxidation states ambiguous. The 1,2-dithiolenes are expected to have more metal–ligand \( \pi \)-bonding than 1,1-dithiolenes (e.g. dithiocarbamates), which is evidenced by the short \( M-S \) bond lengths and facile reversible redox reactions in the former. In contrast, 1,1-dithiolen complexes, with strained four-membered chelate rings and deviation from ideal coordination geometries, are expected to show less reversible redox behavior and have weaker \( M-S \) bonds than 1,2-dithiolenes. Monomeric bis(1,2-dithiolene)
complexes may undergo one, two or three redox processes according to equation 1, where the two dithiolene ligands are represented simply by S_4.

\[
[M-S_4]^{2-} \rightleftharpoons [M-S_4]^+ \rightleftharpoons [M-S_4]^0 \rightleftharpoons [M-S_4]^+ \quad (1)
\]

The expansion in dithiolene chemistry is due to a wide variety of applications of this type of compound in fungicides, pesticides, fingerprint developers, specific analytical reagents and highly electrical conductors. There are a number of examples of 1,2-dithiolene and diselenolene gold complexes, but to our knowledge there are no examples of silver for which electrochemical data are available.

Electrochemical potentials obtained from cyclic voltammetry studies of gold 1,2-dithiolene and diselenolene complexes are listed in Table 37-21. These studies reveal

<table>
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<tr>
<th>Compound</th>
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<th>Ref.</th>
<th>Solvent</th>
<th>Ref.</th>
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<td>[Au(1a)]_2</td>
<td>[Au(mnt)]_2</td>
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<td>14</td>
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<td>[Au(oxdt-dt)]_2</td>
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<td>[Au(C_8H_4S_2)S]_2</td>
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<td>[Au(6a)]_2</td>
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<td>[Au(bd)]_2</td>
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<td>[Au(bdt)]_2</td>
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<td>CH_2Cl_2</td>
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<tr>
<td>[Au(8c)]_2</td>
<td>[Au(Bu-bdt)]_2</td>
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<tr>
<td>[Au(9a)]_2</td>
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<td>DMF</td>
<td>20</td>
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<td>[Au(10b)]_2</td>
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<td>+0.51 (rev)</td>
<td>Fe/Fe^+</td>
<td>DMF</td>
<td>20</td>
</tr>
</tbody>
</table>

^Polarography at dme.
^aNo wave found in the range 0 to -1.5 V.
^bNot observed.
a rich redox chemistry, consistent with the behavior of many other metal dithiolene complexes. There are several prominent features of the data; the redox couples are highly ligand dependent and many of the redox processes are reversible. Transition metal complexes with the maleonitridedithiolate ligand (mnt, 1) have been intensely studied since the mid-1960s when reports began to appear describing the ability of mnt to form highly colored transition metal complexes in interesting oxidation states. Cyclic voltammetry studies of square planar, \([\text{Au(mnt)}_2]^+\) complexes have measured the potentials for the \(0/1^-\), \(1^-/2^-\) and \(2^-/3^-\) couples. The first two redox couples are reversible in \(\text{CH}_2\text{Cl}_2\), DMF and MeCN (see equations 2 and 3). A seemingly wide range of redox potentials has been reported for the \(1^-/2^-\) couple. However, inspection of Table 4 reveals that the reference electrode/solvent systems employed are largely responsible for this difference. For example, the \(1^-/2^-\) couple at \(-0.96\ \text{V Vs Ag/AgClO}_4\) would be approximately \(-0.4 \text{V Vs SCE}\), which compares favorably with other values reported for this couple. While the \(2^-/3^-\) couple of the \([\text{Cu(mnt)}_2]^2-\) analog is electrochemically reversible, \([\text{Au(mnt)}_2]^+\) shows an irreversible electrochemical process in \(\text{CH}_2\text{Cl}_2\) at 200 mV per e\(^{-}\) (equation 4). This was further investigated by infrared spectroelectrochemistry which indicates that a chemically reversible process occurs at longer timescales. These differences were attributable to kinetics of the reactions and the electronic structure of the complexes.

\[
\begin{align*}
\text{[Au(mnt)}_2^+ + e^- & \rightleftharpoons \text{[Au(mnt)}_2^-] & \text{E}_{1/2} = +1.51 \text{ V} \quad (2) \\
\text{[Au(mnt)}_2^- + e^- & \rightleftharpoons \text{[Au(mnt)}_2]^2- & \text{E}_{1/2} = -0.54 \text{ V} \quad (3) \\
\text{[Au(mnt)}_2]^2- + e^- & \rightleftharpoons \text{[Au(mnt)}_2]^3- & \text{E}_c = -1.33 \text{ V} \quad (4)
\end{align*}
\]

The \(0/1^-\) couple in \([\text{Au(tfd)}]^-\) (tfd = bis(trifluoromethyl)dienedithiolate, la) occurs at a slightly lower potential (+1.32 V vs SCE in \(\text{CH}_2\text{Cl}_2\)) than the mnt counterpart. This is in accord with observations that in other transition metal 1,2-dithiolene complexes the ease of oxidation is dependent on X with X = Ph > CF3 > CN. Replacing sulfur with the less electronegative atom, selenium, results in a lower oxidation potential for \([\text{Au(tds)}]^-\) (tds = bis(trifluoromethyl)dienediselenolate, lb) relative to \([\text{Au(tfd)}]^-\). More electronegative substituents make a complex easier to reduce, as expected. Thus, the \(1^-/2^-\) couple for \([\text{Au(mnt)}_2]^+\) occurs approximately 500 mV more positive than the same couple for \([\text{Au(tds)}]^-\).

Similar electronic effects are observed for the cyclic ligands, 2a and 2b. The sulfur complex, \([\text{Au(C}_3\text{S}_2)]^-\), is oxidized quasi-reversibly at +0.72 V vs SCE (Figure 1a) while the selenium complex, \([\text{Au(C}_3\text{Se}_2)]^-\), undergoes an irreversible oxidation at +0.34 V (Figure 1b). Assignment of the \(0/1^-\) couple as a ligand-based oxidation was made on
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FIGURE 1. Cyclic voltammograms for \(4.7 \times 10^{-4}\) M compound in 0.1 M \([\text{Bu}_4\text{N}]\text{ClO}_4/\text{DMF}\) at room temperature and Scan rate of 100 mV s\(^{-1}\): (a) 2a; (b) 2b. Reproduced by permission of the Royal Society of Chemistry from Reference 13

the basis of ESR data, and is consistent with the electrochemical potentials observed. The \(1^-/2^-\) couple for the selenium complex is reversible (Figure 1b) and occurs at a lower potential than for the sulfur counterpart. The reason for the differences in reversibility for the sulfur and selenium derivatives is not apparent.

An interesting feature concerning the redox properties of the complex, \([\text{Au}(\text{dddt})_2]^-\) (dddt = 5,6-dihydro-1,4-dithiine-2,3-dithiolate, 3), is that the one-electron oxidized product, \([\text{Au}(\text{dddt})_2]\), can be isolated\(^\text{14}\). An X-ray analysis of the neutral complex reveals a square planar gold structure stacked in ‘dimeric’ units as a result of intermolecular S — S contacts. Extended Hückel calculations predict that the odd electron resides primarily in a \(\pi^*\) orbital of the ligand and suggests that oxidation of the monoanion is ligand based. Oxidation of the neutral complex to the monocation was also reported to occur at +0.82 V vs SCE\(^\text{14}\).

Incorporation of two of the sulfurs in an eight-membered ring has no apparent effect on the \(0/1^-\) couple, i.e. \([\text{Au}(\text{oxdt-dt})_2]^-\) (oxdt-dt = ortho-xylenedithiodithiolate, 4) oxidizes at the same potential as \([\text{Au}(\text{dddt})_2]^-\), +0.41 V vs SCE. The one-electron oxidized product, \([\text{Au}(\text{oxdt-dt})_2]\), was also isolated and characterized by elemental analysis\(^\text{15}\).

Gold complexes of dithiolene ligands containing many sulfur atoms are expected to be oxidized at lower potentials. This is demonstrated by \([\text{Au}(\text{C}_8\text{H}_4\text{S}_8)_2]^-\) (\(\text{C}_8\text{H}_4\text{S}_8 = 2-(4,5\text{-ethylene})-1,3\text{-dithiole-2-ylidene}-1,3\text{-dithiole-4,5-dithiolate}, 5\)), which oxidizes very readily to the neutral complex at +0.10 V vs SCE\(^\text{16}\). The partially oxidized complex, \([\text{Au}(\text{C}_8\text{H}_4\text{S}_8)_2]^+\), could also be obtained, which is of interest for molecular conductivity.
The electrochemistry of gold and silver complexes

The $0/1^-$ couple for $[\text{Au(dpdt)}]_2^-$ (dpdt = 6,7-dihydro-6-methylene-5H-1,4-dithiepine-2,3-dithiolate, 6D) occurs at +1.28 V vs SCE, which suggests that the electronic properties of dithiolene 6 are intermediate between mnt (1a) and tfd (1b). However, the $1^-/2^-$ couple is reported at +0.63 V vs SCE, which is significantly more positive than the $1^-/2^-$ couples for the other gold dithiolene complexes listed in Table 3. In addition, reduction of the monoanion, $[\text{Au(dpdt)}]_2^-$, is irreversible, in contrast to the other complexes, suggesting that in this case the product dianion is unstable.

A dithiolene ligand incorporating an oxygen atom in the ring backbone has recently been prepared and the corresponding nickel, copper and gold complexes were studied. The gold complex, $[\text{Au(diod)}]_2^-$ (diod = 1,4-dithia-6-oxa-2,3-dithiolate, 7), which was difficult to prepare, shows only a single irreversible oxidation at +0.64 V vs SCE. Reduction to the dianion was not observed up to -1.5 V vs SCE. Apparently, this dithiolene ligand is less able to delocalize negative charge.

A large number of derivatives of $[\text{Au(bdt)}]_2^-$ (bdt = benzene dithiolate, 8a) with different substituents on the aromatic part of the ligand have been prepared (8-11). The monoanionic gold complexes are typically green and contain square planar Au$^{II}$. Oxidation to the neutral complexes occurs at low, positive potentials and is dependent on the electronic properties of the aromatic substituents. The stability of the monoanion relative to the dianion is greater for $[\text{Au(8)}]_2^+$ than for $[\text{Au(mnt)}]_2^+$. An SCF-HF calculation using LANL1DZ core pseudopotentials was carried out on $[\text{Au(bdt)}]_-^2$. The calculation predicts that the HOMO is primarily a ligand-based Ti orbital while the LUMO is a mixed ligand/metal (ca 50% Au d$_{xy}$) orbital (see Figures 2a and 3). The HOMO should therefore be destabilized by electron-releasing substituents while the LUMO may be less sensitive to substituent electronic effects. The electrochemical data are consistent with this orbital description. Within series 9, the complex which is easiest to oxidize is $[\text{Au(9c)}]_2^-$ with two methoxy groups, while the complex which is hardest to oxidize is $[\text{Au(9f)}]_2^-$. Note that the CV data for this series of complexes are referenced against the Fe/Fe$^+$ couple and the sweep rate necessary to achieve chemical reversibility varied. Oxidation of $[\text{Au(9e)}]_2^-$ and $[\text{Au(9f)}]_2^-$ was irreversible even at $v = 1000$ V s$^{-1}$, suggesting that the neutral species was chemically unstable.
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(a)

(b)

LUMO + 1   M(Pz)  \( b_{1g} \)  5.52 eV
LUMO   \( \sigma^*(\gamma\gamma) b_{1g} \)  3.56 eV
HOMO   \( \pi_1 (\chi_2) b_{1g} \)  -4.14 eV
HOMO - 1   \( \pi_2 (\chi_2) b_{1g} \)  -4.98 eV
HOMO - 2   \( \pi_3 (\gamma) b_{1g} \)  -5.52 eV

\[ \Delta_1 \]

LUMO + 1   M(Pz)  \( b_{1g} \)  2.46 eV
LUMO   \( \sigma^*(\gamma\gamma) b_{1g} \)  -0.53 eV
SOMO   \( \pi_1 (\chi_2) b_{1g} \)  -3.18 eV
SOMO - 1   \( \pi_2 (\chi_2) b_{1g} \)  -3.56 eV
SOMO - 2   \( \pi_3 (\gamma) b_{1g} \)  -5.52 eV

\[ \Delta_2 \]

FIGURE 2. (a) Coordinate system of \( [\text{Au}(\text{Sa})_2^-] \) used in the \( \text{ab initio} \) calculation; (b) electronic structure in the valence region of \( I = [\text{Au}(\text{Sa})_2^-] \) (left) and \( I_a = [\text{Au}(\text{Sa})_2] \) (right). Reprinted with permission from Reference 20. Copyright (1995) American Chemical Society

FIGURE 3. Valence molecular orbital basis function coefficients according to the \( \text{ab initio} \) calculations on \( [\text{Au}(\text{Sa})_2^-] \). Reprinted with permission from Reference 20. Copyright (1995) American Chemical Society
9. The electrochemistry of gold and silver complexes

The 1-/2- couple has been reported for only a few members of the \([\text{Au(bdt)}_2]^-\) series. However, the available data suggest that substituent electronic properties also affect the reduction potential of the monoanion. The complex, \([\text{Au(tcdt)}]^-\) (tdt = 3,4,5,6-tetrachlorobenzene-1,2-dithioleate, 10b), with four electron-withdrawing chlorine atoms, is easier to reduce (−1.67 V vs \(\text{Ag/Ag}^+\)) than \([\text{Au(tdt)}]^-\) (tdt = toluene-3,4-dithioleate, 8b) with one electron-releasing methyl group (−1.95 V vs \(\text{Ag/Ag}^+\)).

An SCF-HF calculation on the neutral complex, \([\text{Au(bdt)}_2]\), reveals a similar ordering of the frontier orbitals compared to \([\text{Au(bdt)}_2]^-\) but with significantly different energies (see Figure 2b). Thus the calculation predicts that the odd electron in \([\text{Au(bdt)}_2]\) resides in a ligand-based orbital, consistent with experimental results from other laboratories which suggest that the 0/1- couple in \(\text{Au}^{II}\) dithiolenes is a ligand-based oxidation (vide supra).

### III. DITHIOCARBAMATES

Electrochemical data for gold dithiocarbamate (dtc) complexes are listed in Table 4. Van der Linden and coworkers studied a series of square planar \(\text{Au}^{III}\) dithiocarbamates, \([\text{Au(l2)}_2]\) and mixed 1,2-dithiolene and dithiocarbamate complexes, \(\text{Au(mnt)(dtc)}\) and \(\text{Au(tdt)(dtc)}\). Note that the potentials in these studies were all obtained using a rotating disk electrode. The data suggest that the 1-2- couple in \(\text{Au}^{III}\) dithiolenes is a ligand-based oxidation (vide supra).

<table>
<thead>
<tr>
<th>Compound</th>
<th>Alternative Formula</th>
<th>Redox couples (V)</th>
<th>Ref. Couple</th>
<th>Solvent</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>([\text{Au(12a)}]_2^+)</td>
<td>([\text{Au(dtc)}]_2^+)</td>
<td>0/1-0.29</td>
<td>SCE</td>
<td>CH$_2$Cl$_2$</td>
<td>10</td>
</tr>
<tr>
<td>([\text{Au(1b)}]_2^+)</td>
<td>([\text{Au(Me$_2$dtc)}]_2^+)</td>
<td>0/1-0.22</td>
<td>SCE</td>
<td>CH$_2$Cl$_2$</td>
<td>22</td>
</tr>
<tr>
<td>([\text{Au(1c)}]_2^+)</td>
<td>([\text{Au(Et$_2$dtc)}]_2^+)</td>
<td>0/1-0.26</td>
<td>SCE</td>
<td>CH$_2$Cl$_2$</td>
<td>22</td>
</tr>
<tr>
<td>([\text{Au(1d)}]_2^+)</td>
<td>([\text{Au(Pr$_2$dtc)}]_2^+)</td>
<td>0/1-0.28</td>
<td>SCE</td>
<td>CH$_2$Cl$_2$</td>
<td>22</td>
</tr>
<tr>
<td>([\text{Au(1e)}]_2^+)</td>
<td>([\text{Au(Bu$_2$dtc)}]_2^+)</td>
<td>0/1-0.29</td>
<td>SCE</td>
<td>CH$_2$Cl$_2$</td>
<td>22</td>
</tr>
<tr>
<td>([\text{Au(1f)}]_2^+)</td>
<td>([\text{Au(Ph$_2$dtc)}]_2^+)</td>
<td>0/1-0.19</td>
<td>SCE</td>
<td>CH$_2$Cl$_2$</td>
<td>22</td>
</tr>
<tr>
<td>([\text{Au(1a)}(1a)])</td>
<td>([\text{Au(mnt)(dtc)}])</td>
<td>0/1-0.46</td>
<td>SCE</td>
<td>CH$_2$Cl$_2$</td>
<td>10</td>
</tr>
<tr>
<td>([\text{Au(1a)}(1f)])</td>
<td>([\text{Au(mnt)(Ph$_2$dtc)}])</td>
<td>0/1-0.41 (rev)</td>
<td>SCE</td>
<td>CH$_2$Cl$_2$</td>
<td>22</td>
</tr>
<tr>
<td>([\text{Au(1a)}(1c)])</td>
<td>([\text{Au(mnt)(Et$_2$dtc)}])</td>
<td>0/1-0.45 (rev)</td>
<td>SCE</td>
<td>CH$_2$Cl$_2$</td>
<td>22</td>
</tr>
<tr>
<td>([\text{Au(1a)}(1e)])</td>
<td>([\text{Au(mnt)(Bu$_2$dtc)}])</td>
<td>0/1-0.46 (rev)</td>
<td>SCE</td>
<td>CH$_2$Cl$_2$</td>
<td>22</td>
</tr>
<tr>
<td>([\text{Au(1b)}(1a)])</td>
<td>([\text{Au(tdt)(dtc)}])</td>
<td>0/1-0.87</td>
<td>SCE</td>
<td>CH$_2$Cl$_2$</td>
<td>10</td>
</tr>
<tr>
<td>([\text{Au(12a)}]_2^+)</td>
<td>([\text{Au(Et$_2$dtc)}]_2^+)</td>
<td>0/1-0.80 (rev)</td>
<td>SCE</td>
<td>CH$_2$Cl$_2$</td>
<td>23</td>
</tr>
<tr>
<td>([\text{Au(12c)}]_2^+)</td>
<td>([\text{Au(Ph$_2$dtc)}]_2^+)</td>
<td>0/1-0.82</td>
<td>SCE</td>
<td>CH$_2$Cl$_2$</td>
<td>23</td>
</tr>
<tr>
<td>([\text{Au(12d)}]_2^+)</td>
<td>([\text{Au(Pr$_2$dtc)}]_2^+)</td>
<td>0/1-0.84</td>
<td>SCE</td>
<td>CH$_2$Cl$_2$</td>
<td>23</td>
</tr>
<tr>
<td>([\text{Au(12c)}]_2^+)</td>
<td>([\text{Au(Bu$_2$dtc)}]_2^+)</td>
<td>0/1-0.79</td>
<td>SCE</td>
<td>CH$_2$Cl$_2$</td>
<td>23</td>
</tr>
<tr>
<td>([\text{Au(12g)}]_2^+)</td>
<td>([\text{Au(Bn$_2$dtc)}]_2^+)</td>
<td>0/1-0.75</td>
<td>SCE</td>
<td>CH$_2$Cl$_2$</td>
<td>23</td>
</tr>
<tr>
<td>([\text{Ag(Co(12d)})_2]_2^+)</td>
<td>([\text{Ag(Bn$_2$dtc)}]_2^+)</td>
<td>0/1-1.05</td>
<td>SCE</td>
<td>CH$_2$Cl$_2$</td>
<td>23</td>
</tr>
</tbody>
</table>

*Rev. = cathodic sweep.
*CH$_2$Cl$_2$ = propylene carbonate.
*PC = toluene.
Pt disk electrode. In contrast to the gold 1,2-dithiolene complexes, only one redox couple has been reported for the complexes containing dithiocarbamates. The monocations reduce at less negative potentials than the neutral, mixed complexes. The \( 0/1^- \) couple for \([\text{Au}(12)_2]^{+}\) is irreversible and is fairly insensitive to the substituents bonded to nitrogen. Similarly, in the mixed 1,1- and 1,2-dithiolene complexes, the 0/1\(^-\) couple is more sensitive to the nature of the 1,2-dithiolene ligand rather than to the substituents on the 1,1-dithiolene ligand.

\[
\begin{align*}
(12a) & \quad R = \text{H} \\
(12b) & \quad R = \text{Me} \\
(12c) & \quad R = \text{Et} \\
(12d) & \quad R = \text{Pr} \\
(12e) & \quad R = \text{Bu} \\
(12f) & \quad R = \text{Ph} \\
(12g) & \quad R = \text{Bn}
\end{align*}
\]

Reduction of a series of Au\(^{II}\) dithiocarbamates, \([\text{Au}(S_2CNR_2)_3]\), \(R = \text{Et (12c), Pr (12d), Bu (12e) and Bn (12g)}\), was investigated by polarography, chronamperometry and cyclic voltammetry at a mercury electrode. All the complexes show one main reduction wave in the polarogram in a fairly narrow potential range, \(-0.76 \text{ V to } -0.82 \text{ V vs SCE}\). Constant potential coulometry gave \(n\) values of 2.27–2.93 for the series. The nonintegral values for \(n\) are indicative of a chemical reaction coupled to the electron transfer process. Cyclic voltammograms of the series were more complex than the polarograms. For example, the cyclic voltammogram for \([\text{Au}(12c)_3]\) is shown in Figure 4. The major reduction peak at \(c. -1.4 \text{ V vs Ag/Ag}^+\) (\(-0.8 \text{ vs } \text{SCE}\)) is assigned as the 0/1\(^-\) couple.

**FIGURE 4.** Cyclic voltammogram for \(4.0 \times 10^{-6} \text{ M } [\text{Au}(12c)_3]\) in 0.2 M NaClO\(_4\)/propylene carbonate at 25°C and scan rate of 50 mV s\(^{-1}\). Reproduced by permission of The Australian Journal of Chemistry from Reference 23.
9. The electrochemistry of gold and silver complexes

There are also two smaller reduction waves at more positive potentials. Similar cyclic voltammograms displaying three cathodic reduction peaks and two anodic oxidation peaks were obtained for the other complexes in this series. The main reduction peak for each gold complex is similar to the peak obtained from the polarographic study (see Table 4, values labeled c). The nonintegral $n$ values and the complex CVs were attributed to dissociation of the dithiocarbamate ligand upon reduction of $\text{Au}^{III}(\text{dtc})_3$ to $[\text{Au}^{I}(\text{dtc})_3]^{2-}$, followed by reaction of free dtc with the mercury electrode (see Scheme 1).

$$[\text{Au}^{III}(\text{dtc})_3]^0 + 2e^- \rightarrow [\text{Au}^{I}(\text{dtc})_3]^{2-} \text{(unstable)}$$

$$[\text{Au}^{I}(\text{dtc})_3]^{2-} \rightarrow \text{Au}^{I}(\text{dtc}) + 2(\text{dtc})^-$$

$$(\text{dtc})^- + \text{Hg}^0 \rightarrow \text{Hg}^{II}(\text{dtc}) + e^-$$

$$2\text{Hg}^{II}(\text{dtc}) \rightarrow \text{Hg}^{IV}(\text{dtc})_2 + \text{Hg}^0$$

SCHEME 1

The final entry of Table 4 represents the only example we found of a silver dithiocarbamate complex for which electrochemical data have been reported. Addition of AgBF$_4$ to cobalt tris dithiocarbamate complexes has been reported by Bond and coworkers. In the absence of silver, a fully reversible redox couple occurs which is assigned to the $[\text{Co}(\text{S}_2\text{CN}_{2R})_3]^+/\text{Co}(\text{S}_2\text{CN}_{2R})_3$ couple. When R = Fr (12d), this redox couple occurs at +0.355 V (vs Fe/Fe$^+$). Upon addition of AgBF$_4$ to the toluene/CH$_2$Cl$_2$ solution of Co(12d)$_3$ several new redox couples appear. The electrochemical data are consistent with the existence and stability of the complex cation, $[\text{Ag}([\text{Co}(12d)_3])^+]$, in solution. Reduction of the complex cation occurs at $ca -1.1$ V and this is assigned to a process involving reduction of the silver ion. Oxidation occurs at +0.83 V which is assigned as involving one of the cobalt dtc ligands. The solid state structure of $[\text{Ag}([\text{Co}(12d)_3])^+]$BF$_4$ reveals a central Ag$^+$ ion in a highly distorted tetrahedral geometry coordinated by four sulfurs from the dtc ligands, bridging between Ag and Co. There is no direct Ag–Co bond. The solution interactions of a number of cobalt, rhodium and indium tris dtc complexes with Ag$^+$ were also investigated.

IV. L$_2$Au AND L$_n$Ag COMPLEXES

The series of gold(I) bis(diphenylphosphine) compounds, $[\text{Au}(13a-d)_2]^+$, shown in Table 5, was studied extensively by McArdle and Bossard. Cyclic voltammetry at a gold electrode shows diffusion controlled, reversible or quasi-reversible behavior consistent with a two-electron process ($\text{Au}^{I/II}$ redox couple) occurring at potentials $ca +0.6$ V $\pm 0.2$ V vs SCE. Bulk electrolysis studies on $[\text{Au}(13a)_2]\text{PF}_6$ indicate that 2 electrons (1.81 and 1.83) are removed during oxidation at +0.7 V, while the peak-to-peak splitting in the CV study was 37 mV, indicative of near-idealized two-electron behavior ($0.591/n$). The other complexes showed similar CV peak-to-peak separations. The bulk electrolysis experiment for $[\text{Au}(13b)_2]\text{PF}_6$ was complicated by decomposition of the oxidized product and the generation of another redox active compound. This prevented the authors from completing the electrolysis and resulted in an estimate for the $n$ value of $>1.7$ before the secondary process became significant. The oxidation products of $[\text{Au}(13c)_2]\text{PF}_6$ and $[\text{Au}(13d)_2]\text{PF}_6$ were too unstable for the authors to attempt bulk electrolysis experiments. McArdle and Bossard were also able to gain significant insight into the electrochemical process by performing UV-vis-spectroelectrochemistry
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TABLE 5. Cyclic voltammetry data (V) of L2Au and L4Ag complexes (L = phosphine or arsine, n = 1, 2)

<table>
<thead>
<tr>
<th>Compound</th>
<th>Alternative Formula</th>
<th>Oxidations</th>
<th>Reductions</th>
<th>Ref. couple</th>
<th>Solvent</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>[Au(13a)2]⁺</td>
<td>[Au(dppb)z]⁺</td>
<td>+0.46 (ap)</td>
<td>SCE</td>
<td>MeCN</td>
<td>25</td>
<td></td>
</tr>
<tr>
<td>[Au(13b)2]⁺</td>
<td>[Au(dp Pen)₂]⁺</td>
<td>+0.57 (ap)</td>
<td>SCE</td>
<td>MeCN</td>
<td>25</td>
<td></td>
</tr>
<tr>
<td>[Au(13c)2]⁺</td>
<td>[Au(dppe)z]⁺</td>
<td>+0.46 (ap)</td>
<td>SCE</td>
<td>MeCN</td>
<td>25</td>
<td></td>
</tr>
<tr>
<td>[Au(13d)2]⁺</td>
<td>[Au(dpPh)z]⁺</td>
<td>+0.75 (ap)</td>
<td>SCE</td>
<td>MeCN</td>
<td>25</td>
<td></td>
</tr>
<tr>
<td>Au[P(C₆H₅)₃]₂⁺</td>
<td>+0.78 (ap)</td>
<td>SCE</td>
<td>MeCN</td>
<td>26</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Au[P(OC₆H₅)₃]₂⁺</td>
<td>+1.10</td>
<td>SCE</td>
<td>MeCN</td>
<td>26</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ag(14)⁺</td>
<td>+1.17 (ap)</td>
<td>Ag/AgCl</td>
<td>Acetone</td>
<td>27</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Au(15a)₂⁺</td>
<td></td>
<td>−0.45 (ap)</td>
<td>Ag/AgClO₄</td>
<td>MeCN</td>
<td>28</td>
<td></td>
</tr>
<tr>
<td>Au(15b)₂⁺</td>
<td></td>
<td>−0.17 (ap)</td>
<td>Ag/AgClO₄</td>
<td>MeCN</td>
<td>28</td>
<td></td>
</tr>
<tr>
<td>Ag(15a)₂⁺</td>
<td></td>
<td>−0.03 (ap)</td>
<td>Ag/AgClO₄</td>
<td>MeCN</td>
<td>28</td>
<td></td>
</tr>
<tr>
<td>Ag(15b)₂⁺</td>
<td></td>
<td>+0.26 (ap)</td>
<td>Ag/AgClO₄</td>
<td>MeCN</td>
<td>28</td>
<td></td>
</tr>
</tbody>
</table>

on [Au(13a)₂]PF₆. During oxidation at +1.26 V they found clean conversion of one species to another as evidenced by a series of isosbestic points. They proposed that during oxidation, tetrahedral gold(I) is converted to square-planar gold(II). The differences in the electrochemical behavior of the series were proposed to be a consequence of the lability of the gold–phosphorus bond and the overall rigidity of the four-coordinate gold compounds.

Anderson and coworkers investigated the effect of added phosphine to solutions of Au(PR₃)₃Cl, which results in additional phosphine ligands attaching to a central gold(I) atom as shown in equation 5.

\[
\text{Au(PR₃)₃Cl} + (n - 1)\text{PR₃} \rightleftharpoons \text{Au(PR₃)ₙ}^+ + \text{Cl}^- \quad (5)
\]

\[\text{PR₃} = \text{PPh₃} \text{ or P(OC₆H₅)₃}, \quad n = 2-4\]
9. The electrochemistry of gold and silver complexes

Conductivity data show that adding PPh3 to the nonelectrolyte solution of Au(PPh3)Cl in MeCN produces a weakly conducting solution at 1–2 equivalents of PPh3, and a strongly conducting solution at >4 equivalents of PPh3, indicative of the presence of a 1:1 electrolyte. By keeping the amount of added phosphine low, Anderson and coworkers ensured that the multiple equilibria implied in equation 5 involved predominately \( n = 1 \) and 2, thereby allowing them the opportunity to investigate the electrochemical oxidation of \([\text{Au}(\text{PPh}_3)_2]^+\) and \([\text{Au}(\text{POC}_2\text{Ng})_3)_2]^+\) (see Table 5). Interestingly, the cationic complex, \([\text{Au}(\text{PPh}_3)_2]^+\), is easier to oxidize than \([\text{Au}(\text{PPh}_3)_3]^-\) (\(+1.54 \text{ V vs SCE}\))

Interestingly, the \(+0.2 \text{ V}\) oxidation wave at \(+1.54 \text{ V vs SCE}\) of \([\text{Au}(\text{PPh}_3)_3]^-\) is also in line with the expectations from comparisons of the \(\text{Au}^{III}\) and \(\text{Ag}^{II}\) redox couples discussed in the introduction. Rauchfuss and coworkers also reported that the fully reversible \(\text{Cu}^{II}\) redox couple found for the copper analog, \(\text{Cu}(\text{I})^+\), occurs at \(+0.77 \text{ V vs Ag/AgCl}\).

Reduction of the gold and silver complexes of \(15\) was investigated by cyclic voltammetry at a Pt electrode. These data afford an interesting comparison of the electrochemical behavior of Au vs Ag and P vs As. The Au(I) complexes are harder to reduce than the corresponding Ag(I) complexes, which reflects the relative chemical stability of Au(II) and Ag(I). The Au(III) complex, \([\text{Ag}(15\text{b})_2][\text{ClO}_4]_3\), decomposes readily in the presence of water, chloride, and many organic solvents. A qualitative comparison of the reduction potential of \([\text{Au}(15\text{a})_2]^3+\) (\(-0.45 \text{ V vs Ag/AgCl}\) or \(+0.15 \text{ V vs SCE}\)) with the reversible redox couple for \([\text{Au}(13\text{a})_2]^+\) (\(+0.46 \text{ V vs SCE}\)) is also in line with the difference in electronic properties of methyl vs phenyl groups on P.

V. PHOSPHINE GOLD HALIDES

The electrochemical properties of phosphine gold halide compounds have been the subject of a number of investigations. Anderson and coworkers reported that \(\text{Au}(\text{PPh}_3)_3\) and \(\text{Au}(\text{PET})_3\) undergo oxidations at \(+1.54 \text{ V}\) and \(+1.51 \text{ V}\), respectively (vs SCE), in MeCN solutions at 100 mVs\(^{-1}\) (see Table 6). The oxidation process for \(\text{Au}(\text{PET})_3\) involves a broad irreversible oxidation wave, is diffusion controlled (i.e., \(i_{\text{p}}/n^{1/2}\) is constant) and the value of \(E_{\text{p}}\) shifts positively with an increase in scan rate. On the basis of cyclic voltammetry, bulk electrolysis and UV-vis spectroelectrochemistry studies, the authors conclude that an overall two-electron oxidation of \(\text{Au}^+ \rightarrow \text{Au}^{II}\) occurs, followed by a faster chemical reaction. The \(n\) value for bulk electrolysis of \(\text{Au}(\text{PET})_3\) was found to be \(2.0 \pm 0.5\). Cyclic voltammetry studies for \(\text{Au}(\text{PET})_3\) show no reduction process out to \(-2.0 \text{ V}\), except when the oxidation wave at \(+1.51 \text{ V}\) is scanned, whereby a reduction wave at \(+0.20 \text{ V}\) is observed. The observation is made that the presence of a reduction wave at \(-2.0 \text{ V}\) implies formation of a gold(III) ionic species, similar to the reduction wave which appears for \(\text{K}[\text{AuCl}_4]^{-}\). In addition, reduction of \([\text{AuCl}_4]^{-}\) in the presence of phosphine, PR3, regenerates \(\text{Au}(\text{PR})_3\). Spectroelectrochemical data show that upon oxidation of \(\text{Au}(\text{PET})_3\) at \(+1.45 \text{ V vs Pt pseudoreference}\) a band at 310 nm appears. This band is assigned to \(\text{AuCl}_4^{-}\). The electrochemistry of \(\text{Au}(\text{PPh}_3)_3\) was found to be very similar.
TABLE 6. Electrochemical data (V) of phosphine gold halide complexes

<table>
<thead>
<tr>
<th>Compound</th>
<th>o.x.</th>
<th>Red.</th>
<th>Ref. couple</th>
<th>Solvent</th>
<th>Reference</th>
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</thead>
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<td>Ag/AgCl</td>
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<td>Fc/Fc⁺</td>
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<td>-0.49</td>
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<td>+1.12</td>
<td>SCE</td>
<td>MeCN</td>
<td>31</td>
</tr>
</tbody>
</table>

aReduction wave appearing after oxidation.

Two other studies have appeared which also assign the oxidation of Au(PPh₃)Cl as involving a two-electron Au⁺ → Au⁺⁺ irreversible process\(^{29,30}\). In contrast, Rakhimov and coworkers have recently suggested that the oxidation of Au(PPh₃)Cl is a one-electron process involving phosphine\(^{29}\). Their analysis is based, in part, on similar oxidation currents observed in cyclic voltammetry experiments of Au(PPh₃)Cl solutions containing equal concentrations of ferrocene, a well-known one-electron redox couple\(^{31}\).

Substituting alkyl phosphines for aromatic phosphines or phosphites has only a minor effect on the oxidation potentials in two separate studies\(^{26,29}\). Substitution of less electronegative halides for chloride might be expected to make the oxidation of gold(I)–halide moieties easier. This was indeed observed in cyclic voltammetry studies in 0.05 M [Et₄N]BF₄/MeCN solution at a Pt working electrode where Au(PPh₃)Br and Au(PPh₃)I are 27 mV and 53 mV, respectively, easier to oxidize than Au(PPh₃)Cl\(^{29}\). However, Nelson and coworkers found little change when Br⁻ is substituted for Cl⁻ in cyclic voltammetry experiments run in 0.1 M [Bu₄N]ClO₄/CH₂Cl₂ solution at a Pt working electrode; oxidation of Au(PPh₃)Br occurs at +1.14 V and for Au(PPh₃)Cl at +1.13 V vs Fc/Fc⁺ (see Table 6)\(^{30}\). The oxidation potentials of gold(I) \(1\)-phenyldibenzophosphole (16) halide compounds are also insensitive to halide substitution. Oxidation of Au(16)Cl occurs at +1.07 V vs Fc/Fc⁺ and for Au(16)Br at +1.03 V\(^{30}\). In fact, all four compounds investigated by Nelson and coworkers are reported to oxidize within a narrow range 1.09 V ± 0.06 V (vs Fc/Fc⁺)\(^{30}\). Substitution of more electronegative halides for bromide might be expected to result in making reduction of gold(III) easier. Nelson and coworkers...
9. The electrochemistry of gold and silver complexes

observe this for AuLX₃ compounds (L = PPh₃, 16; X = Cl, Br) where substitution of Br⁻ for Cl⁻ decreases the average Au(III) reduction potential by 150 mV³⁰.

Ligand 17 is believed to act as a monodentate ligand for Au⁺, coordinated through the phosphine only, on the basis of ¹³C NMR data which show that the aromatic carbon atoms bonded to nitrogen remain practically unchanged, in contrast to the carbon atoms bonded to phosphorus which are shielded after complexation. The oxidation of Au(17)Cl and Au(17)₂Cl complexes was studied by Castan and coworkers³¹. The major anodic process of Au(17)Cl is an irreversible wave occurring at +1.75 V (see Table 6) which is assigned as Au⁺ to Au³⁺. A shoulder at +0.95 V occurs which is assigned to oxidation of the free ligand (+0.87 V vs SCE). In the cyclic voltammogram of Au(17)₂Cl, there is also a shoulder at ca 0.95 V and a major oxidation wave at +1.12 V, which is assigned as a Au⁺⁺⁺ oxidation. The authors suggest that increasing the coordination number around gold from two in Au(17)Cl to three in Au(17)₂Cl is responsible for decreasing the oxidation potential. This observation is further supported by comparison with the redox couple for the four-coordinate Au⁺ complex, [Au(13a)₂]⁺, found in Table 5. This simple relationship is illustrated in Figure 5.

![Figure 5. Oxidation potentials vs coordination number: □ Au(17)Cl, +1.75 V; ○ Au(17)₂Cl, +1. 12 V; ▲ [Au(13a)₂]⁺, +0.46 V. All potentials vs SCE.](image-url)
VI. PHOSPHINE GOLD THIOLATES AND MIXED DONOR LIGANDS

The electrochemistry of a series of neutral phosphine gold(I) thiolate complexes has been investigated. The series includes cyclic dinuclear gold(I) complexes formed from 1,2-propanedithiolate (pdt, 18) and bis-chelating phosphines, $\text{Au}_2(\text{dppe})(\text{pdt})$, and open dinuclear gold(I) complexes formed from para-thiocresolate ($\text{p-tc}$, 19) and bis-chelating phosphines, $\text{Au}_2(\text{dppe})(\text{p-tc})_2$, and a mononuclear complex, $\text{Au}(\text{PPh}_3)(19)$. Oxidative cyclic voltammetry experiments were performed at Pt and glassy carbon electrodes in 0.1 M [Bu$_4$N]PF$_6$/MeCN and CH$_2$Cl$_2$ solutions. Adsorption effects occurred in all electrode/solvent combinations investigated and were minimized by wiping the electrode between each CV experiment. Scan rates between 50 and 500 mV s$^{-1}$ were employed and several replications at each scan rate were obtained. Table 7 shows the results of the oxidative cyclic voltammetry experiments at a Pt working electrode in 0.1 M [Bu$_4$N]PF$_6$/CH$_2$Cl$_2$ solution.

![Chemical structure](18) ![Chemical structure](19)

The position and wave shape of the oxidation processes were somewhat dependent on the electrode/solvent combination. The effect of changing the solvent from CH$_2$Cl$_2$ to

<table>
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<tr>
<th>Compound</th>
<th>Alternative formula</th>
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<th>Reductions</th>
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<th>Reference</th>
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<td>$\text{Au}_2(\text{dppe})(\text{pdt})$</td>
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<td>+1.56 (ir)</td>
<td>CH$_2$Cl$_2$</td>
<td>32</td>
</tr>
<tr>
<td>$\text{Au}_2(\text{13g})(\text{19})_2$</td>
<td>$\text{Au}_2(\text{dppe})(\text{p-tc})_2$</td>
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<tr>
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<td>+1.56 (ir)</td>
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</tr>
<tr>
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<td>CH$_2$Cl$_2$</td>
<td>34</td>
<td></td>
</tr>
</tbody>
</table>

$^a$All studies employed a Pt working electrode except as noted. Reference was SCE in all studies, except Reference 35 which was Fc/Fc$^+$. $^b$Adsorption wave appears at +0.47 V. $^c$Glassy carbon working electrode.
9. The electrochemistry of gold and silver complexes

MeCN in cyclic voltammetry experiments of Au₂(13c)(18) at glassy carbon is illustrated in Figure 6. The broadness of the irreversible oxidation wave shown in Figure 6b was noted in the study. The difference between the potential maximum and half currents \(E_{pa} - E_{pa/2}\) was found to be 150 mV. A similar observation about broadness in the oxidation wave of phosphine gold halide complexes was made by Anderson and coworkers during investigation of the oxidation of Au(PEt₃)Cl₂. The first oxidation process of all complexes shown in Table 7 occurs at +0.7 V ± 0.1 V (vs SCE), with the possible exception of Au₂(13c)(18) for which the presence of an adsorption wave at +0.47 makes the exact potential of the first oxidation process somewhat difficult to determine. The first oxidation process is followed by a second one which occurs between +1.2 V and +1.6 V (see Table 7). With the exception noted for Au₂(13c)(18), substituting aromatic thiolate, 19, for alkyl thiolate, 18, shifts both the first and second oxidation processes to lower potentials. Figure 7 shows the 0.0 V to +2.0 V cyclic voltammograms for Au₂(13c)(18) and Au₂(13g)(18) in CH₂Cl₂ or MeCN solutions. Lengthening the bis-chelating phosphine from 13c to 13g has only a small effect on the overall cyclic voltammogram waveshape (compare Figure 7a and 7c). It has been noted that for a particular solvent/electrode combination the first oxidation wave broadens as the length of the bis-chelating phosphine becomes very short (i.e. 13e, not shown) and may indicate weak coupling of the two gold(I) redox centers.

Comparison of the oxidation processes of Au(PPh₃)X (see Figure 8, X = halide) shows an inverse linear relationship between the oxidation potentials and the electronegativity of the X ligand. Since the electronegativity of sulfur is similar to iodine, oxidation of phosphine gold thiolate complexes may be expected to occur near +1.0 V. However, as shown in Table 7, the first oxidation occurs at ca 200–400 mV lower potential. In addition, constant potential electrolysis studies at +1.0 V result in formation of the disulfide, \(p-\text{CH}_3\text{C}_6\text{H}_4\text{S}^{-}\text{SC}_6\text{H}_4\text{CH}_3-p\) and \(n\) values of 1 and 0.5 for the dinuclear and mononuclear gold(I) complexes, respectively. The lowest transition state energy of phosphine gold(I) thiolate complexes has been assigned as a sulfur-to-metal charge transfer. This assignment and the formation of disulfide are consistent with sulfur-based oxidation, in contrast to Au(PPh₃)X where gold-based oxidation was suggested by several authors. This

![Figure 6](image-url)
Ahmed A. Mohamed, Alice E. Bruce and Mitchell R. M. Bruce

FIGURE 7. Cyclic voltammograms at a glassy carbon electrode at room temperature: (a) $4.8 \times 10^{-4}$ M $\text{Au}_2(13\text{c})(18)$ in 0.1 M $\text{[Bu}_4\text{N}]\text{PF}_6/\text{CH}_2\text{Cl}_2$ at scan rate 200 mV s$^{-1}$, (b) $4.7 \times 10^{-4}$ M $\text{Au}_2(13\text{c})(18)$ in 0.1 M $\text{[Bu}_4\text{N}]\text{PF}_6/\text{MeCN}$ at scan rate 50 mV s$^{-1}$, (c) $4.8 \times 10^{-4}$ M $\text{Au}_2(13\text{c})(18)$ in 0.1 M $\text{[Bu}_4\text{N}]\text{PF}_6/\text{CH}_2\text{Cl}_2$ at scan rate 100 mV s$^{-1}$. Reproduced by permission of Freund Publishing House from Reference 32

difference may be significant for the biological activity of phosphine gold thiolate complexes such as Auranofin, since the redox chemistry of gold(I) centers interacting with thiol groups of proteins and enzymes may be critical to the mechanism of action of a drug.

The electrochemistry of gold(I) complexes with pyridine-2-thiolate, 20, was investigated by Laguna and coworkers34. The gold(I) cationic complexes $[\text{Au}_2(13\text{c})(20)]^+$ and $[\text{Au}_2(13\text{c})(20)]^{2+}$ undergo irreversible oxidations at +1.42 V and +1.46 V, respectively, during cyclic voltammetry experiments at a Pt disk working electrode recorded at 200 mV s$^{-1}$ in 0.1 M $\text{[Bu}_4\text{N}]\text{PF}_6/\text{CH}_2\text{Cl}_2$ solution. No reduction waves were observed out to $-1.8$ V. The reference electrode was SCE, which was standardized against either the $[\text{Fe(η-C}_5\text{H}_5)_2]^{2+}$ or the $[\text{Fe(η-C}_5\text{Me}_5)_2]^{2+}$ couple as an internal standard ($E^0 = 0.47$ V and $-0.09$ V, respectively).

The electrochemistry of a square-planar gold(II) complex with 2-(diphenylphosphino) benzenethiolate (21) was reported by Dilworth and coworkers35. Cyclic voltammetry experiments on $[\text{Au}(21)_2]^2\text{BPh}_4$ indicate a reversible redox couple at $-0.862$ V (vs the Fe/Fe$^+$ reference couple) in 0.2 M $\text{[Bu}_4\text{N}]\text{BF}_4/\text{MeCN}$ solution. Peak-to-peak separation of the redox waves was 84.2 mV and convolution methods were used to establish that the redox couple was reversible and involved the same number of electrons as the ferrocene/ferrocenium couple under identical conditions. The reductive scan was assigned
9. The electrochemistry of gold and silver complexes

![Graph](image)

**FIGURE 8.** Electronegativity of halides vs oxidation potentials of phosphine gold(I) halides: (a) Au(PPh3)Cl, +1.54 V; (b) Au(PPh3)Br, +1.27 V; (c) Au(PPh3)I, +1.01 V. The oxidation potentials of Au(PPh3)Br and Au(PPh3)I were converted to the SCE scale using Table 2.

![Structures](image)

(20) (21)

as Au\textsuperscript{+} \rightarrow Au\textsuperscript{II}. The reversibility of the redox couple under slow scan rate conditions (50 mV s\textsuperscript{-1}) indicates that the gold(II) complex is stable over the time scale of the electrochemical experiment. In contrast, the neutral Pt(II) and Pd(II) analogs, Pt(21)\textsubscript{2} and Pd(21)\textsubscript{2}, are electrochemically inactive over the accessible range of DMF (−2.4 V to +1.2 V relative to ferrocene).

The synthesis, characterization and electrochemical investigation of an interesting series of gold(II) complexes with o-aminobenzenethiolate ligands has been reported by Gosh, Manoharan and coworkers\textsuperscript{36}. The ligands are noteworthy, because they have both hard and soft donor atoms which may contribute to stabilizing gold(II) complexes. The dinuclear gold(II) complex, 22a, is prepared by the reaction of NaAuCl\textsubscript{4} with o-aminobenzenethiol. The isomer, 22b, forms after refluxing 22a for 2 hours in dry, degassed methanol, while the mononuclear complex, 22c, is formed upon dissolution, refluxing and workup of 22a in DMF. ESR measurements in DMF solution on 22a and 22b show a seven-line pattern (1:2:3:4:3:2:1) assigned as two interacting gold(II) nuclei (Au, I = \frac{3}{2}, 100%). The
mononuclear complex, \( \text{22c} \), shows a four-line pattern. Close agreement between the ESR experimental results and simulation was found. Cyclic voltammetry experiments at a Pt working electrode in 0.1 M \([\text{Et}_4\text{N}]\text{ClO}_4/\text{MeCN}\) solution at 50 mV s\(^{-1}\) show two sets of reversible redox couples for \( \text{22a} \) and \( \text{22b} \) and one for \( \text{22c} \) (see Table 7). The small shifts in the pairs of redox couples for \( \text{22a} \) and \( \text{22b} \) support the idea that these complexes are isomers with \( \text{Au(I)} \) atoms in slightly different electronic environments. The complexes \( \text{22a-c} \) all display a broad irreversible reduction wave at \( \text{ca} -1.0 \text{ V} \), presumably due to reduction of \( \text{Au}^{2+} \) to \( \text{Au}^+ \). The \( \text{o-aminobenzenethiol} \) ligand does not show any redox behavior in this region.

![Diagram of 22a and 22b complexes]

Ghosh, Manoharan and coworkers have also reported on a pair of isomers formulated as shown below, \( \text{23a} \) and \( \text{23b} \).\(^{37}\) Four-line patterns were observed in the ESR of each of these complexes which appear to originate from one interacting gold nucleus. The authors
9. The electrochemistry of gold and silver complexes

![Diagram]

suggest that the complexes have Au(II)-stabilized radical structures containing oxidized ligands where the unpaired electron is highly delocalized onto the ligand. Cyclic voltammetry experiments demonstrate that the redox behavior of these complexes is somewhat complicated, in contrast to the relatively well-behaved features found in 22a and 22b. On oxidative scans, both complexes show irreversible oxidation processes occurring at about +1.2 V. On reductive scans, a reversible couple occurs near +0.1 V, but there is also a broad reduction wave at ca +0.35 V that appears coupled to two successive oxidative processes occurring near +0.4 V and +0.6 V. The origin of these redox features is not discussed.

![Diagram]

VII. PHOSPHORUS YLIDES

Dinuclear gold(I) and gold(II) phosphorus ylide complexes have been the subject of several separate electrochemical investigations by Fackler and coworkers and Laguna and coworkers. The neutral, cyclic bis-ylide, gold(I) complex, 24, undergoes two quasi-reversible, stepwise oxidations at +0.11 and +0.24 V (vs Ag/AgCl) (see Table 8). The stepwise oxidations presumably involve one electron each, to form a gold(II)-gold(II)
complex. Precipitation of a yellow compound complicated efforts of further electrochemical analysis. The cyclic gold(II)–gold(II) halogen adducts, 25a–c, all show one irreversible reduction wave and the potentials are dependent on the nature of the halogen ligands. The reductions are followed by a chemical reaction that generates 24, which can be clearly detected electrochemically. Bulk electrolysis of the Au(II) halogen adducts yields an n value of 2 electrons per molecule. For 25c two quasi-reversible oxidation waves are seen, whereas for 25a and 25b only ill-defined, irreversible oxidation processes are observed. The electrochemistry of 25d and 25e is complicated by an equilibrium that involves 24 which results in deteriorating electrochemical signals. Therefore, the potentials listed in Table 8 for 25d and 25e were obtained under conditions of excess alkyl halide.

Cyclic voltammetry experiments on cyclic, dinuclear gold(I) ylide dithiocarbamate complexes, 26a–c, show irreversible oxidation processes between +0.30 V and +0.4 V (see Table 8). Electrochemical analysis was complicated by formation of a coating on the Pt electrode surface. These complexes oxidize at potentials which are intermediate between

![Diagram showing cyclic voltammetry data](image)

**Table 8. Cyclic voltammetry data (V) of phosphorus ylide complexes**

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<th>Ox1</th>
<th>Ox2</th>
<th>Red1</th>
<th>Red2</th>
<th>Ref. couple</th>
<th>Solvent</th>
<th>Reference</th>
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<td></td>
<td>Ag/AgCl</td>
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<td>39</td>
</tr>
<tr>
<td>25a</td>
<td>+1.5</td>
<td>-0.92 (ir)</td>
<td></td>
<td></td>
<td>Ag/AgCl</td>
<td>THF</td>
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</tr>
<tr>
<td>25b</td>
<td>+1.22</td>
<td>-0.69 (ir)</td>
<td></td>
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<td>Ag/AgCl</td>
<td>THF</td>
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<tr>
<td>25c</td>
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<td>-0.58 (ir)</td>
<td>-1.18</td>
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<td>THF</td>
<td>39</td>
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<td></td>
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<td>Ag/AgCl</td>
<td>THF</td>
<td>39</td>
</tr>
<tr>
<td>25e</td>
<td>+0.42</td>
<td>-0.68</td>
<td></td>
<td></td>
<td>Ag/AgCl</td>
<td>THF</td>
<td>39</td>
</tr>
<tr>
<td>26a</td>
<td>+0.30 (ir)</td>
<td></td>
<td></td>
<td></td>
<td>SCE</td>
<td>CH2Cl2</td>
<td>40</td>
</tr>
<tr>
<td>26b</td>
<td>+0.37 (ir)</td>
<td></td>
<td></td>
<td></td>
<td>SCE</td>
<td>CH2Cl2</td>
<td>40</td>
</tr>
<tr>
<td>26c</td>
<td>+0.42 (ir)</td>
<td></td>
<td></td>
<td></td>
<td>SCE</td>
<td>CH2Cl2</td>
<td>40</td>
</tr>
<tr>
<td>27</td>
<td>+0.53 (ir)</td>
<td></td>
<td></td>
<td></td>
<td>SCE</td>
<td>CH2Cl2</td>
<td>34</td>
</tr>
<tr>
<td>28a</td>
<td>a</td>
<td>-0.44 (ir)</td>
<td></td>
<td></td>
<td>SCE</td>
<td>CH2Cl2</td>
<td>34</td>
</tr>
<tr>
<td>28b</td>
<td>a</td>
<td>-0.43 (ir)</td>
<td></td>
<td></td>
<td>SCE</td>
<td>CH2Cl2</td>
<td>34</td>
</tr>
</tbody>
</table>

*Oxidation wave observed at +0.55 (ir) after reduction*
9. The electrochemistry of gold and silver complexes

\[ \text{Ph}_2\text{P} \quad \text{Au} \quad \text{S} \quad \text{N} \quad \text{R} \]

(26a) \( R = \text{Me} \)
(26b) \( R = \text{Et} \)
(26c) \( R = \text{Bn} \)

those of \( [\text{Au}_2\{\mu - \text{S}_2\text{CN}(\text{CH}_2\text{Ph})_2\}] \) (irreversible wave at +1.15 V)\(^{40}\) and \( 24 \). Increasing the electron-donating ability of the substituent groups on the dithiocarbamate ligands from Bz to Me leads to a decrease in the oxidation potential.

Dinuclear gold(I) and gold(II) complexes of pyridine-2-thiolate, \( 27, 28a \) and \( 28b \), were studied by cyclic voltammetry at a Pt working electrode in \( \text{CH}_2\text{Cl}_2 \). The dinuclear gold(I) complex, \( 27 \), has an irreversible, extended oxidation process at +0.53 V vs SCE. No reduction wave was observed out to -1.8 V. The cyclic voltammograms for the dinuclear gold(II) complexes show irreversible reduction waves at -0.44 V (28a) and -0.43 V (28b). After reduction, the return oxidation scan shows an irreversible oxidation process at +0.55 V, indicative of the presence of \( 27 \).

\[ \text{Ph}_2\text{P} \quad \text{Au} \quad \text{S} \quad \text{N} \quad \text{X} \]

(27) \( X = \text{Cl} \)
(28a) \( X = \text{Br} \)
(28b)

VIII. ORGANO METALLICS

The electrochemistry of a fairly large number of organometallic gold compounds has been studied (Table 9). With few exceptions, these complexes also contain a triphenylphosphine (or a derivative) ligand. Many of the compounds exhibit ‘typical’ linear, two-coordinate gold, with the organometallic ligand coordinated to gold through a Au-C single bond. Gold–gold bonding is also possible, and there are several examples of three-coordinate gold organometallic compounds that have been investigated.

The prototypical gold(I) organometallic compounds are \( \text{Au(PPh}_3\text{)}\text{R} \) (\( R = \text{Me, Ph} \)). They are oxidized at +1.6 V (vs Ag/AgCl) and reduced at ca -1.6 V (see Table 9)\(^{39}\). Comparing these potentials with those for \( \text{Au(PPh}_3\text{)}X \) (\( X = \text{Cl, Br and I} \), Table 6) suggests that the alkyl and aryl groups in \( \text{Au(PPh}_3\text{)}\text{Me} \) and \( \text{Au(PPh}_3\text{)}\text{Ph} \), respectively, are electronically similar to the chloride anion. The effects of different substituent groups on the oxidation potentials of a series of \( \text{Au(PPh}_3\text{)}\text{R} \) compounds can be explained on the basis of simple electronegativity arguments. Placing an electron-donating methoxy group in the para position of the aryl group makes oxidation of \( \text{Au(PPh}_3\text{)}(4-\text{MeOC}_6\text{H}_4) \) ca 300 mV easier than for \( \text{Au(PPh}_3\text{)}\text{R} \) (\( R = \text{Me, Ph} \)), while a para fluoride makes \( \text{Au(PPh}_3\text{)}(4-\text{FC}_6\text{H}_4) \) ca 400 mV harder to oxidize. Cyanide has a similar effect (\( R = \text{CN, CH}_2\text{CN etc.} \)), as do the other electron-withdrawing groups, \( \text{CH(COR)}_2 \) (\( R = \text{Me, Ph or t-Bu} \)). Note that the
Ahmed A. Mohamed, Alice E. Bruce and Mitchell R. M. Bruce

TABLE 9. Cyclic voltammetry data (V) of organometallic complexes

<table>
<thead>
<tr>
<th>Compound</th>
<th>Oxidations</th>
<th>Reductions</th>
<th>Conditions</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Au(PPh₃)Me</td>
<td>+1.59</td>
<td>−1.63</td>
<td>a</td>
<td>29</td>
</tr>
<tr>
<td>Au(PPh₃)Ph</td>
<td>+1.61, +1.97</td>
<td>−1.73</td>
<td>a</td>
<td>29</td>
</tr>
<tr>
<td>Au(PPh₃)(4-MeOC₆H₄)</td>
<td>+1.28, +1.71</td>
<td>b</td>
<td>a</td>
<td>29</td>
</tr>
<tr>
<td>Au(PPh₃)(4-FC₆H₄)</td>
<td>+2.00</td>
<td>b</td>
<td>a</td>
<td>41</td>
</tr>
<tr>
<td>Au(PPh₃)CN</td>
<td>+2.25</td>
<td>−0.78</td>
<td>c</td>
<td>29</td>
</tr>
<tr>
<td>Au(PPh₃)CH₂CN</td>
<td>+2.24</td>
<td>−0.98</td>
<td>c</td>
<td>29</td>
</tr>
<tr>
<td>Au(PPh₃)CH(COOEt)CN</td>
<td>+2.17</td>
<td>−0.79</td>
<td>c</td>
<td>29</td>
</tr>
<tr>
<td>Au(PPh₃)CH(CO₂Et)CN</td>
<td>+2.30</td>
<td>−1.00, −1.91</td>
<td>c</td>
<td>29</td>
</tr>
<tr>
<td>Au(PPh₃)CH(COME₂)</td>
<td>+2.00</td>
<td>−1.64</td>
<td>a</td>
<td>29</td>
</tr>
<tr>
<td>Au(PPh₃)CH(COME)(COPh)</td>
<td>+2.05</td>
<td>−1.60</td>
<td>a</td>
<td>29</td>
</tr>
<tr>
<td>Au(PPh₃)CH(CO₂Bu-t)₂</td>
<td>+1.96</td>
<td>−1.56</td>
<td>a</td>
<td>29</td>
</tr>
<tr>
<td>Au(PPh₃)CH(CO₂Bu-t)₂</td>
<td>+1.86</td>
<td>−1.60, −1.78</td>
<td>a</td>
<td>29</td>
</tr>
<tr>
<td>Au(PPh₃)CH₄CN</td>
<td>+0.61, +0.80, +2.09</td>
<td>b</td>
<td>a</td>
<td>41</td>
</tr>
<tr>
<td>Au(PPh₃)CH₄CN</td>
<td>+0.57, +0.72, +0.86, +2.13</td>
<td>b</td>
<td>a</td>
<td>41</td>
</tr>
<tr>
<td>29a</td>
<td>+0.76 (ir), +1.01 (qr)</td>
<td>e</td>
<td>42</td>
<td></td>
</tr>
<tr>
<td>29b</td>
<td>+0.74 (ir), +1.03 (qr), +2.05</td>
<td>e</td>
<td>42</td>
<td></td>
</tr>
<tr>
<td>29c</td>
<td>+0.78 (ir), +1.05 (qr), +1.66, +1.73, +1.88</td>
<td>e</td>
<td>42</td>
<td></td>
</tr>
<tr>
<td>29d</td>
<td>+0.74 (ir), +1.05 (qr), +1.27, +1.39, +1.54, +1.70</td>
<td>e</td>
<td>42</td>
<td></td>
</tr>
<tr>
<td>29e</td>
<td>+0.66 (ir), +1.08 (qr), +1.97</td>
<td>e</td>
<td>42</td>
<td></td>
</tr>
<tr>
<td>29f</td>
<td>+0.95 (ir), +1.11 (qr)</td>
<td>e</td>
<td>42</td>
<td></td>
</tr>
<tr>
<td>29g</td>
<td>+0.93 (ir), +1.11 (qr)</td>
<td>e</td>
<td>42</td>
<td></td>
</tr>
<tr>
<td>29h</td>
<td>+0.98 (rev)</td>
<td>f</td>
<td>43</td>
<td></td>
</tr>
<tr>
<td>29i</td>
<td>+1.03 (rev)</td>
<td>f</td>
<td>43</td>
<td></td>
</tr>
<tr>
<td>30a</td>
<td>+0.24</td>
<td>b</td>
<td>a</td>
<td>44</td>
</tr>
<tr>
<td>30b</td>
<td>+0.81</td>
<td>−1.66</td>
<td>a</td>
<td>44</td>
</tr>
<tr>
<td>31a</td>
<td>+0.68, +1.62</td>
<td>−1.62</td>
<td>a</td>
<td>44</td>
</tr>
<tr>
<td>31b</td>
<td>+0.88, +1.81</td>
<td>−1.77</td>
<td>a</td>
<td>44</td>
</tr>
<tr>
<td>32</td>
<td>+0.72, +2.21</td>
<td>−2.21</td>
<td>a</td>
<td>44</td>
</tr>
<tr>
<td>33</td>
<td>+0.48, +1.36, +1.97</td>
<td>−1.84</td>
<td>a</td>
<td>29</td>
</tr>
<tr>
<td>34</td>
<td>+1.52, +1.94</td>
<td>b</td>
<td>h</td>
<td>29</td>
</tr>
<tr>
<td>35</td>
<td>+0.79, +1.08, +1.41, +2.04, +2.08</td>
<td>−1.36</td>
<td>h</td>
<td>29</td>
</tr>
<tr>
<td>36</td>
<td>−0.62, −0.84</td>
<td>i</td>
<td>45</td>
<td></td>
</tr>
</tbody>
</table>

---

*Pt working electrode. 0.05 M [Et₄N][BF₄]/MeCN, Ag/AgCl reference couple.

*No reduction observed at Pt working electrode.

*Glassy carbon working electrode, Ag/AgCl reference couple in CH₂Cl₂, potentials reported vs SCE.

*SCE reference in CH₂Cl₂.

*Reduction of the nitro group.

*Ag/AgCl reference couple in MeCN/CH₂Cl₂ (1:10).

*SCE reference in MeCN.
9. The electrochemistry of gold and silver complexes

electron-releasing t-butyl groups in Au(PPh₃)CH(COBu-t)₂ have only a modest effect on the oxidation potential.

Replacing triphenylphosphine with ferrocenyl-derivatized phosphines adds additional redox centers with very rich organometallic chemistry of their own. The cyclic voltamogram of Au(PPh₃)(4-FC₆H₄) shows an oxidation process at ca +2 V, similar to that of Au(PPh₃)(4-FC₆H₄), and two additional redox processes at +0.61 V and +0.80 V that appear to be associated with coupled, iron-based redox processes.

A number of dinuclear gold(I) complexes containing the 1,1'-bis(diphenylphosphino)ferrocene (dppf) ligand, 29a–i, have been analyzed electrochemically. On the basis of the above discussion, two oxidation processes are expected, one that is ferrocenyl-based and the other associated with the organogold fragment. Indeed, this is what is reported for 29a. However, the situation is obviously more complicated for the other dinuclear gold(I) complexes (29b–i), where up to six anodic processes are reported in the range of 0–2 V (see Table 9). In the dppf chemistry of other transition metals, the dppf ligand is often found chelated to a single metal. This suggests that in solution the two Au'R redox centers might easily encounter each other to produce redox coupling, resulting in splitting of peaks, or perhaps initiating a facile chemical reaction, following the electron transfer process.

There are several other factors that make it difficult to assign the redox processes in 29b–i. The oxidation potential of the dppf ligand is somewhat solvent-dependent. The dppf redox couple is generally reversible; however, in the presence of water, the dppf ligand undergoes a fast chemical reaction following oxidation. In cyclic voltammetry experiments run under similar conditions but employing different electrodes, the oxidation potentials reported for dppf are +0.68 V vs SCE at Pt in 0.1 M [NBu₄]PF₆/CH₂Cl₂ at 100 mV s⁻¹ and +0.97 V vs SCE at glassy carbon in 0.1 M [NBu₄]PF₆/CH₂Cl₂ at 100 mV s⁻¹, which suggests that the nature of the electrode also significantly affects the oxidation potential.

In compounds 29a–g, the quasi-reversible oxidations at ca +1.0–1.1 V occur almost identically where dppf oxidizes at a glassy carbon electrode, which suggests that the redox process at this potential is iron (dppf) based. The anodic waves occurring at lower potentials in the range between +0.66 V and +0.95 V have been assigned as one-electron oxidations of gold in 29a–g. Comparing the first oxidation potential of Au(PPh₃)Ph (+1.61 V) vs Au(PPh₃)(4-FC₆H₄) (+2.00 V), it is expected that the pentafluorinated phenyl substituent in 29h would push gold-based oxidation to much higher potentials, possibly switching the lowest energy oxidation process to a dppf-based oxidation. In cyclic voltammetry experiments on 29h, the first oxidation process (+0.98 V at a Pt electrode) is reversible with peak-to-peak splitting of 60 mV, suggesting that this is indeed what has occurred. Until more data are available, e.g. bulk electrolyses as a function of
potential, it is prudent to reserve judgment about the assignment of these redox processes. Nevertheless, what is evident is the rich electrochemistry of these complexes.

The electrochemistry has been reported for a variety of other structural types, notably compounds where one \( \text{AuPPh}_3 \) is directly attached to a Cp ligand in ferrocene \((30a, b)_4^4\), two \( \text{AuPPh}_3 \) units are bonded to the same carbon on a Cp ring stabilized by intramolecular gold–gold interactions \((31a, b)_4^4\), two \( \text{AuPPh}_3 \) units are coordinated to a sulfur substituent on a Cp ring \((32)\) and a series of compounds where \( \text{AuPPh}_3 \) is sequentially added to cyclopentadiene \((33–35)_2^9\). The reduction potentials for \(30–35\) occur in a fairly narrow range (see Table 9). However, the oxidation processes vary tremendously (e.g. compare \(33\) vs \(34\)) suggesting significantly different electrochemical properties that would be quite interesting to investigate further.

Finally, the electrochemistry of the organometallic gold(III) carborane complex, \(36\), has been reported\(^4^5\). The cyclic voltammogram of \(36\) in MeCN solution shows two redox processes. The first is a reversible redox couple \((-0.62 \text{ V vs SCE})\) that has been assigned as a one-electron reduction to a stable gold(II) complex. The second reduction process...
9. The electrochemistry of gold and silver complexes

involves a quasi-reversible redox couple, presumably to the gold(I) carborane. Strong
evidence that the intermediate redox compound is a gold(II) complex was found by
investigating the electrochemistry of an isolated gold(II) compound made by reduction of
36 with sodium amalgam. The dianionic gold(II) compound displays an initial cathodic
process (−0.92 V vs SCE) similar to that found in the second reduction process of 36
(−0.84 V vs SCE). In addition, a reversible redox process is observed at −0.62 V vs SCE
for oxidation of the gold(II) compound.

![Diagram of gold complex]

**IX. DRUGS**

Although the antibacterial effects of silver and the biological activity of gold have long
been known, few electrochemical studies have appeared on the redox properties of gold
and silver complexes of biological importance. Gold complexes such as [Au(13c)2]+ have
been shown to be potent cardiovascular toxins while complexes such as Auranofin. 37,
have been used successfully to treat rheumatoid arthritis. While the mechanism of action
of anti-inflammatory gold drugs is not clear, the interaction of gold(I) centers with the
thiol groups of proteins and enzymes is believed to play a role.

![Complex structure](image)

Pérez and coworkers investigated the reduction of 37 at a dropping mercury electrode.
Figure 9 shows the electrochemical behavior of 37 in deoxygenated alkaline 0.06 M
K₃PO₄ ethanol/water (1 : 1) solution using dc polarography (a) and differential pulse
polarography (b) techniques. The polarographic techniques were used to establish that the
electrochemical processes are diffusion controlled and reversible in alkaline media. Bulk
electrolysis at −0.8 V leads to an n value of 0.9 electrons per molecule and suggests
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FIGURE 9. Electrochemical behavior of Auranofin, 37, in deoxygenated alkaline 0.06 M K₃PO₄ ethanol/water (1:1) solution: (a) direct current polarography; (b) differential pulse polarography. Reproduced by permission of the American Pharmaceutical Association from Reference 48

FIGURE 10. The pH dependence on $E_{1/2}$ of Auranofin, 37. Reproduced by permission of the American Pharmaceutical Association from Reference 48

that the reduction involves the $\text{Au}^{1/0}$ redox couple. Interestingly, the reduction potential is strongly sensitive to the pH values below 8.5 as shown in Figure 10. Above a pH of 9, there is no proton-dependent pathway and the redox couple appears at $-0.5 \text{ V vs SCE}$ (see Table 10). Below a pH of ca 8.5, a proton-dependent reduction pathway is indicated. Protonation of triethylphosphine (equation 6, $pK_a = 8.69$) is believed to be responsible for the shift in potential as a function of pH. A linear relationship between the limiting current and Auranofin concentration was also noted in the concentration range $3.63 \times 10^{-5}$ to $5.1 \times 10^{-4}$ M. Effects of adsorption processes at the electrode surface
9. The electrochemistry of gold and silver complexes

TABLE 10. Electrochemical data (V) of gold drugs

<table>
<thead>
<tr>
<th>Compound</th>
<th>Alternative formula</th>
<th>Oxidations</th>
<th>Reduction Conditions</th>
<th>Solvent</th>
<th>pH</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>37</td>
<td>Auranofin</td>
<td>-0.5</td>
<td>a</td>
<td>EtOH/H2O</td>
<td>&gt; 9</td>
<td>48</td>
</tr>
<tr>
<td>Au(41)</td>
<td>Au[L-cysteine]</td>
<td>+1.19</td>
<td>b</td>
<td>H2O</td>
<td>1.67</td>
<td>49</td>
</tr>
<tr>
<td>Au(42)</td>
<td>Au[D-penicillamine]</td>
<td>+1.14, +1.35</td>
<td>b</td>
<td>H2O</td>
<td>1.67</td>
<td>49</td>
</tr>
</tbody>
</table>

\(^a\) Polarography, SCE reference, dropping mercury working electrode

\(^b\) Cyclic voltammetry, SCE reference, Pt working electrode

appear at concentrations above \(3 \times 10^{-4}\) M.

\[
P(C_2H_5)_3 + H^+ \rightleftharpoons [P(C_2H_5)_3H]^+ \quad (6)
\]

The reducing properties of antiarthritic drugs such as Auranofin, 37, sodium aurothiomalate (myocrisin), 38, sodium aurothiopropanol sulfonate (allocrysin), 39, and aurothioglucose (solganol), 40, were investigated by Huck and coworkers\(^5\). The standard redox potentials of drugs which instantly react with the oxidant, 5,5'-dithiobis-(2-nitrobenzoic acid), were determined by titration with potassium hexacyanoferrate(III) in a 0.1 M phosphate buffer (pH 7.0, 25°C), at a dropping mercury electrode using a SCE reference. Unfortunately, none of the gold-containing compounds reacted very quickly with the oxidant and the standard potentials could not be measured directly even after long incubation periods in phosphate buffer at 37°C\(^5\).

Anderson and Sawtelle have investigated the aqueous redox processes for the electrogenerated gold(I) species, \([\text{AuCl}_2]^\text{-}\), complexed by biologically relevant ligands such as cysteine, 41, and penicillamine, 42\(^9\). They propose an aqueous reduction mechanism that begins with \([\text{AuCl}_2]^\text{-}\) as illustrated in equations 7–9. The progress of these electron transfer and coupled chemical reactions can be followed by cyclic voltammetry and UV-vis spectroelectrochemistry. Upon formation of \([\text{AuCl}_2]^\text{-}\), addition of 41 or 42 leads to complexation and changes in the electrochemistry which allows an estimation of the oxidation potentials (see Table 10) of the Au[cysteine] and Au[penicillamine] complexes. Cyclic voltammetry control experiments with cysteine, cystine and penicillamine indicate that the observed electrochemical responses do not originate from these free species in solution.

\[
[\text{AuCl}_4]^\text{-} \rightleftharpoons [\text{AuCl}_2]^\text{+} + 2 \text{Cl}^- \quad (7)
\]

\[
[\text{AuCl}_2]^\text{+} + 2 e^- \rightleftharpoons [\text{AuCl}_2]^\text{-} \quad (8)
\]

\[
[\text{AuCl}_2]^\text{-} + e^- \rightleftharpoons \text{Au} + 2 \text{Cl}^- \quad (9)
\]

Anderson and Sawtelle have investigated the aqueous redox processes for the electrogenerated gold(I) species, \([\text{AuCl}_2]^\text{-}\), complexed by biologically relevant ligands such as cysteine, 41, and penicillamine, 42\(^9\). They propose an aqueous reduction mechanism that begins with \([\text{AuCl}_2]^\text{-}\) as illustrated in equations 7–9. The progress of these electron transfer and coupled chemical reactions can be followed by cyclic voltammetry and UV-vis spectroelectrochemistry. Upon formation of \([\text{AuCl}_2]^\text{-}\), addition of 41 or 42 leads to complexation and changes in the electrochemistry which allows an estimation of the oxidation potentials (see Table 10) of the Au[cysteine] and Au[penicillamine] complexes. Cyclic voltammetry control experiments with cysteine, cystine and penicillamine indicate that the observed electrochemical responses do not originate from these free species in solution.

\[
[\text{AuCl}_4]^\text{-} \rightleftharpoons [\text{AuCl}_2]^\text{+} + 2 \text{Cl}^- \quad (7)
\]

\[
[\text{AuCl}_2]^\text{+} + 2 e^- \rightleftharpoons [\text{AuCl}_2]^\text{-} \quad (8)
\]

\[
[\text{AuCl}_2]^\text{-} + e^- \rightleftharpoons \text{Au} + 2 \text{Cl}^- \quad (9)
\]
Kovacic using cyclic voltammetry measurement at either Pt or dropping mercury working electrodes\textsuperscript{52}. Unfortunately, because of the low solubility of 43 in 0.1 M KH\textsubscript{2}PO\textsubscript{4}/0.1 M NaOH solution (pH 7.0), no reduction wave was observed.

X. IMIDES AND ANILIDES

Two series of linear silver salts of imides and anilides, formulated as [Ag(L\textsubscript{2})\textsubscript{2}]NEt\textsubscript{4} (amide = 44a–h) and [Ag(L\textsubscript{2})]Ag (L = 44a–e), have been studied using linear voltammetry, cyclic voltammetry and coulometry at \textsuperscript{6} and vitreous electrodes in acetonitrile\textsuperscript{53,54}. The linear voltammograms obtained for [Ag(L\textsubscript{2})]Ag show two cathodic waves and one anodic wave (see Table 1). The first cathodic wave at $ca -0.2$ V $vs$ Ag/Ag$^+$ for [Ag(44a)\textsubscript{2}]Ag corresponds to reduction of the loosely bound silver ion (equation 10) and the second wave at $ca -1.3$ V $vs$ Ag/Ag$^+$ corresponds to reduction of the tightly bound silver ion (equation 11). As expected, there is only one reduction wave at $-1.35$ V for [Ag(44a)\textsubscript{2}]NEt\textsubscript{4} which corresponds to reduction of the tightly bound silver ion.

$$[Ag(44a)\textsubscript{2}]Ag + e^- \overset{ca -0.2 V}{\longrightarrow} [Ag(44a)\textsubscript{2}]^- + Ag^0 \quad (10)$$

$$[Ag(44a)\textsubscript{2}]^- + e^- \overset{ca -1.3 V}{\longrightarrow} 2[44a]^- + Ag^0 \quad (11)$$

The second cathodic process in [Ag(44a)\textsubscript{2}]Ag is broad and occurs at a very low potential ($-0.5$ V $vs$ Ag/Ag$^+$) compared to the other silver salts in this series. This anomalous behavior was attributed to the lower stability of the silver complex and the presence of several isomeric forms of the acyclic imide ligand.

Both the silver salts and the mixed silver/tetraethylammonium salts show anodic waves that are similar in potential and amplitude, demonstrating similar oxidation processes in both salts. Coulometric measurements and $n$ values show that the oxidation process is irreversible and involves one electron. This process was assigned as a ligand-based oxidation. In general, the complexes with cyclic imide ligands (44a–d) oxidize at $ca +1.5$ V $vs$ Ag/Ag$^+$, the oxidation potentials of the silver complexes with acyclic ligands (44e–h) are more sensitive to changes in ligand composition. The presence of two electron-withdrawing carbonyl groups in 44e gives rise to a higher oxidation potential than those with only one carbonyl group (44f–h). Placing an electron donating methoxy group
9. The electrochemistry of gold and silver complexes

<table>
<thead>
<tr>
<th>Compound</th>
<th>Alternative formula</th>
<th>Oxidations b</th>
<th>Reductions b</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>[Ag(44a)₂]NE₄</td>
<td>[Ag(succinimide⁻)₂]NE₄</td>
<td>+1.48 c</td>
<td>-1.35 c</td>
<td>53,54</td>
</tr>
<tr>
<td>[Ag(44a)₂]Ag</td>
<td>[Ag(succinimide⁻)₂]Ag</td>
<td>+1.48 c</td>
<td>-0.18 c -1.30 c</td>
<td>53</td>
</tr>
<tr>
<td>[Ag(44b)₂]NE₄</td>
<td>[Ag(Me₄succinimide⁻)₂]NE₄</td>
<td>+1.56 c</td>
<td>-1.6 c -1.52 c</td>
<td>53</td>
</tr>
<tr>
<td>[Ag(44b)₂]Ag</td>
<td>[Ag(Me₄succinimide⁻)₂]Ag</td>
<td>+1.50 c</td>
<td>-0.16 c -1.52 c</td>
<td>53</td>
</tr>
<tr>
<td>[Ag(44c)₂]NE₄</td>
<td>[Ag(phthalimide⁻)₂]NE₄</td>
<td>+1.52 c</td>
<td>-0.17 c -1.30 c</td>
<td>53</td>
</tr>
<tr>
<td>[Ag(44c)₂]Ag</td>
<td>[Ag(phthalimide⁻)₂]Ag</td>
<td>+1.52 c</td>
<td>-0.17 c -1.30 c</td>
<td>53</td>
</tr>
<tr>
<td>[Ag(44d)₂]NE₄</td>
<td>[Ag(gluartarimide⁻)₂]NE₄</td>
<td>+1.47 c</td>
<td>-0.18 c -1.38 c</td>
<td>53</td>
</tr>
<tr>
<td>[Ag(44d)₂]Ag</td>
<td>[Ag(gluartarimide⁻)₂]Ag</td>
<td>+1.45 c</td>
<td>-0.18 c -1.38 c</td>
<td>53</td>
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<tr>
<td>[Ag(44e)₂]NE₄</td>
<td>[Ag(benzoxylimide⁻)₂]NE₄</td>
<td>+1.01 c</td>
<td>-0.20 c -0.5 c</td>
<td>53</td>
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<tr>
<td>[Ag(44e)₂]Ag</td>
<td>[Ag(benzoxylimide⁻)₂]Ag</td>
<td>+1.04 c</td>
<td>-0.20 c -0.5 c</td>
<td>53</td>
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<tr>
<td>[Ag(44f)₂]Ag</td>
<td>[Ag(formamidimide⁻)₂]Ag</td>
<td>+0.41 c</td>
<td>-0.27 c -1.38 c</td>
<td>53</td>
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<tr>
<td>[Ag(44g)₂]NE₄</td>
<td>[Ag(succinimide⁻)₂]NE₄</td>
<td>+0.27 c</td>
<td>-1.74 c</td>
<td>54</td>
</tr>
<tr>
<td>[Ag(44h)₂]NE₄</td>
<td>[Ag(succinimide⁻)₂]NE₄</td>
<td>+0.65 c</td>
<td>54</td>
<td></td>
</tr>
</tbody>
</table>

45a Au(PPh₃)NHCOMe | +1.89 c | -1.77 c | 29 |
45b Au(PPh₃)NHCOCH₂Cl | +1.99 c | -1.89 c | 29 |
45c Au(PPh₃)NHCOPh | +2.27 c | -1.92 c | 29 |
45d Au(PPh₃)NH₂C₆H₄NO₂⁻ | +1.54 c | -1.65 c | 29 |
45e Au(PPh₃)NH₂C₆H₄NO₂⁻ | +1.44 c | -1.37 c -1.76 c | 29 |
46 [(AuPPh₃)₂NH₂C₆H₄NO₂⁺]⁺ | +1.36 c | -1.43 c -1.65 c | 29 |
47 [(AuPPh₃)₂NH₂C₆H₄NO₂⁺]⁺ | +2.50 c | -1.43 c -1.84 c | 29 |
48a [(AuPPh₃)₂NH₂C₆H₄NO₂⁺]⁺ | +1.41 c | -1.51 c -1.75 c | 29 |
48b [(AuPPh₃)₂NH₂C₆H₄Me⁻]⁺ | +0.95 c | -1.87 c | 29 |

---

"Electrochemical studies reported at Pt working electrode and Ag/Ag⁺ reference couple in MeCN.

bValues reported in Reference 29 as E₁/₂ and References 53 and 54 as Epc.

cLinear rotating disc voltammetry at ω = 600 rpm.

dCyclic voltammetry.

in the para position of the phenyl ring (44g) makes the silver complex, [Ag(44a)₂]NE₄, easier to oxidize (+0.27 V vs Ag/Ag⁺) than the parent complex, [Ag(44f)₂]Ag (+0.41 V vs Ag/Ag⁺). The silver complex, [Ag(44h)₂]NE₄, with an electron-withdrawing cyanide substituent, is harder to oxidize (+0.41 V vs Ag/Ag⁺).

Finally, in the cyclic voltammetry studies of the silver salts, there are two cathodic waves, with similar potential values as observed in the linear voltammetry studies. However, on the return sweep in the CV, there was an anodic peak at 0 V vs Ag/Ag⁺ which was attributed to oxidation of electrodeposited silver.

A series of triphenylphosphine gold amide complexes (45–48) was studied by Rakhimov and coworkers. The anodic process was in general assigned to a one-electron...
oxidation of the amide or anilide ligands, followed by a series of chemical reactions that resulted in deposition of Au\(^0\) on the platinum electrode. The aniline derivatives can be doubly and triply ‘aurated’ (46–48) by addition of two or three (AuPPh\(_3\))\(^+\) groups. Auration does not have a predictable effect on the oxidation potential (see Table 11). However, changing the substituent on the phenyl ring appears to have a significant effect on the oxidation potential. For example, [(AuPPh\(_3\))\(_3\)NC\(_6\)H\(_4\)Me-p\(^+\)] with an electron-donating methyl in the para position of the ring oxidizes at +0.95 V vs Ag/AgCl, while the para-nitro derivative is harder to oxidize by 560 mV.

The first cathodic process for the amide gold complexes is proposed to be a one-electron reduction. As the number of (AuPPh\(_3\))\(^+\) groups increases, the reduction process
9. The electrochemistry of gold and silver complexes becomes less reversible. The para-nitroaniline complexes also show a second cathodic process with $n$ values of 2.8–4. A scheme was proposed that included initial one-electron reduction of the p-nitroaniline ligand followed by formation of metallic gold and regeneration of a molecule that is electrochemically active in the same potential range.

XI. OTHER LIGANDS AND STRUCTURAL TYPES

This section includes selected examples of electrochemistry of gold and silver complexes with other ligands and structural types that were not included in previous sections. We have also included a list of references divided into the following areas that can be consulted for additional information: sulfur- and nitrogen-containing macrocycles, porphyrins and clusters.

A. Macrocycles

Macrocycles are well known to bind to a variety of metals in several oxidation states and the macrocycle cavity size can be varied to electronically tune redox couples. A number of electrochemical investigations have been conducted on gold and silver macrocycles.

Electrochemical data for complexes with the sulfur-coordinated macrocycles, [9]aneS$_3$ (49) and [18]aneS$_9$ (50) are listed in Table 12. Silver(I) and gold(I) coordinate to two molecules of 49 but only one molecule of 50. In [Ag(49)$_2$]$^+$, the silver atom is six coordinate. In contrast, the X-ray structure of [Au(50)]$^+$ shows a distorted tetrahedral

<table>
<thead>
<tr>
<th>Compound</th>
<th>Oxidations</th>
<th>Reductions</th>
<th>Conditions</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Macrocycles — Sulfur</td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>[Au(49)$_2$]$^+$</td>
<td>+0.12, +0.46</td>
<td></td>
<td>$a$</td>
<td>62</td>
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<td>[Ag(49)$_2$]$^+$</td>
<td>+0.75</td>
<td>−0.57</td>
<td>$a$</td>
<td>57</td>
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<tr>
<td>[Au(50)]$^+$</td>
<td>+0.36, +0.56</td>
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<td>$a$</td>
<td>62,66</td>
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<tr>
<td>[Ag(50)]$^+$</td>
<td>+1.00</td>
<td>−0.42</td>
<td>$a$</td>
<td>57</td>
</tr>
<tr>
<td>Macrocycles — Nitrogen</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>[Au(51)]$^3+$</td>
<td>−0.16, −0.62, −0.98</td>
<td></td>
<td>$b$</td>
<td>70</td>
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<tr>
<td>[Au(52)]$^3+$</td>
<td>−1.28, −1.42, −1.89</td>
<td></td>
<td>$b$</td>
<td>70</td>
</tr>
<tr>
<td>[Ag(51)]$^2+$</td>
<td>+0.86</td>
<td></td>
<td>$b$</td>
<td>68</td>
</tr>
<tr>
<td>Porphyrins</td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ag(53)</td>
<td>+0.55, +1.64</td>
<td>−1.1</td>
<td></td>
<td>80</td>
</tr>
<tr>
<td>[Au(53)]$^+$</td>
<td>+1.68</td>
<td>−0.59</td>
<td></td>
<td>80</td>
</tr>
<tr>
<td>Clusters</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>[Ag$_3$(CO)$_2$$_3$]$_2$</td>
<td></td>
<td>−0.37(rev), −0.65(rev)</td>
<td></td>
<td>107</td>
</tr>
<tr>
<td>[Pd(AuPPh$_3$)$_3$]$_2$</td>
<td></td>
<td>−1.80(rev), −1.98(rev)</td>
<td></td>
<td>110</td>
</tr>
<tr>
<td>[Pt(AuPPh$_3$)$_3$]$_2$</td>
<td></td>
<td>−1.57(rev), −1.72(rev)</td>
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<td>111</td>
</tr>
<tr>
<td>[Au(AuPPh$_3$)$_3$]$_3$</td>
<td></td>
<td>−1.03(rev), −1.11(rev)</td>
<td></td>
<td>111</td>
</tr>
</tbody>
</table>

$^a$MeCN, vs Fe/Fe$^+$ couple
$^b$MeCN, vs SCE
$^c$CH$_2$Cl$_2$, referenced to Ag/AgCl but reported vs SCE
$^d$CH$_2$Cl$_2$, vs Fe/Fe$^+$
geometry with \( \text{Au}^{+} \) coordinated to four of the sulfurs in the ring\(^{62} \). Figure 11 shows a cyclic voltammetry experiment on \([\text{Au}(50)]^{+}\) in MeCN solution\(^{66} \). Two redox couples occur at \(+0.36 \text{ V}\) and \(+0.56 \text{ V} \) (vs Fc/Fc\(^{+}\)) which were assigned as two successive one-electron oxidations: \( \text{Au}^{+} \rightarrow \text{Au}^{II} \) followed by \( \text{Au}^{II} \rightarrow \text{Au}^{III} \). The corresponding Ag' macrocycle complexes, \([\text{Ag}(49)]^{+}\) and \([\text{Ag}(50)]^{+}\), show one oxidation process at higher potentials that have been assigned as the \( \text{Ag}^{1/II} \) couples. The influence of the macrocycle ring size can be illustrated by comparing the oxidation potentials for the complexes with 49 and 50. The gold and silver complexes with 50 are harder to oxidize reflecting the increased stability of \( \text{Au}^{I} \) and \( \text{Ag}^{I} \) coordinated to the larger macrocycle.

Examples of the electrochemistry of nitrogen-containing gold and silver macrocycles are listed in Table 12. Kimura and coworkers have investigated a series of complexes based on cyclams such as \([14\text{aneN}_4](51)\)^\(^{70} \). Cyclic voltammetry experiments of \([\text{Au}(51)]^{3+}\) in 0.1 M \([\text{Bu}_4\text{N}]\text{PF}_6/\text{MeCN}\) solution at a glassy carbon working electrode shows three irreversible reduction waves. The reductions which occur at \(-0.16 \text{ V}, -0.62 \text{ V} \) and \(-0.98 \text{ V} \) vs SCE were assigned as successive one-electron processes. The \( \text{Au}^{III} \) complex with the triphenylphosphine-pendant cyclam, 52, shows dramatic shifts in the reduction potentials, indicating that this gold complex is greatly stabilized toward reduction (see Table 12)^\(^{70} \). Po and coworkers investigated the \( \text{Ag}^{II} \) complex, \([\text{Ag}(51)]^{2+}\)^\(^\text{68} \). Cyclic voltammetry experiments at a Pt electrode in 0.1 M \([\text{Et}_4\text{N}]\text{ClO}_4/\text{MeCN}\) solution show a quasi-reversible redox couple at \(+0.86 \text{ V} \) vs SCE assigned to the \( \text{Ag}^{II/III} \) couple.

**FIGURE 11.** Cyclic voltammetry experiment on \([\text{Au}(50)]^{+}\) in MeCN. Reproduced by permission of Kluwer Academic Publishers from Reference 66.
9. The electrochemistry of gold and silver complexes

B. Porphyrins

There is great interest in studying the electrochemistry of gold and silver porphyrins in aqueous and nonaqueous solutions. The redox reactions for metalloporphyrins include changes in the oxidation state of the porphyrin nucleus and, in some cases, changes in the oxidation state of the metal. The porphyrin ring tends to stabilize the higher oxidation states of silver and gold.

The electrochemical data for many gold and silver porphyrins can be exemplified by considering their complexes with the tetraphenylporphyrin ring. The metal-based oxidation (Ag$^{II}$/Ag$^{I}$ couple) of Ag(53) at +0.55 V vs SCE occurs between the porphyrin ring oxidation (+1.64 V) and reduction (−1.1 V) processes. In contrast, in the Au$^{III}$ analog, [Au(53)]$^+$, gold is inert and only ring-based redox processes are observed.
C. Clusters

The tendency of clusters to undergo facile rearrangements or decomposition upon electron transfer, as well as the presence of a large number of redox centers, can make the assignment of the redox behavior of clusters a challenge. An interesting example is provided by $[\text{Ag}_{13}(\mu_3-\text{Fe(CO)}_4)_8]^{3-}$, a cluster composed of a core of 12 silver atoms arranged in a cuboctahedron structure, with an additional silver atom at the center bridging to the other 12 silver atoms (54). Eight $\mu_3-\text{Fe(CO)}_4$ units cap each triangular face of the cuboctahedron (not shown in 54). Cyclic voltammetry experiments of $[\text{Ag}_{13}(\mu_3-\text{Fe(CO)}_4)_8]^{3-}$ at low concentrations (0.1 mM/MeCN) display two reversible cathodic processes (see Table 12). Controlled potential bulk electrolysis at $-0.5$ V yields an $n$ value equal to one electron per cluster molecule. However, at higher concentrations (2.1 mM), the first redox process remains reversible, but the second becomes irreversible, suggesting a second order following reaction. Figure 12 shows the cyclic voltammogram recorded at the higher concentration using a Pt working electrode and a scan rate of 200 mV s$^{-1}$. The large wave that appears in the cathodic scan at $c. -0.2$ V vs SCE appears to be a silver surface wave, i.e. the result of oxidation of silver metal deposited at the electrode in the reduction scan. The wave is similar in shape and potential to that seen in the analysis of silver during a stripping voltammetry experiment.**

**FIGURE 12. Cyclic voltammogram for $2.1 \times 10^{-4}$ M $[\text{Et}_4\text{N}][\text{Ag}_{13}(\mu_3-\text{Fe(CO)}_4)_8]$ at a platinum electrode in $0.2$ M $[\text{Et}_4\text{N}]\text{ClO}_4$/MeCN at scan rate 200 mV s$^{-1}$. Reproduced by permission of Plenum Press from Reference 107.
9. The electrochemistry of gold and silver complexes

The electrochemistry of \([\text{Pt(AuPPh}_3)_8]\)^{2+} was investigated by cyclic voltammetry and differential pulse polarography in \(\text{CH}_2\text{Cl}_2\) and \(\text{MeCN}\) solutions. This cluster undergoes two stepwise, reversible one-electron transfers, thus showing an EE reduction mechanism (see equations 12 and 13, and Figure 13). It is interesting to note the large shift to more positive potentials as the central metal atom in \([\text{M(AuPPh}_3)_8]\)^{n+} changes from \(\text{Pd}^{II}\) to \(\text{Pt}^{IV}\) to \(\text{Au}^{III}\) (see Table 12).

\[
\begin{align*}
\text{[Pd(AuPPh}_3)_8]^{2+} + e^- & \rightleftharpoons \text{[Pd(AuPPh}_3)_8]^+ \quad E_{1/2} = -1.80 \text{ V vs } \text{Fc/Fc}^+ \quad (12) \\
\text{[Pd(AuPPh}_3)_8]^+ + e^- & \rightleftharpoons \text{Pd(AuPPh}_3)_8 \quad E_{1/2} = -1.98 \text{ V vs } \text{Fc/Fc}^+ \quad (13)
\end{align*}
\]

XII. REFERENCES

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9. The electrochemistry of gold and silver complexes


Ahned A. Mohamed, Alice E. Bruce and Mitchell R. M. Bruce

BIOGRAPHY OF THE AUTHOR

Ahmed Mohamed was born in Sharkia Governorate in Egypt on August 11, 1966. He received his high school education at Zagazig Military High School.

He entered Zagazig University, Egypt in 1984 and obtained his Bachelor of Science degree in 1988. Then he entered Zagazig University in Egypt in 1989 and obtained his Masters of Science degree.

In September 1996 he was enrolled for graduate study in Chemistry at The University of Maine and served as a Teaching Assistant in the Department of Chemistry. He holds a permanent teaching position at Zagazig University in Egypt.

He is a candidate for the Doctor of Philosophy degree in Chemistry from The University of Maine in December, 2000.