

# Examination of Gold (III) Complexes with Possible Chemotherapeutic Properties.

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**Background:** Historically, the coordination chemistry of gold with the oxidation state of +3 has not been pursued. Gold (III) is unstable to reduction which makes it difficult to work with. In aqueous solutions, it has the potential to readily undergo hydrolysis reactions which leads to mixtures of  $\text{AuCl}_4^-$  and  $\text{AuCl}_2^-$  salts that are difficult to characterize and have limited solubility. Additionally, the starting materials necessary for gold (III) reactions traditionally involved separations of material from *aqua regia* in very low yields.

In ancient times, civilizations attributed medicinal character to gold. Amulets and medallions were used as wards against diseases and evil spirits. Potions containing elemental gold were often administered to sick people. In more modern times, gold complexes have been examined as potential agents in the treatment of arthritis, cancer, AIDS, malaria and bronchial asthma. One of the most exciting new fields involves potential gold-based anticancer agents.

Preliminary research has shown gold (III) complexes to be promising in the chemotherapeutic treatment of cisplatin resistant cervical and testicular cell lines. Physically and chemically, Au (III) is very similar to Pt (II). Gold (III) tetraphenylporphyrins (TPP) show exciting promise in these developments. Gold (III) TPP compounds are extremely stable towards reduction in the presence of glutathione (GSH) and stable to demetalation at physiological conditions. These compounds have shown enhanced anti-cancer activity relative to cisplatin.

Although little is known about the development of cisplatin resistant cell lines, one possibility is that GSH plays a role. GSH is present in cells at varying levels (0.5 – 10.0 mM) and functions as a detoxification agent of chemotherapeutic drugs. It has also been shown to have protective effects against cisplatin induced cytotoxicity. Complexes formed between GSH and cisplatin have been shown to have reduced platinum centers (oxidation state = +1). Since GSH effectively recovers native proteins from cisplatin adducts by reducing the platinum, elevated levels of GSH increases this effect. Protein adducts of cisplatin have been implicated in the activity of the drug by binding to human serum albumin which leads to a pathway by which DNA is covalently bound producing cytotoxic effects.

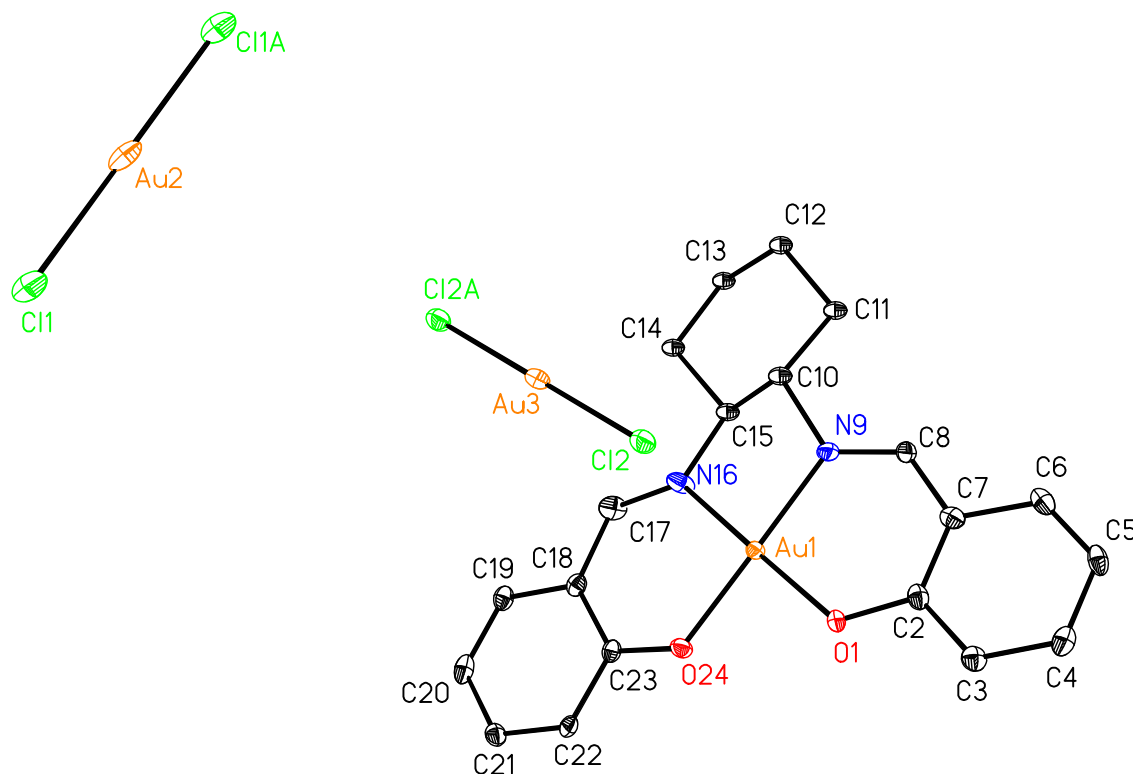
***Student Collaborators:*** Two students were involved in the research: Kathleen Garrett-Roe (sophomore, Chemistry) and Jerry Glass (sophomore, Chemistry). Jerry will continue to work on this project for credit hours in Fall 2006.

***Results and Discussion:*** The research efforts focused on synthesis of various ligand systems for the complexation of gold (III) metal ions. In total, seven different ligand systems were prepared (see Appendices A & B) using literature or modified-literature procedures. Metalation of these ligands was carried out using potassium tetrachloroaurate (KAuCl<sub>4</sub>) and tetrabutylammonium tetrachloroaurate ([Bu<sub>4</sub>N][AuCl<sub>4</sub>]).

Ligand syntheses were fairly straight-forward and accomplished in good yield. A variety of ligand architectures were selected to vary the electronic, steric and polar nature of the resulting compounds.

Metalation of the ligands proceeded well however, the resulting nature of the products was largely dependent on ligand properties. Ligands with strong polar or electronic features (i.e. compounds **2** and **8**) formed metal complexes that were largely insoluble, resistant to crystallization and likely polymeric. Ligands with large non-polar functionalities (i.e. compounds **3**, **5** and **14**) formed soluble complexes more suitable for subsequent study and characterization.

Reaction of **14** with KAuCl<sub>4</sub> produced [Au(sal<sub>2</sub>cy)][AuCl<sub>2</sub>], **15**, in nearly quantitative yield. This product was characterized by low temperature X-ray crystallography.



**Figure 1:** Product **15** showing two  $\text{AuCl}_2^-$  anions at half occupancy.

Compound **15** illustrates square-planar coordination of the Au(III) ion within the ligand framework. Successful synthesis and characterization of this product is an important step in the progression of our research.

Compound **15** is novel from a fundamental perspective. The mechanism by which gold was selectively reduced from Au(III)  $\rightarrow$  Au(I) is unexplained. Additionally, while there are compounds in the literature of mixed valence Au(III)/Au(I) salts, the majority of these are inorganic, polymeric salts. Compound **15** represents a rare example of a mixed valence coordination compound of Au(III)/Au(I).

**Updated Dissemination Plan:** Based on the novel nature of the  $[\text{Au}(\text{sal}_2\text{cy})]\text{AuCl}_2$  salt, further synthetic and mechanistic investigations are needed before full dissemination of this work. A brief presentation on the progress of our gold (III) research will be given during a roundtable discussion at the INRBE annual meeting in August. Based on further research, we anticipate submission of our work for publication during the 2006-07 academic year.

**Future Work:** Future progress on this project will focus on three areas:

- A. Synthesis of additional soluble Au(III) compounds: Results from these experiments have allowed us to refine our target compounds and better identify ligand features that will lead to desirable properties in metal complexes.
- B. Thermodynamic & electrochemical experiments on **15**: Since we have successfully characterized **15**, we will begin thermodynamic and electrochemical experiments on this compound.
- C. Mechanistic investigation of gold reduction in **15**: At present, the reductive pathway for the formation of the mixed valence compound is not understood. A series of mechanistic experiments will be carried out in an effort to determine the pathway by which this compound is formed in high yield.

## Appendix A

### Experimental Procedures

#### Kathleen Garrett-Roe

[C<sub>18</sub>H<sub>20</sub>O<sub>4</sub>N<sub>2</sub>], **1**. Was created by the mixing of C<sub>7</sub>O<sub>3</sub>H<sub>11</sub> (4.65 g, 0.033 mol) to C<sub>2</sub>H<sub>8</sub>N<sub>2</sub> (1.0004g, 0.0166mol, 1.1128 ml) in 50ml of Ethanol solvent. C<sub>2</sub>H<sub>4</sub>N<sub>2</sub> was added to the already stirring solution of C<sub>7</sub>O<sub>3</sub>H<sub>5</sub> and Ethanol an immediate color change from clear to vivid yellow, also an immediate separation of precipitate, like oil on water. Let reflux for 40 minutes. The solution was cooled to room temperature for 15-20 minutes, placed in refrigerator over night. Filtered precipitate (0.48 g, 43%) using suction water filter, yellow salt like crystals formed with a yellow solution that was placed back in to refrigerator. Let precipitate dry on filter paper under hood. Re-crystallized crude product by putting **1** in a beaker with enough ethanol to cover precipitate but not fully dissolve it (20-30ml). Heat was added to the solution for about 20 minutes, to completely dissolve in solution, the gravity filter off the hot plate. Let the precipitate in a funnel dry under hood over night and placed solution in refrigerator. Next day crystals were beginning to form left in refrigerator for several days more. Its melting point is 160°C.

[C<sub>18</sub>H<sub>20</sub>O<sub>4</sub>N<sub>2</sub>], **1**. (0.80 g, 0.0027 mol) dissolved in 60 ml of a 3 to 1 CH<sub>2</sub>CL/Ethanol mixture. KAuCl<sub>4</sub> •H<sub>2</sub>O (0.50 g, 0.0013 mol) was dissolved in 40 ml of Ethanol then slowly added to already stirring solution of KAuCl<sub>4</sub> •H<sub>2</sub>O. There was an immediate color change from yellow to yellow ochre burnt umber mix. After 5 minutes a shiny yellow precipitate formed. Let mix at room temperature for 5 minutes then reflux for 30 minutes followed by cooling in refrigerator over night. Powdery yellow crystals formed collection via filtration (0.11g, 22%) The filtrate was rotovaped solute for half hour resulting in a fine red powder forming. Re-crystallized of solid red powdery product taking one-third of product mixing it with CH<sub>2</sub>Cl<sub>2</sub> (10 ml), one-third of product mixing it with Acetonitrile (10 ml), and one-third of product mixing it with pyridine (10 ml). I let it heat for half hour and then cool to room temperature and cover. The solution was rotovap for another hour forming nothing.

[C<sub>32</sub>H<sub>48</sub>O<sub>2</sub>N<sub>2</sub>], **2**. Was created by mixing C<sub>14</sub>H<sub>22</sub>O<sub>2</sub> (4.39g, 0.0217mol) to C<sub>2</sub>H<sub>8</sub>N<sub>2</sub> (0.6085 g, 0.01085 mol, 0.6769ml) in 50 ml of Ethanol solvent. Added 10ml of Hexane to the solvent while adding C<sub>2</sub>H<sub>4</sub>N<sub>2</sub>. A color change was noticed from a light yellow to a bright yellow. In about 30 seconds a precipitate formed. The precipitate formed so fast you could no longer see the spinner, the solution had become frothy and opaque yellow. Let it reflux for 45 minutes, then cool to room temperature for about 10 minutes, then put in the refrigerator overnight. Filtered using suction water filter, the precipitate seems fluffy like “cotton candy” bright almost neon yellow. The crude product was *re-crystallized* only using 1/10 since there was a lot. Dissolved product in 20 ml of ethanol and heated for 10 minutes then hot gravity filtered and let dry. Its melting point is 181°C.

[C<sub>32</sub>H<sub>48</sub>O<sub>2</sub>N<sub>2</sub>], **2**. (0.5g, 0.00089 mol) was dissolved in 20 ml of CH<sub>2</sub>CL. (Bu<sub>4</sub>N)AuCl<sub>4</sub> (0.362 g, 0.00089 mol) was dissolved in 30 ml of Ethanol. NH<sub>4</sub>PF<sub>6</sub> (0.114 g, 0.000699 mol) solution was added to the already stirring solution (Bu<sub>4</sub>N)AuCl<sub>4</sub> then **2** was added to the stirring solution. A color change from a clear light tan color to a chocolate color was noted. I let it mix at room temperature for 5 minutes then refluxed the solution for 45 minutes. No precipitate formed, letting it cool to room temperature then placing in refrigerator overnight. Metallic looking crystals of **2** were collected via filtration. The solution continued to be rotovaped for a total of 5 hours forming no precipitate in the end. Rotovaped the solution for a total of 6 hours on the last hour it fell into bath only mixing the solution with water. We separated the solution from the water using a titration kind of technique.

[C<sub>36</sub>H<sub>28</sub>O<sub>2</sub>N<sub>2</sub>], **3**. Was created by mixing C<sub>7</sub>O<sub>3</sub>H<sub>11</sub> (0.44 g, 0.0029 mol) to C<sub>20</sub>H<sub>20</sub>N<sub>2</sub> (0.41g, 0.0014 mol) in 30 ml of Ethanol solvent. An addition of 2 pipettes of 30/70 Ethanol/ Hexane. Immediate color change was noted from a caramel-tan color to an orange then red orange after about 10 minutes. A fine precipitate formed (0.44 g, 69.85 %). The solution was refluxed for 45 minutes then let cool to room temperature for 10 minutes and then placed in refrigerator over night. The precipitate was filtered which was a bright red powdery solid. Its melting point is 242°C.

[C<sub>36</sub>H<sub>28</sub>O<sub>2</sub>N<sub>2</sub>], **3**. (0.22 g, 0.000478 mol) was dissolved in 20 ml of CH<sub>2</sub>CL. (Bu<sub>4</sub>N)AuCl<sub>4</sub> (0.32 g, 0.00078 mol) was dissolved in 30 ml of Ethanol. NH<sub>4</sub>PF<sub>6</sub> (0.051 g, 0.00031 mol) solution was added to the already stirring solution (Bu<sub>4</sub>N)AuCl<sub>4</sub> then **3** was added slowly to the stirring mixture. The mixture stirred at room temperature for 5 minutes and then refluxed for 45 minutes. Solution remained a bright yellow mixture with only a slight shiny precipitate forming. The shiny metallic precipitate was then filtered using water suction filter nothing worth keeping. Rotovaped the solution for total of 3 hours no precipitate ever formed, the solution ended up falling into rotovap bath losing everything.

[C<sub>16</sub>H<sub>16</sub>O<sub>2</sub>N<sub>2</sub>], **4**. Was created by mixing C<sub>6</sub>O<sub>2</sub>H<sub>10</sub> (7.39 g, 0.061 mol, 6.448 ml) to C<sub>2</sub>H<sub>8</sub>N<sub>2</sub> (1.8184 g, 0.0303 mol, 2.023 ml) in 20 ml of Ethanol solvent. Once reaction started immediate color change noticed from clear to yellow, precipitate formed causing the solution to look gelatinous. Refluxed for about 10 minutes, the heat caused the precipitate to disappear. I made another solution using same method with less ethanol and no heat. Let cool to room temperature and put both solution in refrigerator over night. The precipitate was filtered which looked a nice yellow salt type crystal (1.814 g, 12.25%). Its melting point is 115°C.

[C<sub>20</sub>H<sub>22</sub>O<sub>2</sub>N<sub>2</sub>], **5**. (0.56 g, 0.0016 mol) was dissolved in 20 ml of CH<sub>2</sub>CL. (Bu<sub>4</sub>N)AuCl<sub>4</sub> (0.12 g, 0.00029 mol) was dissolved in 30 ml of Ethanol. NH<sub>4</sub>PF<sub>6</sub> (0.18 g, 0.0011 mol) solution was added to the already stirring solution (Bu<sub>4</sub>N)AuCl<sub>4</sub> then **4** was added slowly to the stirring mixture. The mixture stirred at room temperature for 5 minutes an immediate color change from yellow to a darker golden color was noted and then refluxed for 45 minutes. A dark small shiny precipitate formed. Let the solution cool to room temperature and then place in refrigerator over night.

## Appendix B

### Experimental Procedures

#### Jerry Glass

$[\{C_{16}H_{14}O_6N_4\}]$ , **6.** Addition of  $[\{C_7H_5O_4N\}]$  (0.75g, 0.0045mol) to  $[\{C_2H_8N_2\}]$  (0.138g, 0.0023mol) in 50ml of ethyl alcohol immediately formed an orange/yellow cloudy solution with precipitate within ten seconds. The solution was refluxed for approximately 45 minutes over moderate heat with little change in color or amount of precipitate. The product was allowed to cool in a refrigerator overnight. The solid precipitate was filtered and dried under vacuum to give the ligand  $[\{C_{16}H_{14}O_6N_4\}]$ , as a yellow/orange powder (0.72g, 45% yield).

$[\{Au(C_{16}H_{14}O_6N_4)+\}] + PF_6^-$ , **7.** Addition of  $[\{Bu_4NAuCl_4\}]$  (0.25g, 0.00043mol) in 10ml of methylene chloride to  $[\{NH_4PF_6\}]$  (0.42g, 0.00258mol) in 10ml ethanol to  $[\{C_{16}H_{14}O_6N_4\}]$  in 10ml methylene chloride, added drop wise, immediately formed a cloudy yellow solution. The solution was refluxed over moderate heat for 45 minutes with some precipitation. The product was allowed to cool for several days in a refrigerator. The solid product was filtered and dried under vacuum to give the metallated product  $[\{Au(C_{16}H_{12}O_6N_4)+\}] + PF_6^-$  (0.48g).

$[\{C_{18}H_{20}O_2N_2\}]$ , **8.** Addition of  $[\{C_8H_8O_2\}]$  (4.03g, 0.03mol) to  $[\{C_2H_8N_2\}]$  (0.902g, 0.015mol) in 50ml of ethanol immediately formed a yellow precipitate that filled the flask. Precipitate was transferred to 250ml round bottom flask and approximately 75ml of ethanol was added. Solution was refluxed over moderate heat for approximately 45 minutes and allowed to cool in a refrigerator for several days. The precipitate was filtered and dried under vacuum to give the ligand  $[\{C_{18}H_{20}O_2N_2\}]$  as a flaky, yellow crystalline solid (3.55g, 80%).

$[\{Au(C_{18}H_{18}O_2N_2)+\}] + AuCl_4^-$ , **9.** Addition of  $[\{KAuCl_4 + H_2O\}]$  (0.25g, 0.00066mol) in 50ml ethanol to  $[\{C_{18}H_{20}O_2N_2\}]$  in 3 to 1 ratio of methylene chloride and ethanol (50ml) produced a clear yellow solution. The solution was refluxed for 45 minutes over moderate heat with little change in appearance. The solution was allowed to cool for several days in a refrigerator and there was precipitation of crystalline yellow substance. This was then filtered and dried under vacuum to give the metalated product  $[\{Au(C_{18}H_{18}O_2N_2)+\}] + AuCl_4^-$  (0.20g).

$[\{C_{24}H_{20}O_2N_2\}]$ , **10.** Addition of  $[\{C_2H_8N_2\}]$  (0.817g, 0.909ml, 0.0136mol) to  $[\{C_{11}H_8O_2\}]$  (4067g, 0.0271mol) in 100ml ethanol immediately produced a cloudy white solution with some precipitates. The solution was refluxed over moderate heat for 45 minutes and allowed to cool for several days in a refrigerator. The precipitate was filtered and dried under vacuum to give the ligand  $[\{C_{24}H_{20}O_2N_2\}]$  (4.42g, 84%).

$[\{Au(C_{24}H_{18}O_2N_2)+\}] + PF_6^-$ , **11.** Addition of  $[\{C_{24}H_{20}O_2N_2\}]$  (0.60g, 0.0016mol) in 10ml methylene chloride (added drop wise) to  $[\{NH_4PF_6\}]$  (0.40g, 0.00244mol) in 10ml ethanol and  $[\{Bu_4NAuCl_4\}]$  (0.24g, 0.00041mol) in 10ml methylene chloride immediately produced a cloudy white solution. The solution was refluxed over moderate heat for 45 minutes and allowed to cool for several days in a refrigerator. The precipitate was filtered and dried under vacuum to give the metalated product  $[\{Au(C_{24}H_{18}O_2N_2)+\}] + PF_6^-$  (0.57g).

$[\{C_{34}H_{24}O_2N_2\}]$ , **12.** Addition of  $[\{C_7H_6O_2\}]$  (0.850g, 0.742ml, 0.00696mol) to  $[\{C_{20}H_{16}N_2\}]$  (0.99g, 0.0035mol) in 100ml ethanol formed a clear yellow solution. The solution was refluxed over moderate heat for 45 minutes with the formation of some precipitates. The solution was allowed to cool for several days in a refrigerator and there was more precipitation. The solids were filtered and dried under vacuum to give the ligand  $[\{C_{34}H_{24}O_2N_2\}]$  (1.47g, 85%).

$[\{Au(C_{16}H_{12}O_6N_4)+\}] + AuCl_4^-$ , **13.** Addition of  $[\{C_{16}H_{14}O_6N_4\}]$  (0.47g, 0.00132mol) in 3 to 1 ratio of methylene chloride to ethanol (50ml total) to  $[\{KAuCl_4 + H_2O\}]$  (0.25g, 0.00066mol) in 50ml of ethanol produced a cloudy yellow solution. The solution was refluxed over moderate heat for 45 minutes with some precipitate formation. The solution was allowed to cool for several days in a refrigerator. The precipitate was filtered and dried over vacuum to give the metalated product  $[\{Au(C_{16}H_{12}O_6N_4)+\}] + AuCl_4^-$  (0.26g).

$[\{C_{20}H_{26}O_2N_2\}]$ , **14.** Addition of  $[\{C_7H_6O_2\}]$  (1.807g, 1.58ml, 0.0148mol) to  $[\{C_6H_{14}N_2\}]$  (0.845g, 0.909ml, 0.0074mol) in 100ml ethanol produced a yellow solution with no precipitation. The solution was refluxed for 45 minutes over moderate heat and allowed to cool for several days in a refrigerator. There was precipitation after cooling. The precipitate was filtered and dried under vacuum to give the ligand  $[\{C_{20}H_{26}O_2N_2\}]$ .

$[\{\text{Au}(\text{C}_{20}\text{H}_{24}\text{O}_2\text{N}_2)\}^+]$  +  $\text{AuCl}_4^-$ , **15**. Addition of  $[\{\text{C}_{20}\text{H}_{26}\text{O}_2\text{N}_2\}]$  (0.89g, 0.00264mol) in 3 to 1 ratio of methylene chloride to ethanol (50ml total) to  $[\{\text{KAuCl}_4 \cdot \text{H}_2\text{O}\}]$  (0.25g, 0.00066mol) in 50ml of ethanol produced a clear yellow solution with no precipitation. The solution was refluxed for 45 to 60 minutes with a little precipitation of solids. The solution was allowed to cool for several days in a refrigerator. After cooling, there was precipitation of more white solid and formation of dark yellow crystals. The crystals were removed and put in a vial under the solvent from the solution. The solid precipitate was filtered and dried under vacuum (0.31g). The crystals were found to have the formula  $[\{\text{Au}(\text{C}_{20}\text{H}_{20}\text{O}_2\text{N}_2)\}][\{\text{AuCl}_2\}]$