Comments on Inorganic Chemistry
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713455155

Perspectives in Inorganic and Bioinorganic Gold Sulfur Chemistry

Ahmed A. Mohamed[a]; Hanan E. Abdou[a]; Jinhua Chen[a]; Alice E. Bruce[a]; Mitchell R. M. Bruce[a]
[a] Department of Chemistry, University of Maine, Orono, ME

Online publication date: 14 September 2010

To cite this Article Mohamed, Ahmed A. , Abdou, Hanan E. , Chen, Jinhua , Bruce, Alice E. and Bruce, Mitchell R. M.(2002) 'Perspectives in Inorganic and Bioinorganic Gold Sulfur Chemistry', Comments on Inorganic Chemistry, 23: 5, 321 — 334
To link to this Article: DOI: 10.1080/02603590215003
URL: http://dx.doi.org/10.1080/02603590215003

Comments on Inorganic Chemistry, 23: 321–334, 2002

0260-3594/02 $12.00 + .00
DOI: 10.1080/02603590290013299

Taylor & Francis
Taylor & Francis Group

Perspectives in Inorganic and Bioinorganic Gold Sulfur Chemistry

Ahmed A. Mohamed, Hanan E. Abdou, Jinhua Chen, Alice E. Bruce, and Mitchell R. M. Bruce
Department of Chemistry, University of Maine,
Aubert Hall, Orono, ME 04469-5706

A detailed picture of the chemical and electrochemical oxidation of a series of mononuclear and dinuclear phosphine Au(I) thiolates is presented. The medicinal implications of the results are illustrated by redox studies on the anti-rheumatoid drug, auranofin,[(2,3,4,6-tetra-acetyl-1-thio-β-D-glucopyranosato)(triethylphosphine) gold(I)]. The phosphine Au(I) thiolate complexes undergo a broad irreversible oxidation in the range, +0.6 to +1.1V, and a second irreversible oxidation at more positive potentials from +1.2 to +1.6V (vs. SCE). Chemical oxidation of the Au(I) thiolate complexes with $(Cp_2Fe)(PF_6)$ results in disulfide and tetragold(I) clusters with bridging thiolate ligands, except for the unusual nine Au(I) atoms cluster obtained by oxidation of $[(dppm)Au_2(p\text{-}SC_6H_4CH_3)_2]$. Chemical oxidation of auranofin with $(Cp_2Fe)(PF_6)$ results in disulfide and a cationic Au(I) cluster with bridging thiolate ligands, $[(Et_3PAu)_2(\mu\text{-}SATg)]_2^{2+}$, typical of mononuclear gold(I) thiolates. The Au(I) clusters react with disulfide to undergo thiolate/disulfide exchange. Comparative rates show clusters react much faster than the mononuclear complex, $Ph_3PAu(SC_6H_4CH_3)$. A mechanism for the oxidation of auranofin and related complexes, and possible biological implications are discussed.

INTRODUCTION

In 1976, auranofin (Ridaura) was approved by the FDA as an orally active drug for treatment of rheumatoid arthritis (RA). It is the last gold-based drug

Received 24 September, 2002; accepted 26 September, 2002.

to win approval in the United States. However, auranofin as well as the injectable gold drugs, gold sodium thiomalate (Myochrysine) and aurothioglucose (Solganol) (see Fig. 1), are still commonly prescribed anti-arthritic drugs. In fact, auranofin and gold sodium thiomalate were recently on nationwide backorder due to increased demand.[1] Gold sodium thiomalate is typically used to treat active RA in juvenile and adult patients, while auranofin is targeted for adult patients who have not responded well to one or more courses of non-steroidal anti-inflammatory drugs (NSAIDS).[2]

Rheumatoid arthritis is an autoimmune disorder in which the body's immune system attacks the joints and surrounding soft tissue, resulting in inflammation and severe pain. Gold drugs are classified as DMARDS, disease-modifying anti-rheumatic drugs. DMARDS are an interesting class of drugs because they slow the biological processes of the disease and thus are among the few avenues to place an inflammatory disease into remission. DMARDs are generally slow acting and patients on gold therapy (chrysotherapy) may wait 3–6 months to experience improvement in joint function and reduction of swelling. Initiating DMARD therapy early in the course of the disease has recognized benefits in preventing joint damage.[3] However, side effects with gold-based therapies are common and a patient's ability to tolerate gold must be counterbalanced against the medication's ability to control the inflammatory response.

Gold drugs are prodrugs, i.e. they are converted into other, as yet unknown, active forms *in vivo* during chrysotherapy.[4] Gold(I) complexes typically undergo rapid ligand displacement reactions and it is likely that *in vivo*, Au(I) coordinates to cysteine sites in glutathione, proteins, and enzymes. Hemple and coworkers concluded that a significant percentage of auranofin is converted into the cationic digold complex, $[(Et_3PAu)_2(\mu\text{-SATg})]^+$ in stomach acid.[5] This cationic complex showed similar activity to auranofin when tested in a rat arthritis model.[6] Another candidate for an active metabolite of gold is $Au(CN)_2^-$,[7] which has been shown to decrease superoxide production by polymorphonuclear leukocytes.[8]

In spite of continued use, the avenue by which gold drugs modify the inflammatory response is still unknown. Many hypotheses about the biological activity have been postulated.[4,9] However, the metabolism, transport, active sites, and mechanism of action are undefined to a great

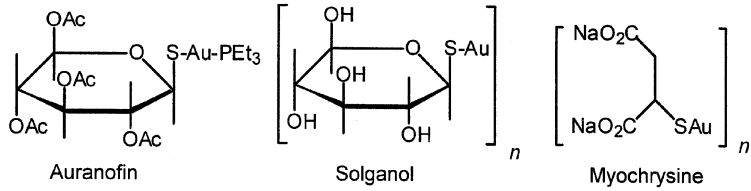


FIGURE 1 Three Au(I) compounds used to treat rheumatoid arthritis.

extent. What we do not understand about the biology of gold greatly outweighs what we do know at this time. Although the inorganic chemistry of gold has been an active area for some time, there also appears to be some fairly large gaps in our understanding of basic reaction mechanisms involving gold-sulfur compounds, especially with regard to redox transformations of gold(I) compounds.

REDOX STUDIES OF GOLD(I) DRUGS AND MODEL COMPOUNDS

Prior to our own work, redox studies of phosphine Au(I), thiolate complexes was limited to at brief report by Mendez et al. on the reduction of auranofin at a dropping mercury electrode.[10] Direct current and differential pulse polarography studies show that auranofin undergoes a diffusion controlled and reversible reduction at $-0.5\,V$ *vs.* SCE at pH greater than 9.5. Bulk electrolysis at $-0.8\,V$ yields an *n* value of 1, indicative of a $Au^{1/0}$ redox couple. Below pH 8.5, a proton-dependent pathway occurs. Protonation of Et_3P ($pK_a = 8.69$) is believed to be responsible for the shift in potential as a function of pH.

A better understanding of the oxidation chemistry of gold(I) compounds is important for the biological reactivity since rheumatoid arthritis has an oxidative pathology. Phagocytic cells at inflamed sites undergo oxidative bursts, releasing hypochlorite, a very strong oxidant.[11] Shaw et al. demonstrated that in acidic solution, hypochlorite oxidizes Au(I) in Myochrysine and auranofin to Au(III) and the ligands are also oxidized. The oxidation processes are complicated and involve a number of intermediates.[12]

Electrochemical studies of a variety of Au(I) complexes with phosphine and/or sulfur ligands show that metal, phosphine or sulfur ligands can be redox sites.[13] For compounds that model auranofin, i.e. phosphine Au(I) thiolates (see Figure 2), experimental studies in nonaqueous solvents demonstrate that sulfur is initially oxidized leading to gold sulfur clusters (*vide infra*).[14]

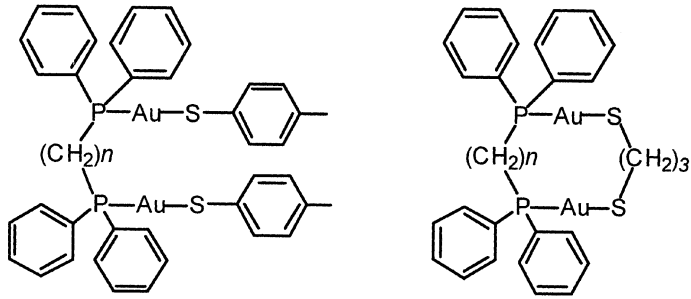
The dinuclear compounds shown in Figure 2 are either open chain (Series A) or cyclic (Series B). The mononuclear and dinuclear complexes in Fig. 2 are white solids, a color which is characteristic of two-coordinate, linear Au(I), with the exception of $(dppm)(AuSC_6H_4CH_3)_2$ (Series A, $n = 1$; dppm = 1,1-bisdiphenylphosphinomethane) which is yellow. Au–Au bonding influences the unique color and reactivity of this complex.[15] The HOMOs of these Au(I) complexes have been characterized as primarily sulfur in character.[15,16]

The Au(I) phosphine thiolate complexes shown in Fig. 2 each undergo a broad irreversible oxidation at about $+0.6 - +1.1\,V$ and a second, sharper, irreversible oxidation at more positive potentials, $+1.2 - +1.6\,V$(*vs.* SCE).[14]

Mononuclear

R_3P-Au-SR' (R = Ph, Et, Me; SR' = $SC_6H_4CH_3$; SATg)

Dinuclear



Series A (n = 1-5) Series B (n = 2-5)

FIGURE 2 Mononuclear and dinuclear Au(I) complexes discussed in this article.

The cyclic complexes in Series B, with the aliphatic dithiolates, are in general easier to oxidize than those in Series A. Auranofin, (Et_3P)Au (SATg) (SATg = 2,3,4,6-tetra-o-acetyl-1-thio-β-D-glucopyranosato-S), is the most difficult to oxidize (see Table 1). Constant potential electrolyses experiments were conducted to determine the number of electrons passed for each oxidation process. The results listed in Table 1 show that for *the first oxidation process*, $n = 0.5$ for the mononuclear complexes and $n = 1.0$ for the dinuclear complexes. For the *second oxidation process*, $n \geq 2$ for the mononuclear complexes and $n = ca.$ 4 for the dinuclear complexes. The products of the *second oxidation* have not been fully characterized. However, the irreversible nature and *n* values are consistent with oxidation of Au(I) to Au(III), followed by a rapid chemical step. The electrochemical results are consistent with the observations made by Shaw, et al. during the chemical oxidation of auranofin and Myochrysine with hypochlorite.[12]

The *n* values for the first oxidation process were unexpected since complete oxidation of a single type of redox center, i.e., phosphine, gold or thiolate, would lead to an *n* value of 1 for the mononuclear complexes and 2 for the dinuclear. Bulk electrolysis experiments were carried out in an electrolyte solution suitable for ^{1}H NMR studies in an attempt to characterize

TABLE 1 Cyclic Voltammetry and Constant Potential Electrolysis Data for Selected Au(I) Compounds

	Cyclic voltammetry[a]		Constant potential electrolysis[b]				
Complexes	$E_{p1}{}^{A}$	$E_{p2}{}^{A}$	Volts	n	Volts	n	ref.
$Au(PEt_3)$(SATg)	1.10[c,d]	1.60[c,d]	1.20[c]	0.50	1.60[c]	>2	14c
$Au(PPh_3)$(*p*-tc)	0.82	1.52	1.00	0.5	1.45	2.2	14a
Au_2(dppe)(*p*-tc)$_2$	0.72	1.54					14a
Au_2(dppp)(*p*-tc)$_2$	0.77	1.54	1.00	0.93[e]	1.50	4.9[f]	14a
Au_2(dppb)(*p*-tc)$_2$	0.83	1.59					14a
Au_2(dpppn)(*p*-tc)$_2$	0.78	1.56	1.00	0.93			14a
Au_2(dppe)(pdt)	0.77[g]	1.20					14a
Au_2(dppp)(pdt)			0.90	0.9	1.30	3.5	14a
Au_2(dppb)(pdt)			0.90	1.0	1.40	4.2	14a
Au_2(dpppn)(pdt)	0.63[h]	1.23	0.90	1.0	1.40	4.2	14a

[a]Cyclic voltammetry experiments employing Pt working electrodes in CH_2Cl_2 in 0.1 M TBAH solution except as noted. All voltages are reported versus SCE reference except as noted. [b]Constant potential electrolysis experiments using a Pt working mesh electrode in 0.1 M TBAH/CH_3CN solution except as noted. [c]Bu_4NBF_4/CH_2Cl_2. [d]Potential vs. Ag/AgCl. [e]Average of three experiments: n = 0.93, 0.87, and 0.99. One experiment performed using 0.1 M KPF_6/CD_3CN solution. [f]Average of three experiments: n = 5.0, 4.8, and 4.9. One experiment performed using 0.1 M KPF_6/CD_3CN solution. [g]A wave at 0.47 V also is observed that may be due to adsorption at the electrode. [h]Very broad wave. The following abbreviations are used: SATg, see text; *p*-tc = *p*-thiocresol; pdt = 1,3-propanedithiol; dppe = 1,2-bis(diphenylphosphino)ethane; dppp = 1,3-bis-(diphenylphosphino)propane; dppb = 1,4-bis(diphenylphosphino)butane; dpppn = 1,5-bis(diphenylphosphino) pentane.

the products of the *first oxidation process*. The disulfides, $(SC_6H_4CH_3)_2$ and $(SCH_2CH_2CH_2S)$, were identified by ^1H NMR after constant potential electrolysis of the Au(I) aromatic thiolates and cyclic Au(I) aliphatic thiolates, respectively.[14] Phosphine and thiolate ligands still appeared to be coordinated to Au(I). Separation of the gold products from the high concentration of electrolyte necessary for electrochemical experiments proved to be difficult. Therefore a chemical oxidant was used to overcome this problem.

Ferrocenium, Cp_2Fe^+, is a mild, one-electron oxidant ($E^\circ = +0.46$ V *vs.* SCE) that is slightly soluble in CH_2Cl_2.[17] Reactions of the mononuclear complexes in Fig. 2 were carried out with one-half molar equivalent of Cp_2Fe^+. The products of the reactions are ferrocene, disulfide, and cationic tetragold(I) clusters containing bridging thiolates (Eq. 1). *All complexes in*

Figure 2 that were tested, react with ferrocenium, in spite of the fact that their peak oxidation potentials are as much as + 0.6 V higher!

$$2\,(R_3P)Au(SR') + Cp_2Fe^+ \rightarrow Cp_2Fe + 0.5(SR')_2 + 0.5[(R_3PAu)_2(\mu\text{-}SR')]_2^{2+} \quad (1)$$

$$R = Ph; SR' = C_6H_4CH_3\ (\mathbf{1})$$

$$R = Et; SR' = SATg\ (\mathbf{2})$$

$$R = Me; SR' = SATg\ (\mathbf{3})$$

Several of the dinuclear gold(I) complexes in Series A and B (Fig. 2) undergo similar reactions (e.g., Eqs. 2, and 3).

$$(LL)Au_2(SC_6H_4CH_3)_2 + Cp_2Fe^+ \rightarrow Cp_2Fe + 0.5(SC_6H_4CH_3)_2 + 0.5[(LL)(Au)_2(\mu\text{-}SC_6H_4CH_3)]_2^{2+} \quad (2)$$

$$LL = dppe\ (\mathbf{4})$$

$$LL = dppb\ (\mathbf{5})$$

$$(LL)Au_2(SC_3H_6S) + Cp_2Fe^+ \rightarrow Cp_2Fe + 0.5(SC_3H_6S) + 0.5[(LL)_2(Au)_4(SC_3H_6S)]^{2+} \quad (3)$$

$$LL = dppb\ (\mathbf{6})$$

Clusters **1, 3,** and **4** have been characterized by X-ray crystallography.[14b,18] ORTEP drawings are presented in Figures 3–5. In **1** and **3**, the four Au(I) atoms are arranged in a square with angles about Au near 90°. A thiolate ligand bridges two golds atoms and each Au(I) is approximately linear (average P-Au-S angle is 175°). The two digold(μ-thiolate) units are held together in a square by Au–Au bonding. The nonbridged Au–Au distance is 3.17 Å for both structures, **1** and **3**. The sulfur bridged Au–Au distances in **3** (3.106 Å) are slightly shorter than that in **1** (3.152 Å), perhaps as a result of less steric interaction between the PMe_3 ligands in **3**. The presence of a bisphosphine ligand (dppe) in cluster **4** changes the structure so that the four gold atoms no longer form a square. The structure is better described as a Au_4S_2 core arranged in a chair configuration. The only Au–Au contact is between the two Au(I) atoms that are coordinated to the same dppe ligand (2.961 Å). The sulfur bridged Au–Au distance is 3.844 Å, which is longer than the van der Waals distance. The Au_4S_2 core represents a fairly common structural motif for Au(I) sulfur clusters.[19]

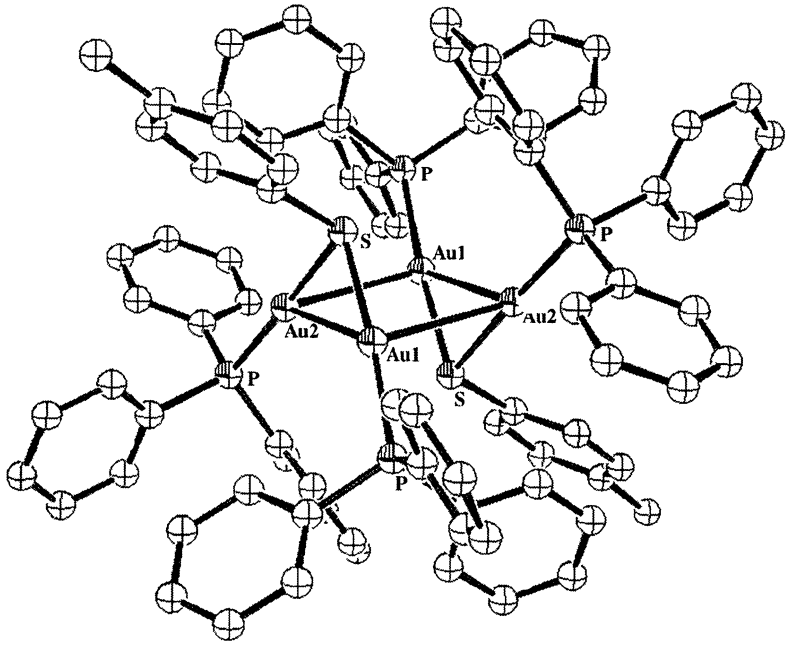


FIGURE 3 ORTEP drawing of **1**.

Complex **3** was obtained by oxidation of the PMe_3 analog of auranofin. We were not able to obtain X-ray quality crystals of **2**, in spite of numerous attempts.[18] It is interesting to note that researchers at Smith Kline and French laboratories have studied **2** previously. Complex **2**, isolated as the NO_3^- salt, showed similar activity to auranofin when assayed in a rat arthritis model.[6] Hill and Elder obtained a preliminary structure of **2** that showed the square of golds with bridging thiolates, but the quality of the data was not high enough to completely solve the structure.[6] This is also the cationic complex that Hemple et al. proposed to form in acidic solution, under conditions designed to mimic the behavior of auranofin in stomach acid.[5]

MECHANISM OF OXIDATION

Our electrochemical and chemical oxidation studies demonstrate that oxidation of phosphine Au(I) thiolate complexes is initially sulfur based rather than metal based. This is consistent with electronic structure studies in which the HOMO was assigned as primarily sulfur in character.[15,16] A mechanism that accounts for the unexpected n value of 0.5 for the mononuclear

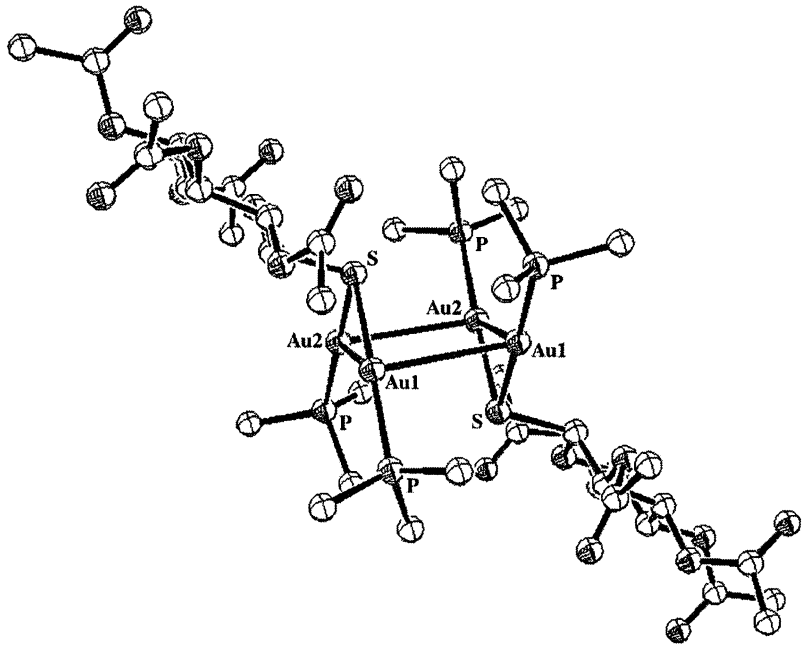


FIGURE 4 ORTEP drawing of **3**.

complexes is shown in Scheme 1.[14b,18] Upon oxidation, an electron is removed from the sulfur HOMO of the mononuclear gold(I) complexes. This leads to cleavage of the Au-S bond and formation of $LAu(I)^+$ and a thiyl radical. The thiyl radical rapidly dimerizes to form disulfide. The coordinatively unsaturated LAu^+ reacts with another molecule of starting material to form a digold cationic complex which then dimerizes via Au–Au bonding to form the observed tetragold(I) cluster. The net result is a one-electron oxidation per two molecules of gold. Thus only one-half equivalent of oxidant is required per mole of mononuclear gold complex to complete the oxidation. Further support of this mechanism is provided by the independent syntheses of clusters **1–3** via reaction of LAuCl with a silver salt (e.g. $AgNO_3$) followed by addition of LAuSR (Scheme 2). Similar mechanisms to that in Scheme 1 can be written for oxidation of the complexes in Series A and B that account for observed n values of 1 and product formation.

Chemical oxidation of one of the complexes in Series A, $(dppm)Au_2(SC_6H_4CH_3)_2$, appears to proceed similarly to those discussed above, in that Cp_2Fe and disulfide are products. However the gold cluster product that forms is very different.[20] The yellow complex, $[Au_9(dppm)_4(SC_6H_4CH_3)_6](PF_6)_3$, **7**, consists of nine gold atoms arranged in an irregular cluster

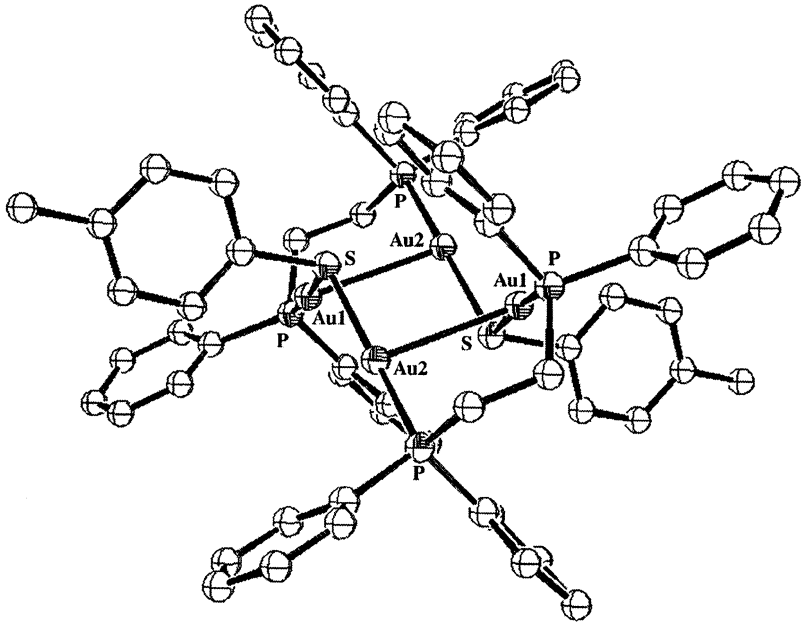


FIGURE 5 ORTEP drawing of **4**.

(Figure 6). Three distinct environments are observed for the gold atoms: sulfur-bridged Au–Au bonds; unbridged Au–Au bonds; and sulfur-bridged non-bonded Au–Au interactions. In addition, one of the gold atoms is coordinated to thiolate and gold but not to phosphorus. The mechanism of oxidation and reactivity of this cluster are currently under investigation.

$$\text{LAuSR} \xrightarrow{-1e^-} \text{LAu}^+ + \text{RS}^\cdot$$

$$\text{RS}^\cdot \longrightarrow {}^1/_2\,\text{RSSR}$$

$$\text{LAu}^+ + \text{LAuSR} \longrightarrow {}^1/_2\,[\text{L}_4\text{Au}_4(\mu\text{-SR})_2]^{2+}$$

$$2\,\text{LAuSR} \xrightarrow{-1e^-} {}^1/_2\,\text{RSSR} + {}^1/_2\,[\text{L}_4\text{Au}_4(\mu\text{-SR})_2]^{2+}$$

$(\text{L} = \text{PPh}_3, \text{PEt}_3, \text{PMe}_3;\ \text{SR} = \text{SC}_6\text{H}_4\text{CH}_3,\ \text{SATg})$

SCHEME 1. Mechanism of Oxidation

$$R_3PAuCl + AgX \longrightarrow R_3PAuX + AgCl$$

$$R_3PAuSR + R_3PAuX \longrightarrow {}^1/_2\,[L_4Au_4(\mu\text{-}SR)_2]X_2$$

(R = Ph, Et, Me; SR = $SC_6H_4CH_3$, SATg ; X = PF_6^-, NO_3^-, $CF_3SO_3^-$, BF_4^-)

SCHEME 2. Synthesis of Clusters

THIOLATE-DISULFIDE EXCHANGE

Several years ago we observed that gold(I) thiolate complexes react with disulfides to undergo a thiolate/disulfide exchange.[21] The bioinorganic implications to this are numerous since it is well recognized that

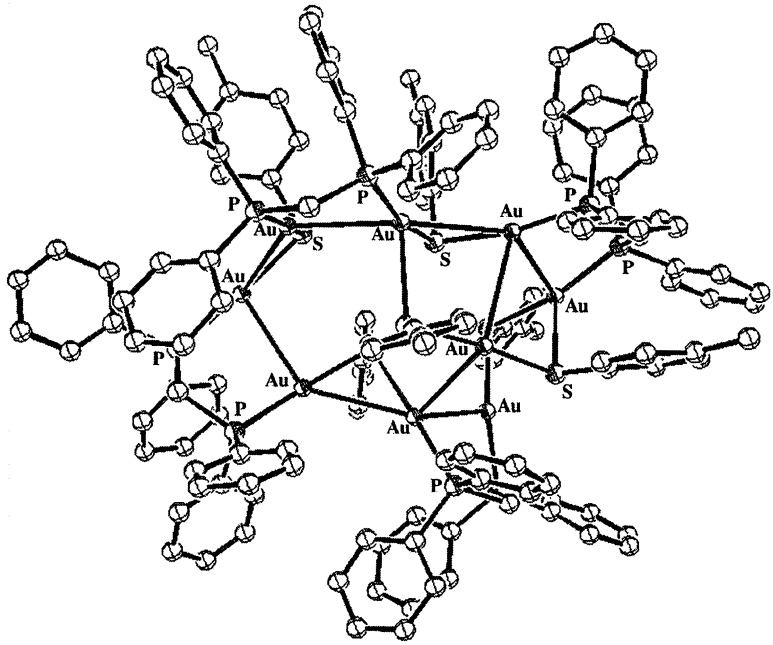


FIGURE 6 ORTEP drawing of **7**.

thiol/disulfide ratios are critically important to many biological regulatory pathways. The thiolate/disulfide exchange reaction can be represented as shown in Eq. 4 and 5 for a mononuclear and a dinuclear complex, respectively.

$$\begin{aligned} &PPh_3Au(SC_6H_4CH_3) + (SC_6H_4Cl)_2 \\ &\quad \rightarrow PPh_3Au(SC_6H_4Cl) + (CH_3C_6H_4S)(SC_6H_4Cl) \end{aligned} \tag{4}$$

$$\begin{aligned} &(dppm)Au_2(SC_6H_4CH_3)_2 + (SC_6H_4Cl)_2 \\ &\quad \rightarrow (dppm)Au_2(SC_6H_4CH_3)(SC_6H_4Cl) + (CH_3C_6H_4S)(SC_6H_4Cl) \end{aligned} \tag{5}$$

^{1}H NMR experiments confirm that the reaction proceeds in a stepwise fashion in which the unsymmetrical disulfide forms first, followed by formation of the symmetrical disulfide. An interesting reactivity trend emerged for several complexes shown in Figure 2: $(dppm)Au_2(SC_6H_4CH_3)_2$, reacts more quickly with *p*-chlorophenyldisulfide than do the other dinuclear or monomeric complexes. It is also interesting to note that the "inverse" of eq. 5, i.e. reaction of $(dppm)Au_2(SC_6H_4Cl)_2$ and $(SC_6H_4CH_3)_2$ is slower. It is not clear whether thermodynamic redox potentials or the stability of kinetic intermediates is most important.

Variable temperature $^{31}P\{^1H\}$ NMR experiments and UV-vis studies suggest that there is a Au–Au bond in $(dppm)Au_2(SC_6H_4CH_3)_2$ but not in any of the other open chain dinuclear complexes in Series A.[15] Thus, it is intriguing to hypothesize that Au–Au bonding influences the observed reactivity toward disulfides. To this end, we have recently carried out comparative rate studies on the reactions of disulfide with several of the clusters discussed above, which have multiple Au–Au bonds.[22] The thiolate/disulfide exchange reaction that was studied in most detail is shown in Eq. 6.

$$\begin{aligned} &[(PPh_3PAu)_4(SC_6H_4CH_3)_2]^{2+} + (SC_6H_4Cl)_2 \\ &\quad \rightarrow [(Ph_3PAu)_4(SC_6H_4CH_3)(SC_6H_4Cl)]^{2+} + (CH_3C_6H_4S)(SC_6H_4Cl) \end{aligned} \tag{6}$$

The rate law is first order in gold complex and first order in disulfide. A comparison of the initial rates for several clusters, dinuclear complexes, and mononuclear complexes is shown in Table 2. The gold clusters have dramatically enhanced reactivity toward thiolate/disulfide exchange reactions. This is an intriguing result that may have biological implications, especially in view of the idea that auranofin is a prodrug, mild oxidation of Au(I) thiolates produces Au(I) clusters, and the fact that cluster, **2,** has similar activity to auranofin in a rat arthritis model.[6]

TABLE 2 Relative Rate Constants for Reaction of Au(I)-thiolates with $(SC_6H_4Cl)_2$

Gold complexes	Rate constant, k (M^{-1} sec^{-1})	Relative rate
$[(Ph_3PAu)_4(SC_6H_4CH_3)_2][PF_6]_2$	6.8×10^{-3}	20
$[(dppb)_2Au_4(SC_6H_4CH_3)_2][PF_6]_2$	7.5×10^{-3}	22
$[(dppm)Au_2(SC_6H_4CH_3)_2]$	1.4×10^{-3}	4
$[(dppe)Au_2(SC_6H_4CH_3)_2]$	2.4×10^{-4}	0.7
$Ph_3PAu(SC_6H_4CH_3)$	3.4×10^{-4}	1

SUMMARY

Gold(I) phosphine thiolate complexes oxidize at relatively low potentials and the oxidation is sulfur-based. The products of the oxidation are disulfide and Au(I) clusters. The gold(I) clusters in turn undergo thiolate/disulfide exchange reactions more rapidly than monomeric gold(I) complexes. Most of the gold clusters consist of four Au(I) atoms with bridging thiolates and Au–Au bonds, a structural motif that appears to be fairly common in gold chemistry. An exception to this motif is the unusual nine-gold structure formed upon oxidation of $(dppm)Au_2(SC_6H_4CH_3)_2$.

Chemical oxidation of the Au(I) complexes can be achieved by using ferrocenium, although its redox potential is significantly lower than some of the oxidation peak potentials measured by cyclic voltammetry. Oxidation of auranofin by Cp_2Fe^+ is especially noteworthy because the potential for the first oxidation measured by cyclic voltammetry (+1.10 V) is approximately 600 mV more positive than the $Cp_2Fe^{+/0}$ couple. Ferrocenium may be acting as an electron transfer catalyst, which suggests that the true redox potentials of auranofin and the other Au(I) complexes listed in Table 1 are lower than what is measured by cyclic voltammetry. If this is the case, then oxidation of auranofin *in vivo* may occur at potentials that are biologically accessible under normal cellular conditions. Alternatively, although Cp_2Fe^+ is generally regarded as an outer sphere electron transfer reagent, it may be acting as an inner sphere reagent in this case, effectively lowering the activation barrier for the electron transfer. We are currently investigating these possibilities.

REFERENCES

1. American Society of Health-System Pharmacists, August 20, 2002. (http://www.ashp.org/shortage/gold-salts.html) Drug Information Service, Univ. of Utah, Salt Lake City, UT.
2. Mosby Year Book. 2002. Aurothioglucose and auranofin in *Mosby's GenRx. The Complete Reference for Generic and Brand Drug*, 12th Ed., St. Louis, MO.

3. American College of Rheumatology Subcommittee on Rheumatoid Arthritis Guidelines. 2002. Guidelines for the management of rheumatoid arthritis. *Arthritis Rheum*. 46: 328–346.
4. Shaw, C. F., III. 1999. Gold-based therapeutic agents. *Chem. Rev*. 99: 2589–2600.
5. (a) Hempel, J. and Mikuriya, Y. 1981. Ligand exchange reactions of Ridaura. *Proceeding of a Symposium on the Bioinorganic Chemistry of Gold Compounds*, Philadelphia, Pennsylvania, 37–46. (b) Bryan, D. L. B., Mikuriya, Y., Hempel, J. C., Mellinger, D., Hashim, M., and Pasternack, R. F. 1987. Reactions of auranofin [(1-thio-β-D-glucopyranose-2,3,4,6-tetraacetato-*S*)(triethylphosphine)gold(I)] in aqueous hydrochloric acid. *Inorg. Chem*. 26: 4180–4185.
6. Hill, D. T., Girard, G. R., DiMartino, M., Calis, G. H. M., Heeg, M. J., and R. C. Elder. 1990. (μ-1-Thio-β-D-glucopyranose 2,3,4,6-tetraaceto-S,S′)bis(triethylphosphine)digold nitrate: synthesis, ^{197}Au Mossbauer, X-ray crystal structure and antiarthritic activity, INORG 274, 199th American Chemical Society National Meeting, Boston, MA.
7. Elder, R. C., Zhao, Z., Zhang, Y., Dorsey, J. G., Hess, E. V., and Tepperman, K. J. 1993. Dicyanogold(I) is a common human metabolite of different gold drugs. *J. Rheumatol*. 20: 268–272.
8. Graham, G. G. and Dale, M. M. 1990. The activation of gold complexes by cyanide produced by polymorphonuclear leukocytes-II. Evidence for the formation and biological activity of aurocyanide. *Biochem. Pharmocol*. 39: 1697–1702.
9. Best, S. L. and Sadler, P. J. 1996. Gold drugs: mechanism of action and toxicity. *Gold Bull*. 29: 87–93.
10. Mendez, J. H., Perez, A. S., and Zamarreno, M. D. 1989. Electrochemical behavior and polarographic determination of auranofin. *J. Pharm. Sci*. 78: 589–591.
11. $E^{\circ} = +1.48\,V$ *vs*. SHE for the reaction $HClO + H^{+} + 2e^{-} = Cl^{-} + H_2O$; Vanysek, P. 1990. *CRC Handbook of Chemistry and Physics* [Chemical Rubber Co. Press] Boca Raton: 8–17.
12. Shaw, G. F., III, Schraa, S., Gleichmann, E., Grover, Y. P., Dunemann, L., and Jagarlamudi, A. 1994. Redox chemistry and cyanide in the formation of gold metabolites. *Metal-Based Drugs* 1: 351–362.
13. See references 7–12 in ref. 14a.
14. (a) Jiang, T., Wei, G., Turmel, C., Bruce, A. E., and Bruce, M. R. M. 1994. Redox chemistry of gold(I) phosphine thiolates: sulfur-based oxidation. *Metal-Based Drugs* 1: 419–431. (b) Chen, J., Jiang, T., Wei, G., Mohamed, A. A., Homrighausen, C., Krause Bauer, J. A., Bruce, A. E., and Bruce, M. R. M. 1999. Electrochemical and chemical oxidation of gold(I) thiolate phosphine complexes: formation of gold clusters and disulfide. *J. Am. Chem. Soc*. 121: 9225–9226. (c) Mohamed, A. A., Bruce, M. R. M., and Bruce, A. E. 1999. Cyclic voltammetry of auranofin. *Metal Based Drugs* 6: 233–238.
15. Narayanaswamy, R., Young, M. A., Parkhurst, E., Ouellette, M., Kerr, M. E., Ho, D. M., Elder, R. C., Bruce, A. E., and Bruce, M. R. M. 1993. Synthesis, structure determination, and electronic spectroscopy of neutral, dimeric gold(I) complexes. gold(I)-gold(I) interactions in solution and in the solid state. *Inorg. Chem*. 32: 2506–2517.
16. Jones, W. B., Yuan, J., Narayanaswamy, R., Young, M. A., Elder, R. C., Bruce, A. E., and Bruce, M. R. M. 1995. Solid State EXAFS and Luminescence Studies of Neutral, Dinuclear Gold(I) Complexes. Gold(I)-Gold(I) Interactions in the Solid State. *Inorg. Chem*. 34: 1996–2001.
17. Connelly, N. G. and Geiger, W. E. 1996. Chemical redox agents for organometallic chemistry. *Chem. Rev*. 96: 877–910.

18. Mohamed, A. A, Chen, J., Krause Bauer, J. A., Hill, D. T., Bruce, A. E., and Bruce, M. R. M. 2002. Formation of a gold(I) cluster and disulfide by oxidation of the antiarthritic gold drug, auranofin. *Inorg. Chem*. submitted.
19. See for example: (a) Wang, S. and Fackler, J. P. Jr. 1990. Gold thiolate complexes with short intermolecular gold-gold distances from reactions of organic disulfides with gold(I) complexes. Syntheses and crystal structures of $[AuI_2(PPh_3)_2(\mu\text{-}SCH_2Ph)](NO_3)$ and $Au_2^{III}Cl_4(\mu\text{-}SPh)_2$. *Inorg. Chem*. 29: 4404–4407. (b) Ku-z'mina, L. G.; Baukova, T. V., Churakov, A. V., Kuz'min, V. S., and Dvortsova, N. V. 1997. Aurophilic interactions in gold(I) thiolate complexes: crystal structures of complexes $[C_6H_5SAuPPh_3]_2$ and $[C_6H_5S(AuPPh_3)_2]_2(BF_4)_2$. *Russ. J. Coord. Chem*. (Transl. Koordinatsionnaya Khimiya) 23: 279–288. (c) Sladek, A. and Schmidbaur, H. 1995. Aurophilicity in polynuclear (phosphine)gold(I) thiolates $\{Me_3CS[Au(PPh_3)]_2\}^+ BF_4^-$ and $\{(CH_2S)_2[Au(PPh_3)]_3\}^+ BF_4^-$. *Chem. Ber*. 128: 907–9. (d) Canales, F., Gimeno, M. C., Laguna, A., and Jones, P. G. 1996. Aurophilicity at sulfur centers. Synthesis and reactivity of the complex $[S(Au_2dppf)]$; formation of polynuclear sulfur-centered complexes. Crystal structures of $[S(Au_2dppf)]\cdot 2CHCl_3$, $[(\mu\text{-}Au_2dppf)\{S(Au_2dppf)\}_2](OTf)_2\cdot 8CHCl_3$, and $[S(AuPPh_2Me)_2(Au_2dppf)](ClO_4)_2.3CH_2Cl_2$. *J. Am. Chem. Soc*. 118: 4839–4845.
20. Chen, J. 1999. Master's Thesis, University of Maine.
21. DiLorenzo, M., Ganesh, S., Tadayon, L., Chen, J., Bruce, M. R. M., and Bruce, A. E. 1999. Reactions of organic disulfides and gold(I) complexes. *Metal-Based Drugs* 6: 247–255.
22. Abdou, H. E. 2000. Master's Thesis, University of Maine.