# Gold-Based Therapeutic Agents

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## *Contents*




C. Frank Shaw III is Chairman of the Chemistry Department at Eastern Kentucky University, a position he recently assumed. A native of the New York City area, he was raised in Delaware. After receiving his Bachelor's degree (with honors in Chemistry) at the University of Delaware, he was trained in classical organometallic chemistry as he earned his Ph.D. under Professor A. Louis Allred at Northwestern University studying group IV compounds, then held postdoctoral positions at Purdue University with the late Professor R. Stuart Tobias (organogold chemistry) and a tutor and with Professor Ian Butler at McGill University (transition-metal carbonyl and nitrosyl chemistry). When he was appointed to his first faculty position at UW—Milwaukee in 1974, however, he quickly succumbed to the siren song of inorganic biochemistry, then a field in its infancy. For the last quarter of a century, he has studied the chemistry, biochemistry, and pharmacology of antiarthritic gold drugs and chemical properties of metallothioneins, a class of ubiquitous, sulfhydryl-rich, metal-binding proteins. He enjoys teaching courses from general chemistry to advanced graduate level. Away from the lab and office, he collects objects with unusual point groups and enjoys the out-of-doors. His interest in land-use planning once dedicated to protecting Lake Michigan and especially its Milwaukee Lakefront will now be transferred to the blue-greener pastures of Kentucky.

## *I. Current and Potential Medicinal Uses*

### A. Introduction

Throughout prehistory and ancient history, most major civilizations attributed medicinal character to gold. In the form of amulets and medallions, it was used to ward off disease and evil spirits. In many cases, potions containing gold powders were administered to ill patients. After the alchemists learned to use aqua regia to dissolve gold, compounds as well as elemental gold were used in medicinal treatments.[1a] A modern descendent of these early treatments is the family of liqueurs variously known as Goldschlager, Goldwasser, and Geldwasser, which contain gold flakes that can be suspended when the bottle is shaken. No medicinal value has been scientifically established for ingested elemental gold, although side reactions are known.[1b,c]

Robert Koch's discovery that $K[Au(CN)_2]$ exhibits bacteriostatic activity brought gold therapies into the realm of rational medicine.[2] The first widespread application of gold compounds was against pulmonary tuberculosis, for which they do not provide an effective therapy. This lead to Jacque Forestier's use of gold drugs to treat rheumatoid arthritis,[3] which was shown by subsequent double-blind studies to be effective for many but not all patients who were treated. Of the many gold thiolates used for this purpose, two remain in active clinical use in the United States: gold sodium thiomalate and gold thioglucose, sold under the trade names Myochrysine and Solgonal. In Europe, sodium bis(thiosulfato)gold(I) and sodium thiopropanolsulfonate-*S*-gold(I) are also used clinically. The only new compound to be introduced into clinical use in the last 30 years is auranofin, triethylphosphine(2,3,4,6-tetra-*O*-acetyl-

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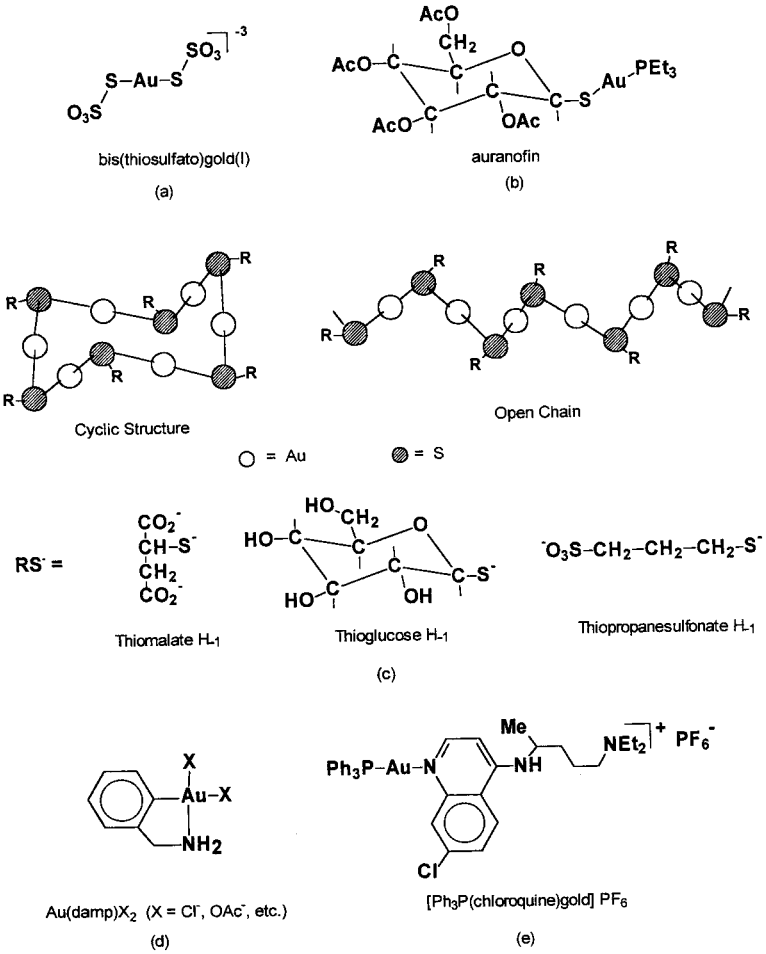


**Figure 1.** Structures of gold complexes with antiarthritic, antitumor, and antimalarial activity. (a−c) antiarthritic drugs; (d) [Au(damp)$X_2$], gold(III) antitumor agents; (c) antimalarial complex of chloroquine.

$\beta$-1-D-thiopyranosato-*S*)gold(I). Their structures are shown in Figure 1a−c.

Asthma and pemphigus, an autoimmune disease of the skin, as well as arthritis, can be treated with gold compounds. In addition, current research shows that new uses of gold for the treatment of cancer, HIV, and malaria are promising. This review will examine the rationale and types of drugs in use or considered for each of these diseases and then report on the chemistry and biochemistry of gold-based medicinal agents.

## B. Rheumatoid Arthritis

Gold(I) thiolates have been the principal compounds used in chrysotherapy, the treatment of rheumatoid arthritis (RA) with gold-based drugs.[4] The introduction of auranofin promised a safer treatment, but metaanalyses of 66 clinical trials shows that it is somewhat less effective than the injectable thiolates.[5] The response of patients to gold therapy is typically manifest only after 3−6 months. One accepted effect of chrysotherapy is antiinflammatory action,[4,6] but this alone cannot account its effectiveness. Gold drugs are considered to be disease-modifying agents which retard and sometimes cause remissions of the disease state.[6] Additional mechanisms of action which may contribute to chrysotherapy are antimicrobial activity, reduction of humoral immunity, inhibition of the complement pathway, effects on lymphocytes, monocytes, and neutrophils (especially inhibition of T-cell proliferation and of polymorphonuclear monocyte activation), and enzyme inhibition. Several mechanisms may operate in parallel, and none is widely accepted as the primary biological action.[4]

## C. Cancer

The design and testing of gold complexes for antitumor activity over the past several decades has been based on three rationales:[7−10] (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 in vitro and P388 leukemia cells in vivo[11] led to the screening of many auranofin analogues (Table 1), but their spectrum of activity was limited.[12,13] A variety of triphenylphosphinegold(I) complexes of various ligands have been screened[14−17] and show significant activity (Table 1). An outgrowth of these efforts was the development of bis(diphos)gold(I) complexes which had promising antitumor properties[18−22] but exhibited cardiovascular toxicity which precluded clinical trials.[23] These efforts have been reviewed extensively elsewhere.[7−10]

**Table 1. Antitumor Activity and Cytotoxicity of Gold(I) and Gold(III) Complexes**

| compound | | | antitumor activity, in vivo ILS (%) | tumor line | cytotoxicity, in vitro $IC_{50}/\mu M$ | cell line | ref |
|---|---|---|---|---|---|---|---|
| | | | $Au^{I}$ Compounds | | | | |
| $(\Phi_3PAu)_2(\mu DTE)$ | | | 67 | Ehrlich Ascites | | | 14 |
| $\Phi_3PAutTP$ | | | | | 0.6 | FLC | 16,87 |
| | | | | | 1.8 | Dox FLC | |
| $\Phi_3PAu$-thymidine | | | 71 | P388 | | | 15 |
| $\Phi_3PAu$(5-fluorouridine) | | | | L1210 | | | 15 |
| $\Phi_3PAu$(tegafur) | | | | L1210 | | | 15 |
| ferrocene$(\mu\text{-}\Phi_2PAuCl)_2$ | | | 40 | | | | |
| $Et_3PAuCl$ | | | 36 | P388 leukemia | 1 | B16 melanoma | 13 |
| $Et_3PAuCN$ | | | 68 | P388 leukemia | 0.4 | B16 melanoma | 13 |
| $Et_3PAuCH_3$ | | | 55 | P388 leukemia | 1 | B16 melanoma | 13 |
| $[(Et_3P)_2Au]Cl$ | | | 36 | P388 leukemia | 1 | B16 melanoma | 13 |
| $Et_3PAuSCN$ | | | 36 | P388 leukemia | 1 | B16 melanoma | 13 |
| $Et_3PAuSCH_3$ | | | 36 | P388 leukemia | 1 | B16 melanoma | 13 |
| $Et_3PAuSG$ | | | 32 | P388 leukemia | 2 | B16 melanoma | 13 |
| $Et_3PAuSTg$ | | | 68 | P388 leukemia | 2 | B16 melanoma | 13 |
| $Et_3PAuSAtg$ (auranofin) | | | 70 | P388 leukemia | 1.5 | B16 melanoma | 13 |
| $Et_3PAuS$-α-Atg (epiauranofin) | | | 65 | P388 leukemia | 4 | B16 melanoma | 13 |
| $[AuSTm]_n$ | | | 24 | P388 leukemia | 60 | B16 melanoma | 12 |
| $[AuSTg]_n$ | | | 15 | P388 leukemia | 166 | B16 melanoma | 12 |
| $[AuSATg]_n$ | | | 14 | P388 leukemia | 150 | B16 melanoma | 12 |
| $DPPE(AuCl)_2$ | | | | P388 leukemia | 8 | B16 melanoma | 21 |
| $DPPE(AuSTg)_2$ | | | | P388 leukemia | 4 | B16 melanoma | 20 |
| $[Au(DPPE)_2]Cl$ | | | | P388 leukemia | 2 | B16 melanoma | 18 |
| $[Au(R_2P\text{-}Y\text{-}PR'_2)_2]X$ | | | | | | | |
| R,R′ | Y | X | | | | | 18,22 |
| Φ | $(CH_2)_2$ | Cl | 83 | P388 leukemia | 4.5 | B16 melanoma | 18,22 |
| Φ | $(CH_2)_2$ | Br | 70,83 | P388 leukemia | | B16 melanoma | 18,22 |
| Φ | $(CH_2)_2$ | $NO_3$ | 90 | P388 leukemia | 4 | B16 melanoma | 18,22 |
| Φ | $(CH_2)_3$ | Cl | 89 | P388 leukemia | 0.16 | B16 melanoma | 18,22 |
| Φ | $CH_2{=}CH_2$ | Cl | 92 | P388 leukemia | 2 | B16 melanoma | 18,22 |
| 3-F-Φ | $(CH_2)_2$ | Cl | 45,55 | P388 leukemia | | B16 melanoma | 18,22 |
| 2-Py | $(CH_2)_2$ | Cl | 75 | P388 leukemia | | B16 melanoma | 18,22 |
| Φ, Et | $(CH_2)_2$ | Cl | 54 | P388 leukemia | 5 | B16 melanoma | 18,22 |
| Et | $(CH_2)_3$ | Cl | 40,30 | P388 leukemia | 17 | B16 melanoma | 18,22 |
| | | | $Au^{III}$ Complexes | | | | |
| Au(Streptonigrin) | | | | | 0.1 | P388 leukemia | 28 |
| $[Me_2AuCl_2][As\Phi_4]$ | | | >20% | | | | 10 |
| $Me_2Au(\mu SCN)_2AuMe_2$ | | | >20% | | | | 10 |
| Au(N-methylimidazole)$Cl_3$ | | | | | 7.2 | L1210 leukemia | 29 |
| Au(2-methylbenzoxazole)$Cl_3$ | | | | | 5.6 | L1210 leukemia | 29 |
| Au(2,5-dimethylbenzoxazole)$Cl_3$ | | | | | 6.3 | L1210 leukemia | 29 |
| $DPPE(AuCl_3)_2$ | | | | | 15 | B16 melanoma | 21 |
| $[Au(damp)Cl_2]$ | | | | | 30 | HT1736 bladder | 27 |
| $[Au(damp)(SCN)_2]$ | | | | | 6.7 | HT1736 bladder | 27 |
| $[Au(damp)(OAc)_2]$ | | | T/C 0.60 | HT1736 Xenograft | 13 | HT1736 bladder | 27 |
| [Au(damp)(malonate)] | | | T/C 0.58 | HT1736 Xenograft | 11 | HT1736 bladder | 27 |
| cisplatin | | | 125 | P388 leukemia | | B16 melanoma | 18,22 |
| cisplatin | | | T/C 0.61 | HT 1736 Xenograft | | | 27 |
| cisplatin | | | | | 2.5 | L1210 leukemia | 29 |

Several dimethylgold(III) complexes examined shortly after the discovery of cisplatin's antitumor potential showed only modest activity (20% ILS).[10] Recently, Fricker has described a systematic strategy for screening metal complexes for antitumor activity and described its application to gold(III) complexes of damp (dimethylaminomethylphenyl), Figure 1d.[24] A wide array of damp complexes, $[Au(damp)X_2]$ have been prepared, characterized, and screened for activity.[24−27] Unlike simple gold(III)tetrahalides which are readily reduced by thiols, $[Au(damp)(OAc)_2]$ is stabilized by the electron-rich phenyl group of the damp ligand and exchanges the acetate ligands in reaction with glutathione.[25] The chloride, thiocyanate, acetate, malonato, and oxalato complexes are similar in their cytotoxicities against a panel of different cell lines. They exhibit some selectivity against HT1376 bladder tumor line (Table 1) and a number of ovarian tumors. The acetato and malonato complexes exhibited activity comparable to cisplatin against the HT1376 xenograft in vivo[24−27] (Table 1). The mechanism of action differs from cisplatin, raising the possibility of clinical use against cisplatin-resistant tumors.[26,27] The gold(III) complex of streptonigrin, an antitumor agent, is stable against reduction to gold(I) in the presence of serum albumin, a good ligand and reducing agent, and exhibits activity similar to the parent ligand (Table 1).[28] The trichlorogold(III) derivatives of methylimidazole, methylbenzoxazole, and dimethylbenoxazole show reasonable cytotoxicities and in vivo antitumor activity.[29] The levels of activity that can be achieved with

**Table 2. Toxicity and HIV-1 Antiviral Activity of Gold Complexes[a]**

| | MTT survival results (%)[b] | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | toxicity ([Au]/$\mu$M) | | | + HIV-1(NL43) ([Au]/$\mu$M) | | | | |
| complex | 1.0 | 0.10 | 0.010 | 500 | 100 | 1.0 | 0.10 | 0.010 |
| $Au(STg)_2^-$ | | | | 90 | 50 | 0 | | |
| $[AuSTg]_n$ | | | | 0 | 0 | 2 | | |
| TgSH | | | | 0 | 1 | 1 | | |
| $Au(STm)_2^{5-}$ | | | | 12 | 51 | 0 | | |
| $[AuSTm^{2-}]_n$ | | | | 0 | 45 | 0 | | |
| $TmSH^{2-}$ | | | | 0 | 0 | 0 | | |
| $Et_3PAuSATg$ | 61 | 97 | 122 | | | 0 | 7 | 4 |
| $Et_3PAuSTg$ | 130 | 108 | 96 | | | 7 | 8 | 0 |
| $Et_3PAuCl$ | 92 | 86 | 96 | | | 1 | 7 | 0 |
| $Me_3PAuCN$ | 0 | 88 | 73 | | | 0 | 9 | 8 |
| $Et_3PAuCN$ | 0 | 78 | 86 | | | 0 | 8 | 8 |
| $^iPr_3PAuCN$ | 0 | 100 | 103 | | | 0 | 6 | 0 |
| $Ph_3PAuCN$ | 0 | 101 | 91 | | | 0 | 8 | 7 |
| $Cy_3PAuCN$ | 60 | 85 | 127 | | | 2 | 6 | 9 |
| $KAu(CN)_2$ | 0 | 71 | 59 | | | 0 | 6 | 6 |
| $AuCl_4^-$ | | | | 0 | 0 | 7 | | |

[a] References 33 and 34. [b] MTT survival assayed using MT-4 cells incubated at 37 for 5 days (the assay is described in ref 33); values are percent surviving T-cells compared to controls.

gold drugs and the clinical experience with chrysotherapy clearly make them good candidates for further animal and clinical testing.

## D. Anti-HIV Activity and AIDS

A variety of gold compounds have been tested against human immunodeficiency virus (HIV) in vitro (Table 2). Interest in chrysotherapy for AIDS has been stimulated by a recent clinical report that an AIDS patient not accepting anti-HIV drugs but treated with auranofin for psoriatic arthritis experienced increasing CD4+ T cell counts,[30] in contrast to the usually irreversible decline of these cells. These findings suggest that gold complexes should be systematically investigated for anti-HIV activity.

Aurocyanide ($[Au(CN)_2^-]$) inhibits proliferation of HIV in cultured T-9 cells (a strain of CD4+ T cells) at levels as low as 20 nM and may have promise in treating AIDS in combination with other drugs.[31] This concentration of aurocyanide is in the range as a metabolite of gold drugs in chrysotherapy patients.[31] Gold thioglucose (AuSTg) inhibits reverse transcriptase (RTase) in cell-free extracts,[32] but since it and its metabolites do not readily enter cells, which is necessary for effective inhibition of RTase, it is ineffective when used against HIV in cell culture tests.[33] The bis(thioglucose)gold(I) complex, $[Au(STg)_2^-]$, actively protects MT-4 cells against HIV strain HL4-3 by reacting at Cys-532 on gp160, a viral coat protein, but lacks activity against more virulent strains.[33] A number of trialkylphosphinegold(I) cyanides were tested against the same system but were sufficiently cytotoxic that the MT-4 cells died at concentrations ($\sim$1 $\mu$M) below the onset of antiviral activity.[34]

## E. Bronchial Asthma

Considerable experience with the treatment of bronchial asthma in Japan suggests that chrysotherapy (particularly gold thioglucose) is an effective treatment.[35−38] Favorable rates of clinical improvement of extrinsic asthma have been reported: 74% for one study involving 1056 patients;[37] 68% for 28 treated patients vs 44% for the 36 controls in another;[38] while 5 of 14 patients in a long-term study of gold therapy remained symptom-free after 3 years.[36] As with rheumatoid arthritis, a significant proportion of patients receiving gold therapy encounter side effects. Some are able to continue after a short break in the therapy, while others must drop the treatment.[36−38]

## F. Malaria

Several antimalarial drugs which are useful for treating rheumatoid arthritis exhibit pharmacological profiles similar to gold drugs, which suggests that there might be common features in the mechanisms of antiarthritic and antimalarial action. Thus, the role of gold as a potential enhancer of antimalarial activity is under investigation.[39] The chloroquine (CQ) complex of triphenylphosphinegold(I), $Au(PPh_3)$-CQ, Figure 1e, shows promising activity against two strains of *Plasmodium falciparum* and one of *Plasmodium berghei*. The $IC_{50}$ values of $5.1 \times 10^{-9}$ and $23 \times 10^{-9}$ against FcB1 and FcB2, respectively, two chloroquine-resistant strains of the human malaria, *P. falciparum*, are 4−9-fold higher than the activity of chloroquinediphosphate and other metal complexes.[39]

# *II. Structures of Gold Drugs, Metabolites, and Analogues*

## A. Oxidation States of Gold

Compounds of gold in all possible oxidation states ranging from −I through +V are well documented. The elemental forms of gold, principally metallic and colloidal gold, are extremely stable under a wide range of conditions including aqueous systems, although in the presence of stabilizing ligands they can be auto-oxidized to gold(I) or gold(III). The +I and +III oxidation states have extensive chemistries

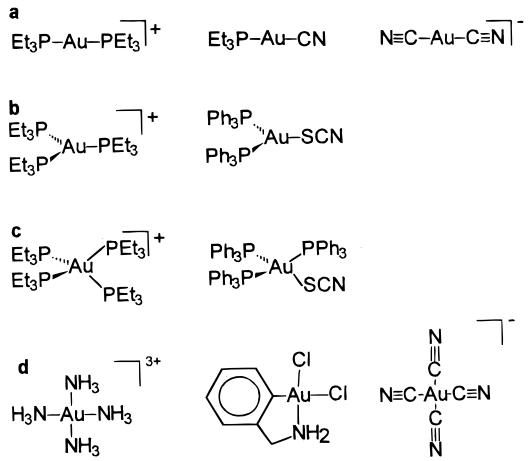


**Figure 2.** Typical gold(I) and gold(III) coordination geometries.

including those in aqueous media and biological systems. In contrast, the oxidation states −I, +II, +IV, and +V are less common. Stability of the −I and +V states in water is improbable, given their redox properties, which suggests that they will not play important roles in biological systems. On the other hand, many binuclear gold(II) complexes stabilized with chelating ligands are known, and they may have unrealized potential as medicinal agents.

## B. Gold(I) Coordination Geometries

Relativistic effects play an important role in the physical and chemical properties of gold.[40] In the third transition series, they arise from the accelerating effect of the large nuclear charges (+79 for gold) on the outer 6s electrons, and the effect maximizes at gold as one traverses the third-row elements. Relativistic calculations predict that the Au(I) radius is actually shorter (62 pm) than the radius of Ag(I) (68 pm).[40] This relativistic contraction has been confirmed by the measurement of the M−P bond distances in the bis(trimesitylphosphine)gold(I) and -silver(I) cations of the isomorphous tetrafluoroborate salts, which crystallize in the trigonal space group $P3_12_1$.[41] The Au(I)−P distance of 235.2 pm is 9 pm shorter than the 244.1 pm distance for Ag(I)−P. These distances yield covalent radii of 133 pm for Ag(I) and 125 pm for Au(I) in two-coordinate complexes.[41]

Gold(I) has a $d^{10}$ closed-shell configuration which gives rise to three principal coordination geometries: linear two-coordination, trigonal three-coordination, and tetrahedral four-coordination. Typical examples are shown in Figure 2a−c. Relativistic effects increase the 6s−6p energy gap of gold, which in turn enhances the stability of the linear two-coordinate geometry over three- and four-coordinate structures, compared to the case for the lighter elements of the coinage triad, Ag(I) and Cu(I), and the neighboring $d^{10}$ metal centers, Pt(0) and Hg(II). Thus, cyanide, thiolate, and other high affinity anionic ligands form $AuX_2^-$ ions, but the homoleptic three- and four-coordinate complexes, $AuX_3^{2-}$ and $AuX_4^{3-}$ have not been reported.[42] On the other hand, phosphines, arsines, and other neutral ligands readily form the cationic complexes $AuL_3^+$ and $AuL_4^+$ in addition to the two-coordinate $AuL_2^+$ ions. Neutral three- and four-coordinate complexes, $L_2AuX$ and $L_3AuX$, are more common than the anionic species $LAuX_2^-$ and $L_2AuX_2^-$. Three- and four- coordination were recently surveyed in this journal.[42]

## C. Gold(III) Coordination Geometries

The dominant coordination geometry is square planar, Figure 2d. Bond lengths are shorter than the corresponding gold(I) bond lengths but do not differ greatly. Five- and six-coordinate complexes typically exhibit elongated axial bond lengths perpendicular to the square plane and frequently involve ligand structures that constrain the axial donor atoms.

## D. Auranofin

The only licensed second-generation gold drug is a phosphinegold(I) thiolate, Figure 1b. In contrast to most of the parenteral agents, it is a discrete monomeric complex (MW 678.5).[43] The bond lengths and bond angles are similar to those in the related gold(I) complex, $(C_6H_5)_3PAuSC_6H_2Pr^i_3$[44,45] (Table 3). The phosphine ligand confers membrane solubility and alters the pharmacological profile. The tetraacetylthioglucose ligand is lost rapidly in vivo followed by

**Table 3. Bond Lengths (pm) and Angles of Chrysotherapy Agents and their 2,4,6-Triisopropylphenylthiolatogold(I) Analogues[a]**

| compound | $d_{Au-S/P}$ | ∠S−Au−S/P | ∠Au−S−C/S | $d_{Au-A}$ | ∠Au−S−Au | ref |
|---|---|---|---|---|---|---|
| | | Oligomeric Gold(I)Thiolates, −[−AuSR−]$_n$− | | | | |
| $[CsNa_2HAu_2(STm)_2]_n$ | 228 ± 1 | 170, 179 | | 323, 348 | 99 | 46 |
| $Au_n(STm)_m$ | 230 | | | 335 | 94 | 47 |
| $[Au(SC_6H_2Pr^i_3)]_6$ | 229 ± 1 | 176 ± 1 | 108 ± 2 | 356 ± 10 | 102 ± 4 | 51 |
| | | Bis(thiolato)gold(I) Complexes, $[Au(SR)_2^-]$ | | | | |
| $[Au(STm)_2]^{5-}$ | 226 ± 1 | 179 | 108 ± 1 | | | 48 |
| $[Au(S_2O_3)_2]^{3-}$ | 228 ± 1 | 177 | 104 ± 1 | | | 49,50 |
| $[Au((SC_6H_2Pr^i_3)_2^-]$ | 229 | 176 | 105 ± 3 | | | 45 |
| | | Phosphinegold(I)thiolates, $R'_3PAuSR$ | | | | |
| $Et_3PAuSAtg$ | 229 (S)<br>226 (P) | 174 | 106 | | | 43 |
| $(C_6H_5)_3PAuSC_6H_2Pr^i_3$ | 229 (S)<br>226 (P) | 176 | 105 | | | 44,45 |

[a] Error limits are the range for independent bond lengths or angles in a structure. Individual crystallographic standard deviations are less than 1 pm or 1° and are not given.

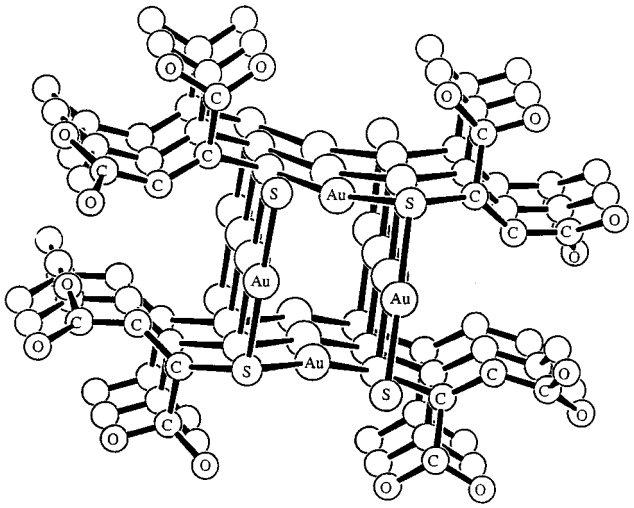

**Figure 3.** Solid-state structure of crystalline $[CsNa_2HAu_2(STm)_2]_n$, prepared by vapor phase deposition, which is related to the drug myochrisine, consists of intertwined helices.[46]

slower displacement and concomitant oxidation of the phosphine to $Et_3PO$. Mechanisms for these reactions in serum are discussed in the protein chemistry section below.

## E. Oligomeric Gold(I) Thiolates

A variety of thiolate ligands have been used to administer gold. Formulations containing thiomalate (Myochrysine), thioglucose (Solganol), and thiopropanolsulfonate (Allochrysine) are the most commonly used in current clinical practice. None of them seems to be as straightforward as the representation of the principal constituents shown in Figure 1.

After many decades of effort, the myochrysine analogue $[CsNa_2HAu_2(STm)_2]_n$ has been crystallized and its structure determined by X-ray crystallography, Figure 3.[46] The immediate coordination sphere of the gold(I) ions is in good agreement with the description previously obtained by EXAFS spectroscopy.[47] The bridging Au−S bond distances, 228.3 and 228.6 pm, are little changed from those in mononuclear bis(thiolato)gold(I) complexes,[45,48−50] phosphinegold(I) thiolates,[43−45] and the hexamer $[Au(SC_6H_2Pr^i_3)]_6$,[51] Table 3. The structure consists of helices containing two interpenetrating strands. Helices of opposite handedness occur in equal numbers: the right-handed helices contain exclusively *R*-thiomalate and the left-handed ones exclusively *S*-thiomalate.[46] This aspect of the structure has a striking parallel in crystalline $(NH_4)_5[Au(STm)_2]$, which contains equal numbers of mononuclear *R*,*R*- and *S*,*S*-bis(thiomalato)gold(I) ions.[48] Since the counterions and packing are quite different between the polymeric and mononuclear structures, the spontaneous segregation of the chiral ligands may be driven by interactions across the gold(I) ions.

Commercial and medicinal preparations of myochrisine are more complex, due to the presence of excess thiomalate ligand over the 1:1 ratio.[52,53] Solutions of the drug or the optically pure *R*- and *S*-analogues exhibit tetramers by ESI-MS, which suggests that the intertwined helix structure may not persist in solution.[52]

## F. Gold Protein Complexes

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.

Although no complete structure determination of a medicinally relevant gold-protein complex has been reported to date, EXAFS, Mössbauer, and NMR data (Table 4) provide the coordination environments and bond lengths for a variety of proteins known to complex gold upon reaction with the drugs or metabolites.

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. The gold thiomalate derivatives of serum albumin were examined by EXAFS and Mössbauer spectroscopy, which revealed that the gold remains in the +1 oxidation state and is coordinated by two sulfur-donor

**Table 4. Gold Ligation and Spectroscopic Parameters of Gold−Protein Complexes**

| | | | Mössbauer | | | |
|---|---|---|---|---|---|---|
| | | | IS[b] | QS | | |
| complex[a] | ligation | $d_{Au-X}$/pm | mm s$^{-1}$ | | NMR $\delta$/ppm | ref |
| Alb−S−$(AuSTm)_{0.74}$[a] | S−Au−S | 228 (S) | | | | 54 |
| Alb−S−$(AuSTm)_{2.0}$[a] | S−Au−S | | 3.11 | 6.68 | | 54 |
| | | | 2.93 | 6.50 | | |
| Alb−S−$(AuSTm)_{.7.4}$[a] | S−Au−S | 230 (S) | | | | 54 |
| Alb−S−$(AuSAtg)_{0.45}$[a] | S−Au−S | 228 (S) | | | | 55 |
| Alb−S−$(AuPEt_3)$[a] | S−Au−P | 227 (S) | 4.90 | 8.76 | 38.8 $^{31}$P | 55,58 |
| | | 220 (P) | | | | |
| Alb−$N_{His}$−$(AuPEt_3)_{0.78}$ | N−Au−P | 206 (N) | | | 27−28 $^{31}$P | 55 |
| | | 225 (P) | | | | |
| Alb−S−$(AuPEt_3)_2$[a] | S−Au−P | | | | 36.5 $^{31}$P | 59 |
| Alb−SH·$[Au(CN)_2]$ | C−Au−C | | 4.73 | 10.65 | 152.5 $^{13}$C | 60,61 |
| Alb−SH·$[Au(CN)_2]_3$ | C−Au−C | | 4.78 | 10.41 | 152.5 $^{13}$C | 60,61 |
| Hb−$(SAuPEt_3)_{1.7}$ | S−Au−P | | | | 34.0 $^{31}$P | 62 |
| Au,Cd,Zn−MT | S−Au−S | 229 (S) | | | | 66 |
| $(TmSAu)_{20}$MT | S−Au−S | 230 (S) | | | | 66 |

[a] Stoichiometries are gold per reduced cysteine-34 residue. [b] Relative to gold metal (+1.23 vs Au in Pt source).

atoms.[54] In conjunction with radiotracer and other chemical evidence, the data support coordination to the albumin cysteine 34 residue and thiomalate to form albumin−S−Au−Stm and albumin−S−(Au−$\mu$Stm)$_n$−Au−STm. The acetylthioglucose derivative albumin−S−AuSAtg was also characterized by EXAFS spectroscopy.[55] The Au−S distances of the thiomalate and acetylthioglucose derivatives are typical of gold−thiolate bonds, 228−230 pm (Table 4). The formation of albumin−S−AuPEt$_3$ at cysteine 34 was first established by $^{31}$P NMR spectroscopy[56,57] and confirmed by EXAFS spectroscopy[54] and Mössbauer spectroscopy[58] (Table 4). Et$_3$PAuCl, like auranofin, reacts at cysteine 34 to form albumin−SAuPEt$_3$, but easy displacement of the chloride ligands allows further reactions to form albumin−S(AuPEt$_3$)$_2^+$ and to form Et$_3$PAu$^+$ adducts of the 17 histidine residues, reactions favored by the easy displacement of chloride.[59] Aurocyanide, [Au(CN)$_2^-$], a gold drug metabolite, binds to albumin principally at anion binding sites with retention of both cyanide ligands.[60] The unique Mössbauer signature of [Au(CN)$_2^-$] confirms that the anion remains intact in its 1:1 and 3:1 complexes with albumin[61] (Table 4).

Hemoglobin has been investigated because it reacts with Et$_3$PAu$^+$ taken up by red cells exposed in vitro to Et$_3$PAuCl,[56,57,62] although it may not be a significant red cell binding site at the lower concentrations that prevail during clinical use of auranofin.[63] $^{31}$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.[56,57,62]

Under conditions mimicking chrysotherapy, gold binds to metallothionein (MT) in animal models. MT is a heavy metal binding protein found in mammalian kidneys and livers, where it binds to Zn(II), Cd(II), Hg(II), Cu(I)Ag(I), Au(I), Pt(II), and Bi(III) under a variety of normal physiological conditions, metal loadings, and other stresses.[64,65] It can bind seven Cd(II) or Zn(II) ions in two metal clusters generated from its 20 cysteine residues. The N-terminal $\beta$ domain forms a cluster with the composition M$_3$S$_9$, and the $\alpha$ domain has the composition M$_4$S$_{11}$, where the S represents the sulfurs of the cysteine thiolate residues and M is Cd(II) or Zn(II). The metal−protein stoichiometry depends on the metal ions bound and varies with the organism's physiological state in vivo and with reaction conditions in vitro.[64]

In vitro reactions demonstrate that the ligation of gold depends on the gold complex and the conditions of the reaction. MT displaces the thiomalate from AuSTm when the protein is in excess and coordinates the bound gold with two cysteine residues to form Au,Cd−MT or Au,Cd,Zn−MT (Table 4) depending on the initial metal loading of the MT.[66] Excess aurothiomalate can displace all of the initially bound metals to saturate the 20 cysteine residues and form (TmSAu)$_{\sim 20}$MT (Table 4) with retention of the thiomalate ligands.[66] Auranofin does not react with M$_7$MT but does react with the metal-free apoprotein.[67] The acetylthioglucose ligand is displaced completely, and the phosphine ligand is only partially retained in the product.[67] Et$_3$PAuCl, from which the chloride is very easily displaced, reacts with M$_7$MT to form a product which contains gold(I) bound both with and without the phosphine ligand.[68]

## *III. Bioinorganic Pharmacology*

### A. Gold Drugs Are Prodrugs: Ligand Displacement Reactions

Biological studies in humans and laboratory animals show that the gold drugs used clinically undergo rapid metabolism in vivo and, hence, should be considered prodrugs. A prodrug is a substance that is altered (or activated) in vivo to form the active species (e.g., deacetylation of aspirin). The use of radiolabeled ligands reveals that gold and its carrier ligands have different distributions and excretion times.[68−70] The phenomenological term "dissociation" is sometimes applied in the medical literature to the loss of the carrier ligands but is inappropriate because ligand exchange reactions with endogenous ligands are the primary mechanism of metabolism and free gold ions are not generated. Ligand displacement is the preferred terminology. Rapid displacement of the ligands from $^{198}$Au$^{35}$STg in mice and $^{198}$Au$^{35}$STm in rats has been reported.[68,70] $^{198}$Au is retained in various organs more efficiently than the $^{35}$S label from the thiolate ligands. Likewise, each component of triply labeled auranofin (Et$_3$32P−$^{195}$Au−$^{35}$SATg) is metabolized differently in vivo: Et$_3{}^{32}$P═O and $^{35}$S are excreted with half-lives of 8 and 16 h, respectively, while the half-life for gold excretion is 20 days.[69]

Studies of auranofin added to whole blood showed that the ligand displacements are dramatically faster than the excretion rates quoted above and confirmed that the three components of the drug have very different fates.[70] Within 20 min the gold in the serum is primarily protein-bound and the triethylphosphine is distributed in 1:2:2 ratio among the serum proteins, red cells, and a low-molecular-weight species known to be phosphine oxide (Et$_3$PO).[70]

In human patients, low concentrations of free thiomalate have been detected in human blood after administration of myochrysine[71] and Au(CN)$_2^-$ has been detected as a common metabolite of all three drugs used in the United States.[72] These findings confirm the significance of ligand exchange reactions in humans and the assignment of chrysotherapy agents as prodrugs.

### B. Auranofin and Serum Albumin

The most extensively studied metabolic reactions of a gold drug are those of serum albumin with auranofin. Gold does not have a useful NMR nucleus, since the 100% abundant $^{197}$Au has a quadrupolar ground state. Yet, $^{31}$P, $^{1}$H, and $^{13}$C NMR studies under biomimetic conditions have provided a wealth of data about chemical transformations of chrysotherapy agents.[73] Auranofin reacts at cys-34 via a ligand exchange reaction that displaces the sulfhydryl group[55−57,67] (Figure 4a). Both deacetylated auranofin (which has thioglucose instead of tetraacetylthioglucose as the anion) and Et$_3$PAuCl will form the

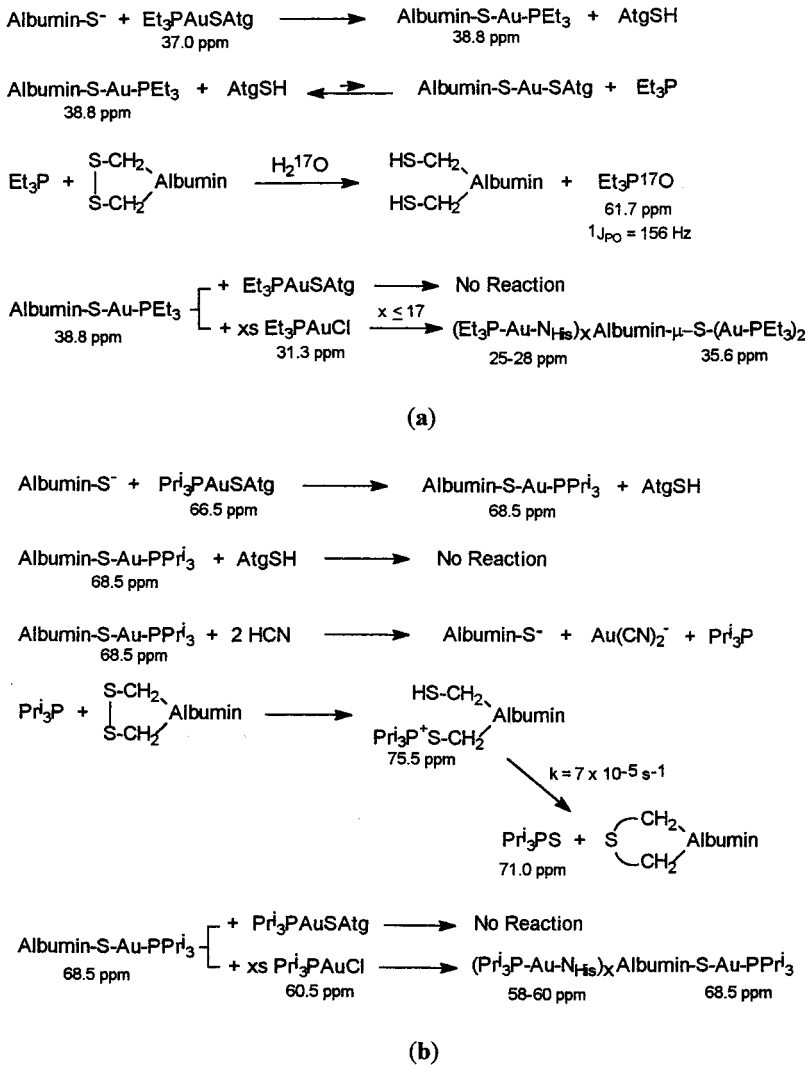


**Figure 4.** Reactions of serum albumin with auranofin and auranofin analogues: (a) $Et_3PAuX$ complexes; (b) $^iPr_3PAuX$ complexes. Reactions were conducted in buffered aqueous solutions buffered at pH values near physiological pH; following a convention employed among biochemists, protons appearing as reactants and products are not explicitly included in the equations.

same product, $AlbSAuPEt_3$, by displacement of the anion. Thus, studying reactions with auranofin, instead of the unstable, deacetylated auranofin, presents significant experimental advantages. Under conditions approximating those in vivo, complex formation is first-order in auranofin and has a rate constant of $2.9 \pm 0.2\ s^{-1}$, which indicates that auranofin (and probably its deacetylated metabolite) will have a very short lifetime after entering the bloodstream where albumin is present in large excess ($\sim$400 $\mu$M AlbSH and $\sim$10−25 $\mu$M Au).[74] Sadler and colleagues reported a conformational change in albumin that accompanies gold binding to cys-34.[75] 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, which may be concomitant with the crevice opening.

The free acetylthioglucose liberated from auranofin reacts further with the cysteine 34 disulfide bonds to liberate cysteine[76] and also displaces the $Et_3P$ ligand, leading to its oxidation[77] (Figure 4a). Physiological thiol ligands such as glutathione (GSH) also drive the displacement of phosphine.[77] The oxidant for the phosphine can be either molecular oxygen or albumin disulfide bonds (Figure 4a), yet the reaction proceeds at a similar rate and to about the same extent aerobically or anaerobically.[78] Since free $O_2$ is not present in serum, it is likely that disulfide bonds are the in vivo oxidants.[78]

Structure-function studies that substituted $Me_3P$, $^iPr_3P$, or $(NC{-}CH_2CH_2)_3P$ for $Et_3P$ of auranofin in these reactions have established that the basicity of the phosphine strongly affects the rate and extent of $R_3PO$ formation:[78−80]

$$Me_3P \approx (NC{-}CH_2CH_2)_3P > Et_3P \gg iPr_3P$$

The triisopropylphosphine ligand is sufficiently basic so that it is not easily displaced by AtgSH (Figure 3b), but if the high affinity cyanide ligand is present, a phosphonium thiolate intermediate in the phosphine oxidation reaction can be detected and monitored as it decays with a half-life of $7 \times 10^{-5}$ s.[79] When the triisopropylphosphonium intermediate is hydrolyzed, the steric bulk of the isopropyl groups directs the reaction to the methylene group of the cysteine residue resulting in a slower reaction than

for triethylphosphine and generating $Et_3P{=}S$ as the hydrolysis product (Figure 4b).

Examination of the effect of the anionic ligand in auranofin analogues, $Et_3PAuX$, revealed that the rate of $Et_3P{=}O$ formation increased with the affinity of the thiols for gold(I):

$$AtgSH > TgSH > GSH$$

Replacement of the $AtgS^-$ ligand by $CN^-$ or the selenium analogue, $AtgSe^-$, which have greater affinities than thiols for gold, was expected to slow initial reaction with cysteine 34 and generate a longer lived drug molecule. Surprisingly, the high-affinity anions accelerate the formation of $Et_3P{=}O$.[81,82]

These studies provide a set of mechanisms for the conversion of auranofin into albumin complexes. The displacement of both the acetylthioglucose and triethylphosphine ligands is consistent with the in vivo radioisotope studies described above. The accumulating knowledge of gold drug metabolism gleaned from biomimetic inorganic studies in vitro will aid development of the next generation of gold drugs.

## C. The Thiol Shuttle and Gold(I)–Thiolate Equilibration Models

Mononuclear and oligomeric gold(I) thiolates ($Au(SR)_2^-$ and $[AuSR]_n$) and their metabolites are not readily taken up by cells in vitro or in vivo, which is reflected in their cytotoxicity values ($IC_{50}$), Table 1. They can, however, bind to cell surface thiols and by mechanisms such as inhibiting nutrient uptake or cell signaling pathways may affect the cells' overall metabolism.[83,84] In contrast, both the $Et_3PAu^+$ moiety derived from auranofin or its analogues and the $[Au(CN)_2^-]$ metabolite, resulting from immunogenesis of cyanide and/or absorption of cyanide from cigarette smoke, are taken up by cells.

Gold from auranofin is taken up quickly and extensively by various cell types.[69,85,86] The acetylthioglucose ligand is displaced before gold is transported into cells, while the triethylphosphine enters the cell but accumulates to a lesser extent than the gold itself.[69,85] Mirabelli and co-workers proposed a sulfhydryl shuttle model, based on studies in cultured macrophage cells, as a mechanism for the uptake and efflux of $Et_3PAu^+$ derived from auranofin (Figure 5).[85] Sulfhydryl-dependent membrane transport proteins (MSH) provide a vehicle for movement of the $Et_3PAu^+$ across the cell membrane. Within the cell, $Et_3PAu^+$ is transferred to other cell sulfhydryls (CSH) and can then undergo several fates. Further reaction with additional cell sulfhydryls (C′SH) may lead to displacement of the $Et_3P$ ligand and its oxidation to $Et_3P{=}O$. With or without the $Et_3P$ bound, the gold(I) can be shuttled out of the cell via the membrane sulfhydryl proteins.[85,86]

Gold uptake is mediated by membrane sulfhydryl proteins but it is not an energy-dependent, active-transport process.[85] Therefore, intracellular gold concentrations should be in equilibrium with the extracellular sources of gold. This was tested in two ways. Serum albumin, which has a relatively high affinity for gold, was added to the media of cultured

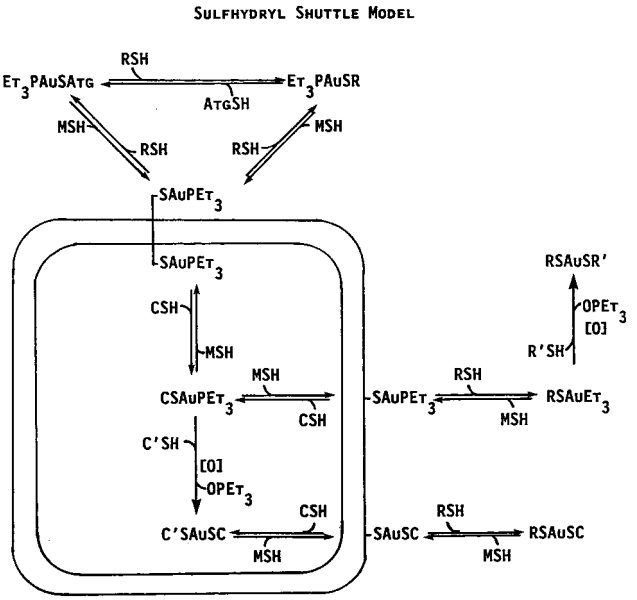


**Figure 5.** Thiol shuttle model for $Et_3PAu^+$ uptake and efflux from cells. RSH and R′SH represent extracellular thiols and CSH represents cytosolic thiols. These may be protein or low molecular weight thiols.

macrophages[85] and B16 melanoma cells[12] in increasing amounts. This led to slower and less extensive uptake of the gold, consistent with an equilibrium distribution. The cytotoxicity to tumor cells of both thiotheopyllinato(triphenylphosphine)gold(I) and auranofin is decreased by increasing the fetal calf serum (fcs) content of the media. The additional serum albumin introduced in the fcs binds the gold and reduces its uptake.[12,87] An equilibrium must be reversible, and red cells that had accumulated gold upon exposure to auranofin were shown to have more extensive gold efflux when resuspended in fresh serum or a buffered albumin solution than in isotonic salt solution.[86] These findings strongly support the existence of an equilibrium between intra- and extracellular auranofin metabolites. Thus, the model of rapid equilibration of gold among protein and nonprotein thiols, first proposed to explain its distribution in kidney cell cytosols[88] and later described for the transfer of $Et_3PAu^+$ from hemoglobin to albumin,[62] can be extended to the equilibration of gold between intracellular and extracellular environments.[86]

## D. Cyanide Metabolites

$[Au(CN)_2^-]$ can be considered a well-established metabolite of chrysotherapy drugs and also exhibits anti-HIV activity, as discussed earlier in this review. The first evidence of $[Au(CN)_2^-]$ as a metabolite was the report that tobacco smoking enhances the ability of patients' red cells to accumulate gold metabolites of AuSTm and AuSTg, although animal red cells do not.[89,90] The inhaled smoke of tobacco products contains up to 1700 ppm of HCN, which is absorbed through the lungs. Because of the strong affinity of cyanide for gold(I), $\log \beta_2 = 36.6$,[91] it can react with gold to form $[Au(CN)_2^-]$, which facilitates the transfer of gold into red cells and other cells.[90] [Of course, this phenomenon has not been observed in laboratory animals, since their life expectancies fall short of the

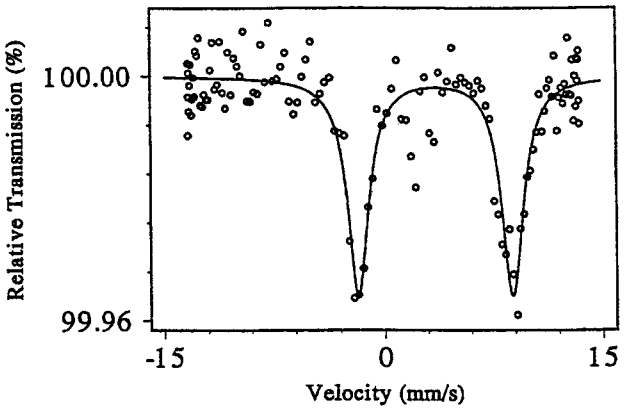


**Figure 6.** $^{197}$Au Mössbauer spectrum of the Albumin−[Au(CN)$_2$-] adduct. The large IS value (10.65(7) mm s$^{-1}$ relative to gold foil, obtained by adding 1.23 mm s$^{-1}$ to the experimental value obtained relative to the Pt source) is a characteristic signature of aurocyanide.[61]

legal age for purchasing tobacco products.] The perturbation of gold metabolism by cyanide can also explain the higher incidence of side effects from gold drugs in patients who smoke, since it facilitates uptake into cells.[89,90] The mechanism of uptake is sensitive to added cyanide but not to the effect of DIDS (diisothiocyanatostilbene-2,2′-disulfonic acid), an anion channel blocker. These findings are consistent with [Au(CN)$_2^-$] uptake via the sulfhydryl shuttle mechanism described above (Figure 4).

Research on the interactions between gold compounds and the immune system led to the finding that [Au(CN)$_2^-$] is generated by stimulated polymorphonuclear leukocytes. Thiocyanate (SCN$^-$) acts as a substrate for the formation of cyanide by the action of myleoperoxidase. This formation of Au(CN)$_2^-$ may be a critical metabolic process at the inflammed sites in the arthritic joints of patients and related to the mechanism of action.[93,94] The Au(CN)$_2^-$ is taken up into the cells and can limit the extent of the oxidative burst.[92−94]

Au(CN)$_2^-$ is present in the urine (5−560 nM) and blood (5−25 nM in the ultrafiltrates, ≤10 000 Da) of patients, independent of their smoking habits, although the concentrations are somewhat higher in smokers.[72] Thus, it is a common metabolite of all three gold drugs (AuSTm, AuSTg, and auranofin) used clinically in the United States.[31,72] It must be transported from the inflamed sites to the kidneys for urinary excretion. Intact [Au(CN)$_2^-$] binds to serum albumin at one high-affinity site ($K_1 = 5.5 \times 10^4$) and three weak binding sites ($K_2 = 7 \times 10^3$), although only the former is physiologically significant.[60] Mössbauer measurements confirm that intact aurocyanide binds to albumin (Figure 6). The strong binding interaction is sufficiently large to minimize the free [Au(CN)$_2^-$] in the blood serum.[60] Yet the binding is labile and easily reversed, and is, thus, consistent with aurocyanide uptake from the bloodstream by red cells.

These newly found roles of Au(CN)$_2^-$ may open the door to new research and mechanisms of action that will end the long uncertainty about where and how the gold drug metabolites exert their effects on the inflamed joints and/or immune systems of patients.

## E. Oxidation States in Vivo

A considerable body of evidence suggests that in vivo gold exists, primarily as gold(I). Gold drugs exposed to body fluids and proteins react predominantly by ligand exchange reactions that preserve the gold(I) oxidation state,[85,86,95−98] exemplified by the protein reactions described above. 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.[97,98] Thiols and thioethers, including cysteine and methionine residues in proteins and peptides, are capable of reducing gold(III) to gold(I).[99−102] Even disulfide bonds react rapidly to reduce gold(III).[100,103] Thus, it appears that the bulk of the 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.

Gleichmann and co-workers have observed that gold drugs can be activated in vivo to a gold(III) metabolite that is responsible for some of the immunological side effects observed in chrysotherapy.[104,105] This finding is based on the observation that after mice have been treated with AuSTm (gold sodium thiomalate, Figures 1c and 3) for several weeks, gold(III) elicits a response in the popliteal lymph node assay (PLNA) but AuSTm does not. The PLNA is important because it discriminates between the effects of a drug and those of its metabolites to determine which is immunogenic. Subsequently, T cells from human chrysotherapy patients were found to be sensitized against gold(III) but not gold(I).[106] Thus, the formation of gold(III) in vivo first demonstrated in lab animals is demonstrably relevant to human therapy.

Hypochlorous acid (HOCl), which is generated by the enzyme myeloperoxidase during the oxidative burst at inflamed sites, can oxidize the gold in AuSTm to Au(III) in vitro.[60b,107] This finding has been extended to additional gold compounds.[60b] For example, gold(I) thiolates including auranofin are oxidized to Au(III) with preliminary or concomitant oxidation of the ligands.

$$1/n[\mathrm{AuSR}]_n + 4\ \mathrm{OCl^-} + 2\mathrm{H^+} \rightarrow \mathrm{AuCl_4^-} + \mathrm{RSO_3^-} + \mathrm{H_2O}$$

$$\mathrm{Et_3PAuSAtg} + 5\mathrm{OCl^-} + 2\mathrm{H^+} \rightarrow \mathrm{AuCl_4^-} + \mathrm{AtgSO_3^-} + \mathrm{Et_3P{=}O} + \mathrm{H_2O} + \mathrm{Cl^-}$$

As shown in Figure 7, the conversion of auranofin into the final oxidation products, followed by $^{31}$P, $^{13}$C, and $^{33}$S NMR and UV spectroscopic methods, involves a multitude of intermediates and is not a trivial matter, since there are three oxidizable moieties. [Au(CN)$_2^-$] is oxidized to dicyanogold(III) complexes, which form in a equilibrium mixture of hydroxo and chloro species.[108] These reactions clearly establish the feasibility of gold(III) formation in vivo by the action by hypochlorite and provides a plausible mechanism for the findings of Gleichmann[104,105]and Verwilghen.[106]

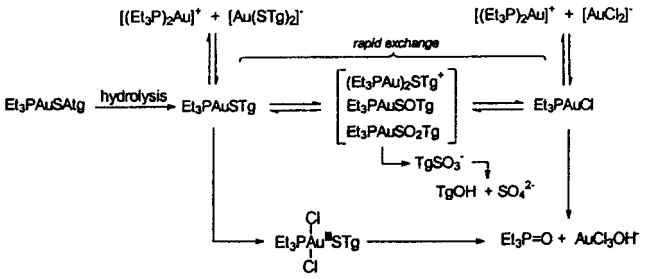


**Figure 7.** Oxidation of auranofin by hypochlorite involves multiple stages of reaction as both ligands and the gold(I) center are oxidized.[108]

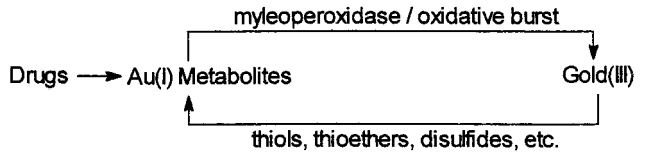


**Figure 8.** Biological redox cycling of gold(I) and gold(III).

There is an apparent dichotomy between the observations that gold is present primarily as gold(I) in vivo and that T cells are sensitized to gold(III), rather than the gold drugs themselves; the redox cycle shown in Figure 8 provides an explanation.[60b,104] The operation of such a cycle is consistent with observations that while relatively low concentrations of gold are achieved during chrysotherapy (10−25 $\mu$M Au), the changes in tissue levels of essential metals, thiols, proteins, etc., in responding patients are much larger than can be accounted for on the basis of a stoichiometric reaction with the gold present.

## IV. Conclusions

Gold drugs have proven effectiveness in treating rheumatoid and psoriatic arthritis and bronchial asthma. Despite 70 years of clinical use, their mechanisms of action are poorly understood. This results in part because gold is widely dispersed in the body and does not effectively target high-affinity sites of action. Over the years, many different mechanisms of action have been proposed. Two which are receiving considerable attention are the formation of aurocyanide, which targets certain immune cells involved in the inflammatory response, and the generation of gold(III) in vivo. These have been described in detail elsewhere by Graham et al.[92] and Gleichmann et al.[105,60b] Aurocyanide formation has been documented in patients taking all three drugs used clinically in the United States and its ability to inhibit the polymorphonuclear monocytes is well established.[92] Likewise, the correlation between therapeutic benefit and T cells reactive to gold(III) strongly suggests that the oxidation is not a fortuitios process. Yet the links between the chemistry and the mechanism of antiarthritic action are not yet established. Despite the lack of a widely accepted therapeutic mechanism, the bioinorganic chemistry of gold has been defined by research from a number of chemical and pharmacological labs. The transformations of gold complexes which occur in vivo have been delineated and metabolites identified and studied. Continuing investigation of the metabolites and their ability to affect biological processes will help to test the gold(III) and aurocyanide hypotheses.

For many inorganic medicinal chemists, on the other hand, the opportunity to develop new drugs targeted to cancer, AIDS, and malaria will be the most exciting challenge in the next decade.

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