

Advances in Chrysotherapy. Novel Gold(I) Compounds
and Insight into Metabolic Reactions

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Literature Seminar

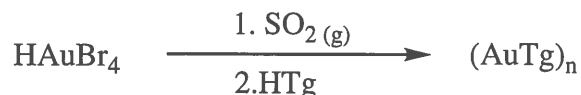
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The use of gold for medicinal purposes dates back to 2500 B.C., when it was used by Chinese and Arabic cultures as a "cure-all" drug. Modern chrysotherapy, or gold therapy, began in 1890 A.D. when Koch discovered that $\text{Au}(\text{CN})_2^-$ inhibits the growth of tuberculosis bacilli [1]. Since then several gold(I) compounds have proven to be effective treatments for rheumatoid arthritis. Rheumatoid arthritis (RA) is a disease of the immune system in which the white blood cells attack the connective joint tissue. Two main types of drugs are used to treat RA. Non-steroidal anti-inflammatory drugs (NSAIDS), such as aspirin or ibuprofen, relieve pain and decrease the swelling of inflamed joints. Remission inducing drugs (RIDS), such as the gold(I) compounds, actually slow the degeneration of the connective joint tissue [2].

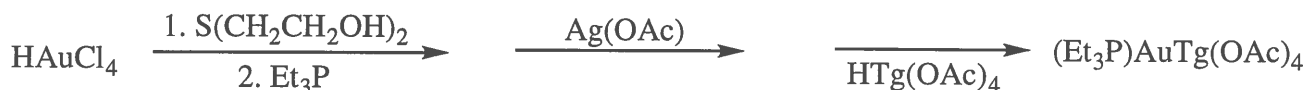
One of the first anti-rheumatic gold(I) drugs to be developed was Sanocrysin, $\text{Na}_3\text{Au}(\text{S}_2\text{O}_3)_2 \cdot 2\text{H}_2\text{O}$. The structure of Sanocrysin is typical of gold(I), which prefers a two-coordinate linear geometry [3]. There are currently three main anti-rheumatic gold(I) drugs prescribed for RA: Myochrisine, Solganol, and Auranofin. Myochrisine, Na_2AuTm where Tm=thiomalate, is formed by the following reaction [4].



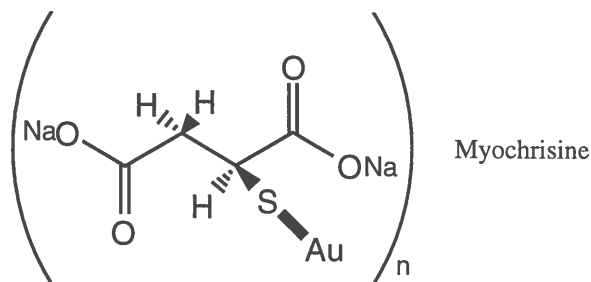
The reaction to produce Solganol (AuTg , Tg=thioglucose) is [5].

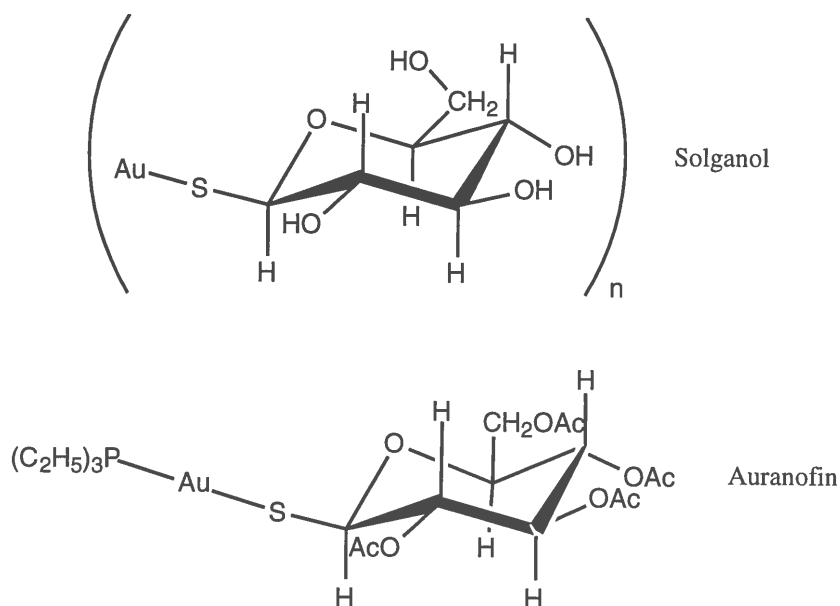


Myochrisine and Solganol are oligomeric and contain between seven to nine gold-thiolate units. Auranofin, $(\text{Et}_3\text{P})\text{AuTg}(\text{OAc})_4$, is monomeric and formed according to the following reaction [6].



The structures of these three compounds are shown below.





There are two methods of administering the gold(I) drugs: intramuscular injection which is the method of choice for Myochrisine and Solganol, and oral tablets for Auranofin. Injections are administered once a week and contain between 25-50 mg of drug; in contrast 6 mg oral tablets can be given daily. The initial distribution of the drugs in the body differs slightly depending on the method of administration: the intramuscularly injected drugs are more quickly taken-up into the blood and the organs. After 24 hours, however, both the injected and the orally administered drugs have approximately the same distribution throughout the body [6].

In whole blood there are numerous potential binding sites for the drugs. Gold(I) is a soft metal ion which binds strongly to donor ligands such as CN^- and RS^- [7]. In the blood, the drugs bind to serum albumin, a protein which is used to transport fatty acids from the tissue to the kidney. This protein is the principal source of sulfur in the blood, and contains one sulfhydryl group on cysteine-34 and seventeen disulfide bonds. Shaw and co-workers proposed that Myochrisine binds preferentially to the sulfhydryl group in albumin [8]. They synthesized a series of Na_2AuTm /Bovine Serum Albumin (BSA) complexes with different ratios of Na_2AuTm to BSA. [9]. By using radio-labeled ^{35}S , they determined that the thiomalate ligand is not displaced from the Au(I) center upon binding to BSA. Furthermore, the amount of bound drug never exceeded the amount of sulfhydryl groups which were available in the albumin; this result confirmed that Myochrisine binds exclusively to cysteine-34, and not to the disulfide bonds [9]. Reglinski and co-workers used lipoic acid, a naturally occurring disulfide which is used in cellular redox, as a model to study the binding of Na_2AuTm to disulfides. They determined that Myochrisine does add to the disulfide bond of lipoic acid, [10] but that the reaction occurs very slowly. Thus the reaction of gold(I) drugs with disulfide linkages in the body probably does not occur to any significant extent. Auranofin also binds to BSA and does so with retention of the Au-P bond [11].

Zhang and co-workers recently studied the binding of gold(I) based anti-rheumatic agents with red blood cells (RBCs). The main source of sulfhydryl groups in RBCs is hemoglobin, which is approximately the same molecular weight as serum albumin. Interestingly, size-exclusion chromatography showed that most of the gold(I) did not bind to hemoglobin, but that it was bound instead to a much higher molecular weight protein, ca 330,000 Da, a protein of intermediate molecular weight, ca 85,000 Da, and to some lower molecular

weight components [12]. Reverse phase chromatography established that $\text{Au}(\text{CN})_2^-$, Na_2AuTm , and several gold-glutathione complexes were also present in the RBCs [12]. This result is consistent with the established affinities of various thiols for gold(I): albumin>Tg>glutathione, cysteine> Tm>hemoglobin. Zhang et al. have not yet determined the identities of the 330,000 Da protein or the 85,000 Da protein which were identified chromatographically. They also discovered that Auranofin, when compared to Myochrisine, has a greater affinity for red blood cell lysate, while Myochrisine remains outside the red blood cell membrane [12].

When Auranofin passes through the walls of the intestine, the Au-P and Au-S bonds remain intact, but the acetyl groups on the thioglucose ligand are hydrolyzed [13]. Elder and Eidsness used XANES, X-ray absorption near edge spectroscopy, to establish that the passage of Auranofin and Sanocrysin through the kidney affords identical products. The XANES spectra of these two compounds did not show an absorption at 11.92 keV characteristic of Au(III) nor did they exhibit the two broad peaks for Au(0). The XANES spectra of Sanocrysin and the Sanocrysin-metabolite were identical, which indicates that the drug remains intact as it passes through the walls of the kidney. In contrast, the XANES spectrum of Auranofin shows that the Au-P bond is cleaved when Auranofin passes through the walls of the kidney [11].

Various studies have shown that smoking affects the uptake of gold, and this effect has been attributed to the fact that tobacco smoke contains HCN. The cyanide ion binds strongly to gold(I), even more strongly than cysteine or other thiols [2]. As a result, smokers undergoing chrysotherapy have higher levels of gold in their blood and are more likely to exhibit toxic reactions than non-smokers. Lewis and Shaw used resonance Raman spectroscopy to show that CN^- displaces thiolate ligands from gold-containing drugs. Addition of one equivalent of KCN to gold(I) thioglucose, $(\text{AuGt}_2)^-$, or gold(I) thiomalate, (Na_2AuTm) , resulted in the displacement of one of the thiolate ligands, and a second equivalent of KCN displaced the other thiolate ligand [14].

In an attempt to lower the toxicity of gold-containing antirheumatic drugs and to increase the uptake efficiencies, chemists have synthesized numerous other gold compounds, many of which are analogues of the successful anti-rheumatic drug Auranofin. So far none has proven more effective towards RA than those drugs which are currently administered. Many of these other compounds are also being tested for activity towards various tumors and cancers like P388 leukemia [15-18].

Chrysotherapy has proven effective towards RA despite a lack of understanding of the mode of action of the drugs [19]. Several theories have been advanced to explain why these drugs are effective [20]. One mechanism suggests that the gold(I) binds to the thiolates of hydrolytic enzymes of the lysosomes found in white blood cells, inactivating the lysosomes. Another mechanism proposes that gold(I) prevents the formation of antibodies in connective tissues of the joints. A third proposed mechanism is that gold(I) deactivates singlet oxygen which protects the lipids and proteins in the joints from oxidation. Finally, the dicyano-gold(I) ion may inhibit the functioning of white blood cells only in areas of inflammation, thus preventing degradation of the connective joint tissue. Determining the exact mechanism responsible for the activity of gold(I) drugs remains an important goal in this area.

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