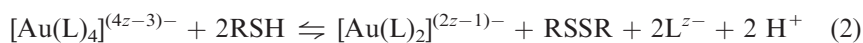
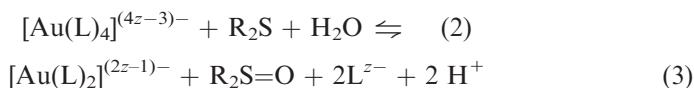


to contribute to bonding and only the 6s and 6p orbitals need be considered so that linear 2-coordination, trigonal 3-coordination or tetrahedral 4-coordination might be expected. In fact, because gold is such a heavy atom, its electrons are subject to additional effects predicted by the theory of relativity. These lead to a contraction of the Au(+1) ion so that the radius of Au in Au(+1) compounds is less than that of Ag in Ag(+1) compounds despite Ag having fewer electron shells. There is also an increased difference in energy between the 6s and 6p subshells in Au compared to expectations from a non-relativistic model. This leads to less involvement of the 6p subshell in bonding so favouring linear 2-coordination for Au(+1) over higher coordination numbers.

In water the Au(+1) ion is a strong reducing agent unless incorporated in a complex with an appropriate ligand such as CN^- , thiolate, or phosphine. Since Au(+1) is a large polarisable, 'soft' (Section 2.7.2), metal ion it tends to form its most stable complexes with 'soft' donor atoms such as P or S. In addition Au(+1) has a strong affinity for cyanide because of its negative charge and π -acceptor properties. Both CN^- and thiolate are important ligands in the medicinal chemistry of Au(+1). Disproportionation of Au(+1) to Au(0) (elemental gold) and Au(+3) is possible, particularly where a suitable ligand for stabilising Au(+1) is absent. This provides a pathway for converting Au(+1) to elemental gold even where direct reduction of Au(+1) to Au(0) should not occur. The Au(+3) ion is isoelectronic with Pt(+2) and forms many similar complexes but is more prone to reduction. The compound potassium tetrachloroaurate, $\text{K}[\text{AuCl}_4]$, dissolves in water and undergoes hydrolysis to form $[\text{AuCl}_3(\text{OH})]^-$ in a similar manner to Pt(+2) chloro complexes. However, unlike $[\text{PtCl}_4]^{2-}$, $[\text{AuCl}_4]^-$ can also oxidise water to produce dioxygen. Thiolates readily reduce Au(+3) to Au(+1) forming disulfides (Equation (2)) and, depending on the nature of the ligands present, disulfides or thioethers may also reduce Au(+3) (Equation (3), for example).



(L^{z-} represents a unidentate ligand and R a hydrocarbyl group)



4.4.3 Gold Compounds for the Treatment of Rheumatoid Arthritis

Various gold compounds have been used in the treatment of rheumatoid arthritis. All are Au(+1) complexes containing thiolate ligands, although the exact structures of all these compounds are not known. Sanochrysin, $\text{Na}_3[\text{Au}(\text{S}-\text{SO}_3)_2]$ **119**, is a purely inorganic compound and contains the bithiosulfato-gold(+1) anion in which Au^+ is bound to the terminal S atoms of two thiosulfate ions. Other clinically important gold drugs are the thiomalate complex Myochrysin, **120**, the thioglucose complex Solganol, **121**, and the thiopropane sulfonate complex Allochrysin[®], **122**, all of which are oligomeric

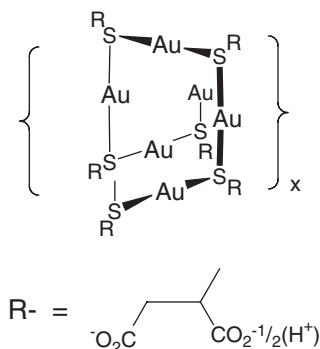
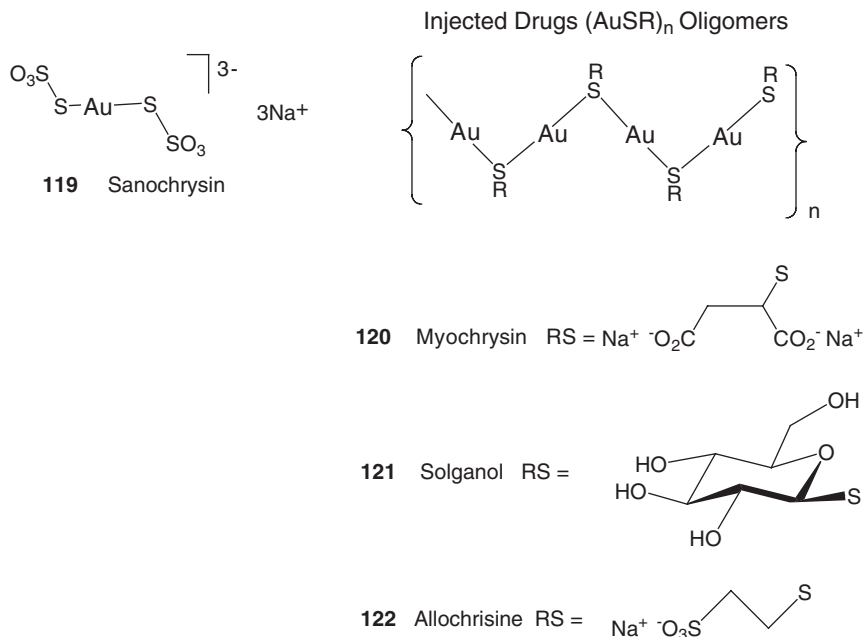
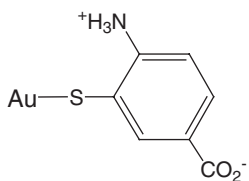
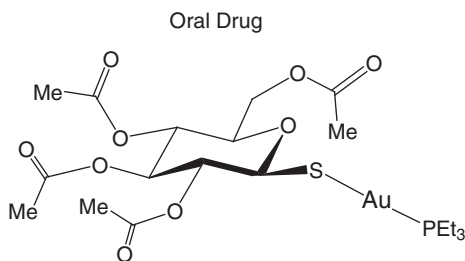


Figure 17 A part of one of the two interpenetrating chains in the solid state structure of $\text{Na}_{2n}\text{Cs}_n[\text{Au}_2\{\text{SCH}(\text{CO}_2^-)\text{CH}_2\text{CO}_2^-\}\{\text{SCH}(\text{CO}_2^-)\text{CH}_2\text{CO}_2\text{H}\}]_n$

and administered by intramuscular injection. The complexes form chains of notional formula $\{\text{Au}(\text{SR})\}_n$ containing alternating Au^+ ions and RS^- ligands with the sulfur atoms acting as bridges between the Au^+ centres. Cyclic and open chain structures are, in principle, possible for these oligomers and the exact compositions of Myochrysin, and Solganol are more complicated than the notional formula $\{\text{Au}(\text{SR})\}_n$ would suggest, the Au:RS ratios not being exactly 1:1. The solid state structure of $\text{Na}_{2n}\text{Cs}_n[\text{Au}_2\{\text{SCH}(\text{CO}_2^-)\text{CH}_2\text{CO}_2^-\}\{\text{SCH}(\text{CO}_2^-)\text{CH}_2\text{CO}_2\text{H}\}]_n$, a Myochrysin analogue, has been determined and this contains interlocking spiral like chains with near linear S-Au-S angles of 170° and 179° and Au-S-Au angles of 99° (Figure 17). This structural arrangement is



**123 Krysolgan****124 Auranofin**

typical of Au(+1) thiolates and a number of model compounds similarly have near linear S-Au-S cores. Of course, once the compound is dissolved the structures of the complexes present in solution may be quite unlike those in the solid state, although oligomeric species are still thought to be present. Another example of a gold compound administered by injection is Krysolgan, **123**, which was initially used to treat tuberculosis early in the 20th century and is of historic interest. The most recently introduced drug Auranofin (also known as Ridaura), **124**, may be taken orally and has a monomeric structure which contains an essentially linear (174°) P-Au-S core in the solid state.

It turns out that the gold compounds should really be thought of as pro-drugs in that they do not represent biologically active species but rather they provide a source of biologically available gold. Thus the primary function of the ligands used in the gold drugs is to provide a soluble gold complex suitable for administration to the patient and sufficiently stable for transportation and storage prior to clinical use. Improved aqueous solubility is conferred by the carboxylate groups in Myochrysin, the hydroxyl groups in Solganol and the sulfonate group in Allochrysin. The triethyl phosphine ligand in the oral drug Auranofin is lipophilic and confers membrane solubility on the complex. After administration to the patient the ligands are soon lost from the complex *in vivo* and the Au⁺ ion transferred to other binding agents. The affinity of Au(+1) for thiolate ligands suggests that and free thiol groups associated with proteins or GSH in the blood would be the first to compete with the thiolate ligands in the pro-drug for the Au⁺ ions. The serum albumin is found to carry some 80–95% of gold circulating in the blood and, in the case of Auranofin added to whole blood, the transfer of the Au⁺ to protein occurs within about 20 min.

In the structure of the principle form of albumin, mercaptoalbumin (albS⁻), a cysteine residue is present at position 34 (Cys34) which carries an acidic thiol group. This is normally deprotonated at physiological pH and offers a potential binding site for Au⁺. However, kinetic and spectroscopic studies of the interaction between mercaptoalbumin and Auranofin indicate that a rearrangement of the albumin structure to an active form, alb*S⁻, is required before the Au⁺ ion is bound (Figure 18, Equation (4)). This involves the relocation of the Cys34 thiolate group within the protein to the protein surface where it is accessible to Au⁺ species in solution.



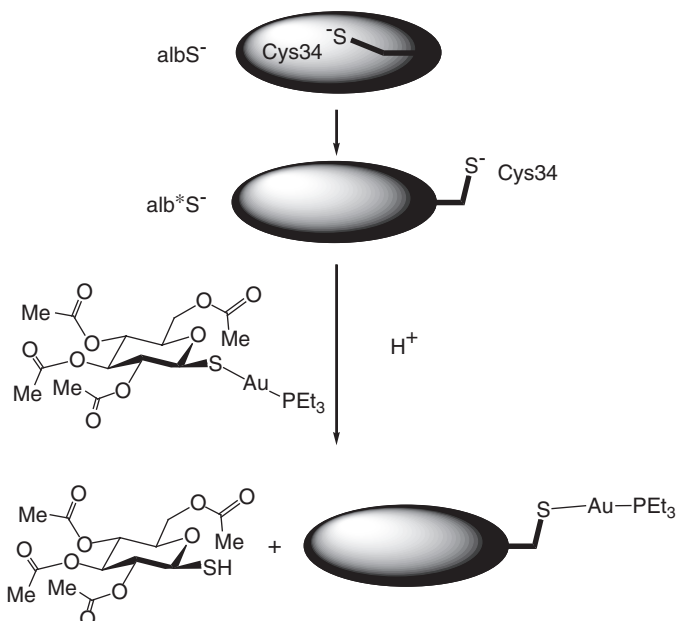
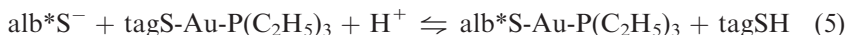


Figure 18 A schematic view of the binding of Au^+ to an externalised thiolate group on albumin

The exposed thiolate group of the activated protein is then able to compete with the tetra-acetoglucothiolate (tagS^-) for the Au^+ (Equation (5))



The complex of the activated protein then relaxes to its final form (Equation (6)).



In patients undergoing chrysotherapy with Auranofin the gold concentrations *in vivo* may be 5–15 μM compared to *ca.* 400 μM for mercaptoalbumin so that mercaptoalbumin can compete effectively with tagS^- for the Au^+ . The reactions are sufficiently rapid that the process appears to be first order with a rate constant of 2 s^{-1} . Similar reactions are thought to occur with Myochrysin in that a thiolate group of mercaptoalbumin binds to an Au^+ centre in a gold thiomalate oligomer. Redistribution of the remaining Au^+ centres to other mercaptoalbumin molecules follows ultimately transferring all the Au^+ from the oligomeric pro-drug to protein molecules.

The mechanism by which the Au^+ subsequently produces its anti-inflammatory and antiarthritic effects remains uncertain and various explanations have been proposed. These lie beyond the scope of this discussion but three aspects of gold chemistry deserving mention can be found among the proposals. One involves the binding of Au^+ to thiolate groups present naturally *in vivo*, a second to the formation of $\text{Au}(+1)$ cyanide complexes and the third to the formation of $\text{Au}(+3)$ complexes.

4.4.3.1 Gold Thiolate Complexes

The importance of Au^+ thiolate interactions is illustrated by two proteins known as Jun and Fos. These can combine to form the Jun–Fos conjugate and the homodimer Jun–Jun both of which can bind to DNA and stimulate the expression of genes which promote an inflammatory response. Jun and Fos both contain cysteine residues which appear at the DNA binding sites of Jun–Fos or Jun–Jun. Both gold(+1) thioglucose and gold(+1)thiomalate have been shown to react with Jun–Fos and Jun–Jun inhibiting their ability to bind to DNA. This effect can be reversed by adding excess thiolate such as GSH which presumably competes with the protein for the Au^+ . Furthermore, replacement of the cysteines at the DNA binding sites of Jun–Fos and Jun–Jun with serine affords proteins which bind to DNA more strongly than the native proteins. However, the binding of these mutant proteins to DNA is no longer inhibited by gold(+1)thiomalate. This suggests that Au^+ binding to cysteine thiolate groups at the DNA binding sites of Jun–Fos or Jun–Jun inhibits their binding and so suppresses their ability to trigger inflammatory effects.

4.4.3.2 Gold Cyanide Complexes

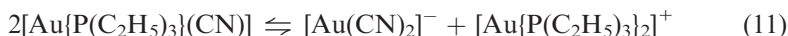
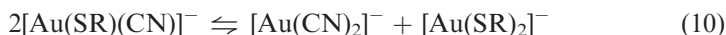
Because of its high toxicity, cyanide is perhaps a surprising ligand to find bound to gold *in vivo*. However, gold cyanide complexes have been found in the urine of patients treated by chrysotherapy and appear to be formed at sites of inflammation. There is evidence that cyanide can be produced naturally *in vivo* from glycine and from thiocyanate present in extracellular fluids. Smoking offers a less natural source of CN^- and inhaled tobacco smoke may contain up to *ca.* 1700 ppm HCN which can enter the bloodstream *via* the lungs. Both Au(+1) and Au(+3) form complexes with cyanide and the linear Au^+ complex, $[\text{Au}(\text{CN})_2]^-$ and the square planar Au^{3+} complex $[\text{Au}(\text{CN})_4]^-$ are well known. The binding of CN^- to Au^+ is particularly strong and overall stability constant values of $\log \beta_2 = 36.6$ and 39 have been reported for the formation of $[\text{Au}(\text{CN})_2]^-$ from Au^+ and CN^- . In a biological context CN^- can compete with the ligands in the gold pro-drug for the Au^+ centre but an equilibrium will arise between the CN^- and thiolate groups present. This leads to the formation of different complexes depending on the relative concentrations of the species present. The apparent equilibrium constant for the reaction of gold(+1) thiomalate, $[\text{Au}(\text{Stm})]_n$, with HCN according to Equation (7) is reported to be 6×10^2 at pH 7.4.



In the case of Auranofin the thiolate ligand is replaced by CN^- in preference to the phosphine ligand but if CN^- is present in excess both ligands can be substituted to form $[\text{Au}(\text{CN})_2]^-$ as shown in Equations (8) and (9).



Mixed ligand Au(+1) complexes containing a CN^- ligand as well as a thiolate (RS^-) or phosphine [*e.g.* $\text{P}(\text{C}_2\text{H}_5)_3$] are also known and undergo ligand redistribution reactions as shown in Equations (10) and (11) leading to an equilibrium mixture of the three complexes in each case.



The formation of $[\text{Au}(\text{CN})_2]^-$ appears to be important in the metabolism of gold drugs and may contribute to the cellular uptake of gold. Notably smoking has been found to increase the uptake of gold drug metabolites in red blood cells. This is attributed to the higher cyanide concentrations in the blood of smokers and red cells exposed to $4.5 \mu\text{M}$ $[\text{Au}(\text{CN})_2]^-$ can absorb up to 95% of the gold present. Albumin also binds $[\text{Au}(\text{CN})_2]^-$ and *in vitro* experiments suggest that as many as 10 ions may bind to an albumin molecule. Since albumin has multiple binding sites for anions such as Cl^- , Br^- and SCN^- this is not surprising, although $[\text{Au}(\text{CN})_2]^-$ is a much larger ion. Thus albumin might transport gold, either through direct binding of Au^+ to thiolate residues, particularly at Cys34, or through the binding of $[\text{Au}(\text{CN})_2]^-$.

The ease of cellular uptake of gold is dependent on the form of gold present in the extracellular medium. Oligomeric or mononuclear gold thiolates, $[\text{Au}(\text{SR})_n]$ or $[\text{Au}(\text{SR})_2]^-$, are not readily taken up by cells but Auranofin and $[\text{Au}(\text{CN})_2]^-$ are taken up. It is thought that a shuttle operates in which Au^+ from extracellular gold complexes is exchanged onto thiolate groups associated with membrane transport proteins at the cell surface. These proteins transfer the Au^+ across the membrane to the inner surface where the Au^+ exchanges onto thiol groups associated with molecules within the cytoplasm. In the case of Auranofin the thioglucose ligand is lost before the Au^+ enters the cell but the $\text{P}(\text{C}_2\text{H}_5)_3$ ligand can accompany the Au^+ into the cell. Once in the cell the $\{\text{Au}\{\text{P}(\text{C}_2\text{H}_5)_3\}\}^+$ moiety may return to the extracellular medium by a similar process to its entry, or the $\text{P}(\text{C}_2\text{H}_5)_3$ ligand may be displaced and oxidised to $\text{O}=\text{P}(\text{C}_2\text{H}_5)_3$. The Au^+ then remains bound to thiolate groups present inside the cell but may undergo exchange with thiolate groups of the membrane transport protein once again and be transported back to the extracellular medium. The transport of gold across the cell membrane is not an active-transport process so that the concentrations of gold inside the cell and in the extra-cellular fluid ultimately reflect the thermodynamic equilibrium for complexation at intra- and extra-cellular gold binding sites.

4.4.3.3 Gold(+3) Complexes

It might be expected that gold(+3) would be unimportant in a medicinal context since many compounds present *in vivo* have the capacity to reduce Au(+3) to Au(+1) and Au(+1) is the form normally observed in biological media. However,

it has been found that Au(+3) compounds can produce a popliteal lymph node assay response in animals treated with gold thiomalate for several weeks. Similar effects are not produced by gold thiomalate itself. This suggests that an Au(+3) metabolite is involved in the immunological response. It has also been found that human T-cells from chrysotherapy patients are sensitive to Au(+3) but not Au(+1). A mechanism by which Au(+3) might be produced *in vivo* has been proposed involving hypochlorite, OCl^- , generated by the enzyme myeloperoxidase during oxidative bursts. It has been shown that OCl^- can oxidise gold thioglucose and Auranofin to $[\text{AuCl}_4]^-$ or $[\text{Au}(\text{CN})_2]^-$ to $[\text{Au}(\text{CN})_2\text{X}_2]^-$ ($\text{X}=\text{Cl}$ or OH) depending on the pH of the medium. Another relevant observation is that changes in tissue concentrations of thiols, proteins and metals during chrysotherapy are much larger in responding patients than the tissue concentration of gold. This implies that a redox cycle is operating in which Au(+1) is oxidised as a result of enzyme activity then reduced by thiols or other reducing species in the tissue so that repeated cycles of gold oxidation and reduction consume reductants in superstoichiometric amounts compared to gold.

The exact role of Au(+3) produced in this way is uncertain but Au^{3+} has been shown to form peptide complexes such as **125** and **126**. This implies that Au^{3+} can bind to proteins and any such binding will change the structure and possibly the *in vivo* behaviour of the protein. It is also possible that Au(+3) could oxidise proteins, for example thiol groups might be oxidised to form disulfide links or the thioether group of methionine might be oxidised to sulfoxide, either process inducing a structural change. If a gold induced change in the structure of a protein prevents its being recognised as foreign by the immune system, this could result in immunosuppressive or anti-inflammatory effects. Binding of Au(+1) to proteins might also cause structural changes with similar consequences. In model systems, devised to test the ability of gold compounds to modify proteins or protein fragments which induce an immune response, a variety of other metal ions were found to exert an immunosuppressive effect. The utility of the gold drugs may arise from their having more suitable chemistry *in vivo* for allowing them to be transported to their site of action rather than that they have unique properties for suppressing the immune response.

