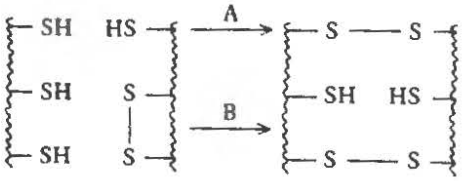
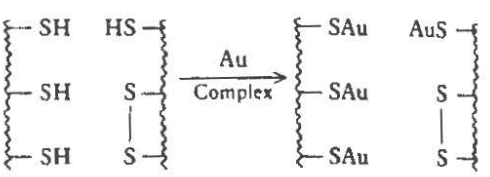
Anti-arthritic Gold Drugs: A Bioinorganic Approach

Mary Mills March 28, 1985

Chrysotherapy, the use of gold complexes in the treatment of rheumatoid arthritis (R.A.), originated in the work of the French physician, Jacques Forestier, who reported on the anti-inflammatory effect of gold thiopropanol sodium sulfonate in 1929. Since that time additional gold-containing compounds have been found effective in treating R.A., but as yet no mechanism of action has been firmly established. Proposed modes of action [1] for the gold drugs rely on the great affinity of gold for sulfur ligands and on its preference for a two-coordinate linear geometry. As one possibility, it is suggested that gold binds to reduced thiol functionalities (cysteine residues) in the affected joint and thereby protects certain critical thiol groups from oxidation via inter- or intramolecular disulfide bond formation [2].

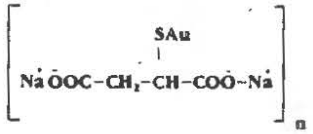


Protein thiol oxidation and disulfide interchange

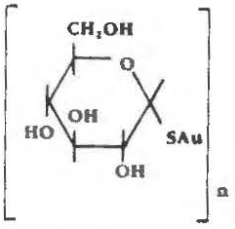


Thiol blockage by gold complex

The two most commonly used gold drugs in the U. S. are sodium gold(I) thiomalate (1) and gold(I) thioglucose (2) shown below.



1



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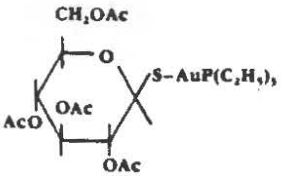

3

Another gold(I) complex, (2,3,4,6-tetra-O-acetyl-1-thio-β-D-glucopyranosato-S)(triethylphosphine)gold(I) (generic name auranofin, 3), shows potent anti-arthritic activity and has several advantages compared to the gold(I) thiolates. One of these is the ability of auranofin to be administered orally rather than through intra-muscular injection [3].

The electronic configuration of gold(I) is d^{10}, making traditional spectroscopic techniques such as electronic paramagnetic resonance and ultraviolet-visible spectroscopy uninformative. However, improvements in nuclear magnetic resonance (nmr) [4] and ^{197}Au Mössbauer spectroscopy [5] have made these techniques very useful for *in vitro* and *in vivo* studies. More recently, both Extended X-Ray Absorption Fine Structure (EXAFS) and X-Ray Absorption Near Edge Structure Spectroscopy (XANES), have also been used with considerable success [6]. The use of these techniques to probe gold-containing complexes in biological systems requires thorough initial *in vitro* studies in which relevant model complexes are characterized. These studies reveal trends and spectral patterns which are enormously useful once *in vivo* investigations have begun.

Model studies based on ^{197}Au Mössbauer Spectroscopy have utilized the well-established linear relationship between isomer shift and quadrupole splitting to determine not only gold oxidation state and coordination number, but the nature of the coordinating ligands as well [7]. Similarly, x-ray absorption spectroscopy yields information about the number and kinds of ligands around the gold atom as well as its oxidation state. The results obtained are quite accurate due to the presence of unusual spectral features in both the edge and EXAFS regions [8].

With model studies serving as a foundation, *in vivo* investigations may be undertaken. Most of these studies have concentrated on drug interactions with a few known biological target molecules, among them, serum albumin (SA), glutathione (GSH), and metallothionein (MT). These very different molecules are attractive binding sites for gold because each has at least one reduced thiol group, with which the gold drug is thought to interact. Interaction of gold(I) drugs with GSH and SA seems to occur via ligand exchange reactions, thus allowing the gold atom to remain two coordinate [9]. XAS and nmr studies on auranofin reveal that the complex binds to the protein thiol group with concomitant loss of its thioacetylglucose ligand [10]. This result is expected, considering the excellent trans-labelizing nature of phosphines. The behavior seen for the gold(I) thiol complexes (1 and 2) also seems to involve ligand exchange reactions [11].

Further interesting results come from isolation and examination of cell bodies called lysosomes following administration of 1 or 3. These lysosomes, termed aurosomes, accumulate very high concentrations of gold within 18 hours after administration of the gold drug. Most intriguing is the fact that by XAS the gold environments in aurosomes treated with 1 and 3 are *identical*, indicating ligation to two sulfur atoms [8]. This result suggests that the gold-phosphine bond has been broken, raising new questions about the active forms of these drugs.

These limited bioinorganic experiments still leave unanswered some of the important questions concerning the medically active form of gold drugs and the importance of the gold atom in drug activity. Future work in this area will benefit greatly from improvements in the spectroscopic probes applicable to the study of gold-containing systems.

References

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