Progress Towards More Effective Gold-Based Pharmaceuticals

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Gold compounds were introduced in medicine when alchemists such as Paracelsus used them as a cure-all for everything from paralysis and fevers to syphilis and alcoholism.\(^1\)\(^-\)\(^3\) In 1890, Robert Koch was the first to note the bacteriostatic activity of gold when he observed K[Au(CN)\(_2\)] inhibiting the growth of tuberculosis bacilli.\(^2\) Today, gold(I) thiolate complexes are used as treatment for rheumatoid arthritis. Myochrysine\(^6\) and Solganol\(^8\) are injectable gold-containing pharmaceuticals used for this purpose.\(^3\) Riduara\(^5\), or Auranofin, is a gold phosphine anti-rheumatic agent taken orally. Auranofin is safer than the injectables, but less effective.\(^2,4,a,b\) In addition to its anti-rheumatic properties, Auranofin also displays anti-tumor activity.\(^5,a,b\) Gold complexes are currently being studied as potential therapy for HIV, malaria, asthma, and a host of other maladies in addition to their anti-tumor and anti-rheumatic properties.\(^3\)

The most common oxidation states of gold are +I and +III.\(^6\) The inherent problem of side effects is commonly attributed to gold(III) metabolites generated under the oxidative conditions in inflamed tissue.\(^7\) It is postulated that the active species of the rheumatoid arthritis drugs and anti-tumor drugs are also metabolites of the administered substances, thus explaining the variable clinical responses to gold therapy in terms of side effects and efficacy.\(^3\)

Investigation of the chemistry and anti-tumor properties of gold(III) complexes is one area of active research toward the development of gold-based drugs. Since gold(III) and platinum(II) are isoelectronic, it is plausible that a gold analogue of cisplatin could be developed for chemotherapy. Studies of four coordinate square-planar complexes of gold(III)(damp), where damp= bidentate 2-((dimethylamino)methyl)phenyl, display anti-tumor activity with substituents of acetato or malonato.\(^8,a,b\) Anti-tumor activity was also evident in similar complexes containing salicylate and thiosalicylate moieties.\(^9\) It is believed that gold binds to DNA in a fashion analogous to cisplatin, although the varied response from different tumor types suggests a different mechanism of cytotoxicity.\(^8,a\)

Since the mechanism of gold-drug action and toxicity remains unknown, studies of gold(III) reactions with amino acids, peptides, and proteins are a priority in gold-drug
development. Earlier work in this area showed that cystine and methionine are oxidized by gold(III) (see below). It was recently determined that [AuCl₄] deaminates glycine, alanine, and possibly any N-terminal amino acid. Studies of gold(III) reactions with proteins will provide a more accurate model of gold-drug action by factoring in the effects of secondary and tertiary structure on gold binding sites.

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\text{[AuCl₄]} + \text{H₂N-} - \text{COOH} \rightarrow \text{[AuCl₄(NH₂)]} + \text{H-} - \text{COOH}
\]

The use of a toxic enantiomer of a drug can lead to ineffectiveness, or worse, undesirable side effects. Thalidomide, a drug with sedative qualities, was used to treat nausea in pregnant women in the late 1950s. Unfortunately, (S)-thalidomide produced horrible birth defects. In light of this possibility, using functionalized P-chiral phosphine ligands may alter the effectiveness or toxicity of phosphine containing gold drugs such as Auranofin. Using recent techniques involving chiral organopalladium catalysts, optically pure P-chiral phosphines may be obtained. Although it is not yet certain whether chiral ligands will affect the biological activity of gold complexes, the possibility appears promising.

The development of more effective gold-based pharmaceuticals remains an important goal as increasing numbers of ailments, viral, autoimmune, and cancerous, are becoming resistant to existing treatments. With three areas of active research in the inorganic community, chemists are an integral part of improved gold-based drug design. It is probable that advances in the field of gold chemistry will contribute to making the approaching millennium a healthier one.

References


development.\textsuperscript{10,11} Earlier work in this area showed that cystine and methionine are oxidized by gold(III) (see below).\textsuperscript{12,13} It was recently determined that [AuCl₄]⁻ deaminates glycine, alanine, and possibly any N-terminal amino acid.\textsuperscript{14} Studies of gold(III) reactions with proteins will provide a more accurate model of gold-drug action by factoring in the effects of secondary and tertiary structure on gold binding sites.\textsuperscript{11}

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\text{[AuCl}_4^- + \text{H}_2\text{N}-\text{COOH} \rightarrow \text{[AuCl}_4((\text{NH}_2)) + \text{H}-\text{C}-\text{COOH}}
\]

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References


Copper Chaperones: A Bioinorganic Approach to Understanding Copper Trafficking

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Metal ions are required in biological systems, where they perform a variety of specific functions associated with life processes.\textsuperscript{1} Metal ions involved in biological redox catalysis can be detrimental to cells, however, by catalyzing unwanted reactions and modifying proteins and nucleic acids via the formation of hydroxyl radicals.\textsuperscript{2,3} Organisms must often balance the level of these metal ions between low levels that would cause deficiency in the cells and high levels that could be toxic; both cases can lead to cellular dysfunctions.\textsuperscript{4} Living systems have complex mechanisms for regulation of cellular levels of metal ions (homeostasis) and intracellular metal ion uptake, transport, and placement into enzymes (trafficking).\textsuperscript{5} Recently, a new class of proteins, copper chaperones, has been implicated in copper homeostasis and trafficking.

Copper chaperones are a class of proteins found in plant, bacterial, yeast, and animal cells. These proteins are responsible both for copper trafficking and for preventing copper ions in transit from damaging cellular components.\textsuperscript{5,6} The majority of the copper chaperones, known today contain one or more copies of a metal binding motif consisting of a conserved amino acid sequence.\textsuperscript{5-10} Most chaperones, despite their conserved sequences and similar secondary and tertiary structures, are specific for their target protein. This specificity is based on slight structural differences between chaperones.\textsuperscript{5,11} Several genetic disorders, including Menkes disease and Wilson disease, involve disruption of copper transport via mutations in the structure of copper chaperone-like proteins.\textsuperscript{4,12,13}

Recent studies of model compounds and native structures of several copper chaperone proteins have provided new insight into the mechanisms of copper binding in cellular copper chaperones.\textsuperscript{6,7,14,15} No crystal structures of metallochaperones were determined before 1999, so model compounds were used to study the metal binding properties of these proteins. Model compounds of Cu(I) with two or three sulfur ligands and those with 4 nitrogen ligands have been compared spectroscopically with Cu(I) bound to Atx1, a cytoplasmic copper chaperone. X-ray absorption near edge structure (XANES) data\textsuperscript{9} (Figure 1) demonstrate that the model compound giving the closest spectrum to that of the native enzyme has copper bound in a trigonal planar fashion to three sulfur atoms. A more recent structural study, however, disputes the three coordinate binding of copper in chaperones and chaperone-like proteins.\textsuperscript{16}

Mercury NMR has been used as a copper analogue to determine the coordination environments in several copper proteins.\textsuperscript{17,18} The mercury derivative of Atx1\textsuperscript{16} (Figure 2) was used to determine the crystal structure. In this structure, the first published crystal structure of a metallochaperone, the mercury is bound by only two sulfur ligands. The copper form of Atx1 was successfully crystallized, but the metal binding loop was consistently disordered, therefore the exact coordination of bound copper in Atx1 remains unresolved.\textsuperscript{6}