4th International Conference on Gold and Silver in Medicine

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The 4th International Conference on Gold and Silver in Medicine was held at the University of Wisconsin, Milwaukee, May 31 - June 1 1998, in conjunction with the 31st Great Lakes Regional American Chemical Society Meeting. The highlights are summarized here.

The meeting was organized and hosted by Professor C Frank Shaw III of the Chemistry Department at UWM and was sponsored by the Gold and Silver Institutes, both of Washington, DC. This meeting brought together scientists from a diversity of disciplines including synthetic and structural chemistry, tumour biology, microbiology and immunology. All of the participants shared a common interest and enthusiasm, *ie* the medical uses of gold and silver.

The interdisciplinary and international content of the meeting was immediately in evidence with the opening talk given by Sue Berners-Price (Griffith University, Australia) on the selective antitumour activity of gold and silver complexes of bidentate pyridylphosphine ($R_2P(CH_2)_2PR_2$ where $R = 2$ -pyridyl, 3-pyridyl, and 4-pyridyl). These compounds are hydrophobic cations and were investigated following the observation that the uptake of hydrophobic cations is greater in tumours than normal tissue. The gold(I) 4-pyridyl derivative was found to be active against a cisplatin-resistant ovarian tumour cell line, and to have *in vivo* activity against the colon 38 tumour. Parish (UMIST, UK) also addressed the antitumour activity of gold complexes and discussed the rationale for the use of gold(III) complexes as potential antitumour drugs. In a biological environment Au(III) is readily reduced to Au(I). In order to counteract this, a group of stable Au(III) dimethylbenzylamine derivatives was synthesized, and their biological activity against microorganisms and mammalian cell lines investigated. A screening strategy for metal-based anticancer drugs was described by Fricker (AnorMED, Canada) utilizing an *in vitro* panel

of human tumour cell lines which could also be grown as xenografted solid tumours in immune-deprived mice. In collaboration with Parish, this methodology was used to demonstrate the antitumour activity of the Au(III) dimethylbenzylamine complexes. Furthermore, mechanistic studies were able to show that these compounds possess a mechanism of action different from that of the Pt(II) antitumour drugs such as cisplatin. Boron neutron capture therapy is an experimental radiotherapy technique for treating brain tumours. Laguna (Universidad de Zaragoza, Spain) described the synthesis of ortho-carborane (1,2-dicarbo-closo-dodecaborane) derivatives of gold and silver with high coordination numbers. The ability to incorporate high concentrations of boron atoms into the molecule makes these derivatives suitable candidates for boron neutron capture therapy.

Chrysotherapy, utilizing Au(I) thiolates, is used by physicians for the treatment of rheumatoid arthritis. This is an autoimmune disease, and a number of speakers discussed the interaction of gold compounds with the immune system. One of the most interesting recent discoveries on the mechanism of action of these drugs is their apparent ability to inhibit transcription of genes whose products are key components of the immune response. Dicyanogold, a major metabolite of the Au(I) thiolates, was shown to inhibit transcription of the cytokines Interleukin-2 and Interleukin-1 β . Tepperman (Cincinnati, USA) postulated that the molecular target was the transcription factor AP-1. An alternative mechanism that has been proposed for the action the antiarthritic gold drugs is to control cell damaging oxidants. The influence of ligand type and coordination geometry upon the electronic structure of

gold(I) complexes and their potential ability to remove potent oxidants such as reactive oxygen species from cells was investigated by Fackler (Texas, USA). The importance of $\text{Au}(\text{CN})_2^-$ was further elaborated by Elder (Cincinnati, USA). This metabolite has been shown to be an inhibitor of the reverse transcriptase of HIV. The cellular targets for HIV are T lymphocytes, and monocytes. It was shown that dicyanogold could be taken up into the cytoplasm of the Jurkat T cell line, bound to a protein of molecular weight 20kD. Gold was also found in the cell nucleus, the intracellular target for HIV. Some of the side effects of the anti-arthritic gold drugs have been attributed to the oxidation of Au(I) to Au(III). Best (London, UK) discussed this hypothesis and demonstrated the interaction of $[\text{Au}(\text{dien})\text{Cl}]\text{Cl}_2$ with model tripeptides, Gly-Gly-gGy, Gly-Gly-His, and Val-Ile-His-Asn. It was postulated that the formation of Au-His chelates within peptides and proteins might be responsible for the hypersensitivity reaction to Au(III). Shaw (Wisconsin, USA) also described the immunological response to gold-peptide complexes in the poster session. In mice, Au(I) thiomalate inhibits T cell recognition of a bovine insulin peptide, InsulinA 1-14. This peptide was synthesized and characterized by 2D ^1H -NMR, and the structure modelled using molecular dynamics computations.

A number of speakers addressed the structural aspects, and reactivity of gold complexes. By using electrospray mass spectrometry Howard-Locke (McMaster University, Canada) was able to show that Au(I) sodium thiomalate exists as a cyclic tetramer with the thiol ligands bridging pairs of gold atoms. The gold(I) thiolate drugs can undergo ligand exchange with naturally occurring thiols. The reactivity of gold compounds with a variety of thiols was

addressed by several speakers. The interaction of Au(I) with disulfides such as cystine was postulated to be a potentially important biochemical reaction for gold(I). Alice Bruce (Maine, USA) presented studies on the kinetics and mechanism of the substitution reactions of dinuclear gold(I) phosphine thiolate complexes such as $[\text{Au}_2(\text{dppm})(\text{SC}_6\text{H}_4\text{CH}_3)_2]$ with the phenyldisulfide $(\text{SC}_6\text{H}_4\text{Cl})_2$ as a model for the interaction of gold with disulfides. The important factors in this reaction were shown to be the electronic and steric properties of the reactants, and the presence of an Au-Au bond. The electronic structure of dinuclear gold(I) complexes $[\text{Au}_2(\text{dppee})\text{X}_2]$ where X = halide and dppee = diphenylphosphinoethylene) was investigated by Mitchell Bruce (Maine, USA) using quantum yield measurements combined with electrochemical studies. Garcia (Santiago de Compostela, Spain) examined the different coordination modes of Au(I) and Ag(I) tripod phosphine complexes, where tripod = 1,1,1-tris(diphenylphosphinomethyl)ethane. Crystal structures of $[\text{Au}_3(\text{tripod})\text{X}_2]\text{X}$ (where X=halide) were obtained and geometries confirmed using ^{31}P NMR.

There was also a series of interesting papers on the medical uses of silver, and altogether this was a small, highly focused meeting, bringing together experts in the fields of bioinorganic chemistry and medicinal uses of gold and silver, and providing an effective update of the subject area. Professor Shaw is to be congratulated on organizing a stimulating, and successful meeting. We should all look forward with anticipation to the 5th meeting. The full proceedings of the 4th meeting are to be published in a special edition of 'Metal-Based Drugs', and will be dedicated to the memory of the late Professor Colin Locke, who was a major contributor to the field, and previous Gold and Silver meetings.