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Medicinal Inorganic Chemistry: Introduction

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Many metallic elements play a crucial role in living systems. A characteristic of metals is that they easily lose electrons from the familiar elemental or metallic state to form positively charged ions which tend to be soluble in biological fluids. It is in this cationic form that metals play their role in biology. Whereas metal ions are electron deficient, most biological molecules such as proteins and DNA are electron rich. The attraction of these opposing charges leads to a general tendency for metal ions to bind to and interact with biological molecules. This same principle applies to the affinity of metal ions for many small molecules and ions crucial to life, such as O_2. Given this wide scope for the interaction of metals in biology, it is not surprising that natural evolution has incorporated many metals into essential biological functions. Metals perform a wide variety of tasks such as carrying oxygen throughout the body and shuttling electrons.[1] Hemoglobin, an iron-containing protein that binds to oxygen through its iron atom, ferries this vital molecule to body tissues. Metal ions such as zinc provide the structural framework for the zinc fingers that regulate the function of genes in the nuclei of cells. Similarly, calcium-containing minerals are the basis of bones, the structural framework of the human body. Zinc is a natural component of insulin, a substance crucial to the regulation of sugar metabolism. Metals such as copper, zinc, iron, and manganese are incorporated into catalytic proteins—the metalloenzymes—which facilitate a multitude of chemical reactions needed for life.[1]

Since nature has made such extensive use of metal ions in biological systems, the following questions arise: "Can metal ions be incorporated into drugs? Are coordination compounds potential medicinal agents? Can coordination chemistry be used for medicinal purpose?" We term this area of scientific inquiry medicinal inorganic chemistry—it is the subject of this dedicated issue of *Chemical Reviews.*

Medicinal inorganic chemistry as a discipline has only existed for about the last 30 years, since the discovery of the antitumor activity of cisplatin, *cis*-$[Pt(NH_3)_2Cl_2]$. By the field existing as a discipline, we specify where a known chemical compound has been discovered to have a specific activity and where studies have been done both to elucidate the mechanism of action as well as to optimize and improve

Chris Orvig (right) and Mike Abrams (left) have been close friends and colleagues for 20 years. After completing undergraduate degrees at McGill University and Bowdoin College, respectively, they were graduate students with Alan Davison at Massachusetts Institute of Technology where they completed their Ph.D. degrees in 1981 and 1983, respectively. After Chris completed an NSERC of Canada postdoctoral fellowhip with Kenneth N. Raymond at Berkeley, Chris and Mike were reunited in 1983–84 at McMaster University in the labs of the late Colin J. L. Lock, where Mike was a NATO postdoctoral fellow. In 1984, Chris joined the faculty in the Chemistry Department at the University of British Columbia, where he remains, and Mike joined Johnson Matthey where he rose to become Manager of Biomedical Research, Worldwide, before starting AnorMED (where he is President and CEO) in 1997 with some of his Johnson Matthey colleagues. Mike is also an adjunct professor in the Chemistry Department at UBC. Both Chris and Mike are deeply interested in medicinal inorganic chemistry and outdoor activities.

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the activity of (e.g., platinum) compounds in general. Pt-based combination chemotherapy is *still* the mainstay for the treatment of solid malignancies (especially testicular, ovarian, and small cell lung cancers). Newer Pt analogues are emerging that expand the spectrum of activity of the original drugs. The unique lesion made by Pt has not, to date, been mimicked by any organic drugs—clearly the metal−biomolecule interaction is critical to the antitumor activity of platinum, as it is, in general, for the activity of any metallodrug.

Medicinal inorganic chemistry has been practiced, however, for almost 5000 years.[2,3] As far back as 3000 BC the Egyptians used copper to sterilize water. Gold was used in a variety of medicines in Arabia and China 3500 years ago, more as a result of the precious nature of gold than of its known medicinal activities. (There was a tendency, when a precious metal was discovered or determined to be of considerable value, to believe that it must hold health properties of benefit as well.) Various iron remedies were used in Egypt about 1500 BC, around the same time that zinc was discovered to promote the healing of wounds. In Renaissance era Europe, mercurous chloride was used as a diuretic and the nutritional essentiality of iron was discovered. It is in the last 100 years, however, that the medicinal activity of inorganic compounds has slowly been developed in a rational manner, starting in the early 1900s with $K[Au(CN)_2]$ for tuberculosis, various antimony compounds for leishmaniasis, and the antibacterial activity of various gold salts in a number of different conditions.

When one thinks of drugs, one often thinks of organic compounds such as the antibacterial penicillins, the nutrient vitamin C, and the psychoactive drugs, such as LSD, THC, etc. The biochemical literature of the last 30 years chronicles the burgeoning understanding that many of the biological activities of proteins and enzymes can be ascribed to the metal centers, with the organic backbone acting as a scaffold to hold the metal ion in place for the requisite transformation.[1] Because of this rapid growth of biological inorganic chemistry, it seems logical to explore in parallel the medicinal properties of the various metal ions that are found naturally and even of those that are not known to have essential benefit. In the last 50 years, knowledge of the central importance of inorganic elements in organisms has opened up the possibility for inorganic chemists to contribute to the health and well-being of man and all other organisms.[4]

It is ironic to note that the first structure−activity relationship, which was developed by Paul Ehrlich (see cover of this issue) in the first decade of the 20th century, involved the development of the *inorganic* compound arsphenamine (otherwise known as Salvarsan or Ehrlich 606) as a successful treatment for syphilis.[5] Ehrlich was the founder of chemotherapy, which he defined as the use of drugs to injure an invading organism without injury to the host. He also discovered the preferential accumulation of lead in the central nervous system, first formulated the chemotherapeutic index as well as the "magic bullet" concept, and was awarded the Nobel Prize in 1908 for his discovery of immunochemistry. Many of these ideas are considered to be the fundamental concepts of medicinal chemistry, which is mostly based on the development of organic molecules, yet this first structure−activity relationship evolved from medicinal inorganic chemistry.

Medicinal inorganic chemistry comprises the introduction of a metal ion into a biological system either by fortuity or by intention. After a fortuitous introduction, medicinal inorganic chemistry considers ways to chelate the metal out of the biological system in order to avoid effects from either the overload of an essential metal or a poisoning from an excess of a toxic metal. One can also consider under this area the more recent concept of altering the homeostasis of an essential metal ion with the use of a metal ion chelator, an example being the development by British Biotech and others of zinc binding matrix metalloproteinase inhibitors for the treatment of cancer and inflammatory diseases.

The intentional introduction of a metal ion into a biological system will be for either therapeutic or diagnostic purpose. As was noted by Peter Sadler some years ago,[3] most of the elements of the periodic table up to and including bismuth, with an atomic number of 83, have potential uses in the design of new drugs and diagnostic agents. Sadler also pointed out that medicinal inorganic chemistry provides active metal complexes, active metal ions, or even active ligands, as potential agents.[3] In diagnostic medicinal inorganic chemistry, the γ-emitting radiopharmaceuticals (e.g., ^{99m}Tc—involved in millions of nuclear medicine scans per year), the magnetic resonance imaging contrast agents (there are now four complexes of Gd^{3+} on the market), and X-ray contrast agents ($BaSO_4$) are all in heavy clinical use.

Following on these uses in diagnosis, we believe that there will be a huge growth in the therapeutic application of metal complexes in the next 10−20 years. In British Columbia, Canada, companies such as AnorMED and Kinetek Pharmaceuticals, both of which are investigating a variety of therapeutic uses of metal ions and both of which currently have metal complexes in clinical trials, are part of a vibrant and growing biotechnology industry with a significant emphasis on medicinal inorganic chemistry.

Chemotherapeutics, such as the anticancer agents, metal-mediated antibiotics, antibacterials, antivirals, antiparasitics, antiarthritics, and radiosensitizing agents, also appear in therapeutic medicinal inorganic chemistry, as do radiopharmaceuticals (β-emitters are being intensively studied for selective radiation therapy). Many of these are discussed in various papers in this special issue of *Chemical Reviews*. Cisplatin (an active complex) is the archetypal inorganic drug—it contains not one atom of carbon.

Any metal ion or complex, or indeed any chemical compound, is subject to the potential limitations in the Bertrand diagram (Figure 1), which is usually used in discussing the essentiality of elements.[6] The area of optimum physiological response will vary greatly according to the element, its speciation and

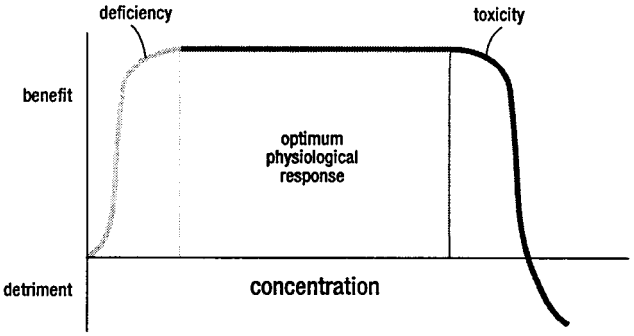

Figure 1. Bertrand diagram[6] indicating the relationship between benefit/detriment from an element and its concentration. Great variations are found in each region depending on the nature of the element (there may be no area of optimum physiological response, for instance).

oxidation state, and the biochemistry of the specific compound in which it is found. Therefore, the areas of deficiency, toxicity, and optimum physiological response can be dramatically varied by considering a combination of these variables, as well as design features of the potential ligand which may be altered to tune the delivery of that metal ion into the biological system. This refinement of the biological properties of metal complexes by ligand modification, along with the design of ligands to alter the homeostasis of endogenous metal ions, will provide many new therapeutic and diagnostic agents over the coming years and will direct medicinal inorganic chemistry into a discipline of central importance in medicine and science.

References

(1) In *Bioinorganic Enzymology*; Holm, R. H.; Solomon, E. I., Eds.; *Chem. Rev.* **1996**, *96* (7).

(2) Howard-Lock, H. E.; Lock, C. J. L. In *Comprehensive Coordination Chemistry;* Wilkinson, G., Gillard, R. D., McCleverty, J. A., Eds.; Pergamon: Oxford, 1987; Vol. 6, Chapter 62.2, pp 755−778.

(3) Sadler, P. J. *Adv. Inorg. Chem.* **1991**, *36*, 1−48.

(4) Williams, R. J. P. Personal communication.

(5) Albert, A. *Selective Toxicity*, 7th Ed.; Chapman and Hall: New York, 1985; pp 206−219.

(6) Bertrand, G. *8th Int. Conf. Appl. Chem.* **1912**, *28*, 30.

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