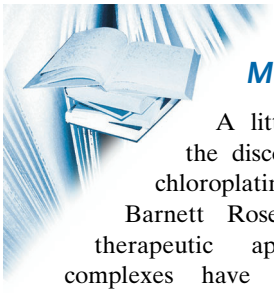


Bioinorganic Medicinal Chemistry

A little over 40 years after the discovery of *cis*-diammindichloroplatin(II) (cisplatin) by Barnett Rosenberg, diagnostic and therapeutic applications of metal complexes have significantly expanded beyond the use of platinum complexes in anticancer chemotherapy. During the last 10 to 15 years, the field of bioinorganic medicinal chemistry has seen a tremendous development both in terms of classes of compounds studied as well as breadth of applications in human medicine. Thus, it is certainly time now to summarize these interesting developments in one coherent book. Enzo Alessio from the University of Trieste, himself actively involved in the development of antimetastatic ruthenium complexes, has brought together leading experts in the field from around the world to cover all relevant aspects of medical applications of inorganic compounds in the thirteen chapters of *Bioinorganic Medicinal Chemistry*.

As an introduction (Chapter 1), Farrer and Sadler briefly summarize the most important features of metal complexes which determine their properties important for medicinal applications and then present selected examples for their use as antimicrobial as well as antiviral agents, while the largest section presents, element by element, the application of metal compounds in anticancer chemotherapy. The chapter also includes a table which lists areas of medical interest for all elements of the periodic table and concludes with a very brief outlook on the future of the field. This approach contrasts with a historic outline of the development of the field of bioinorganic medicinal chemistry, which would probably have much better guided the non-expert reader towards the field.

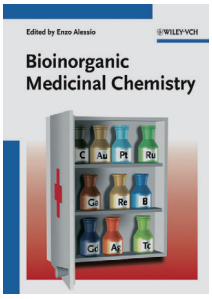
In Chapter 2, Norman and Hambley discuss strategies for the targeting of metal complexes. On the way through the body and into cells, bioactive metal compounds encounter a multitude of potential binding partners as well as barriers in the form of membranes. To achieve a selective accumulation in aberrant tissue or external pathogens, approaches to control the biodistribution and activity of metal complexes is a very important aspect in the field which has only rather recently received the attention it deserves. Thus, the chapter nicely summarizes differences between tissues in terms of oxygen concentration and pH as well as methods to achieve specific binding of metal complexes to bio(macro)molecules like enzymes and DNA, and how these can be exploited for novel therapeutics. This aspect of bioinorganic medicinal chemistry has rarely been covered in reviews so far.

The following Chapters 3 and 4, provided by Lippard and Guo, respectively, focus on the application of platinum complexes in anticancer chemotherapy, which is probably the most well-established use of metal compounds in medicine, with sales of platinum chemotherapeutic agents of several billion Euro per year. Although this field has extensively been covered in reviews over the last decades, the authors still provide an insightful overview of the most important compounds advanced to clinical trials and the molecular mode of action of cisplatin as the parent system. Furthermore, Guo presents a multifaceted view of next-generation platinum complexes which deviate significantly from cisplatin, like mononuclear *trans*-platinum(II) compounds, polynuclear platinum(II) systems, and platinum(IV) compound which usually require in vivo (photo)reduction for activation. The section also covers numerous platinum conjugates with delivery vectors for selective enrichment in malignant cells.

The next part of the book (Chapter 5) by Keppler, Alessio, and co-workers, deals with the anticancer activity of most other non-platinum complexes, although there is a separate chapter devoted to gold. Not surprisingly, the focus is on ruthenium compounds and a detailed discussion of ruthenium(III) as well as organometallic ruthenium(II) complexes is provided. Other elements like titanium, which has recently seen a revival in the form of novel titanocene dichloride derivatives, iron, and arsenic are also briefly touched. Compared to the vast selection of elements available to the medicinal inorganic chemist, this rather short section (just 25 pages compared to over 70 pages devoted to platinum alone) can therefore only provide a very cursory treatment of the many significant recent developments in this field.

In contrast, Chapter 6 takes a totally different approach to the main theme of the book. Instead of presenting additional classes of compounds, Boccarelli, Pannunzio, and Coluccia discuss different cell viability assays as well as genomics and proteomics methods which are indispensable to elucidate the molecular targets of metal-based anticancer drugs. Although such methods are essential to identify novel modes of biological activity important for the treatment of previously non-responsive or resistant cancer cells lines, these techniques are rarely treated in adequate depth in the literature easily accessible to the inorganic chemist and thus are a very welcome addition to this book.

Gold-based therapeutic agents are the subject of the next Chapter 7 provided by Berners-Price. A short outline of the history of gold compounds for use in medicine is followed by a detailed discussion of the biological activity of gold(I) as well as



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gold(III) complexes with a focus of antiarthritic and anticancer drugs. Gold compounds certainly hold a special position in medicinal inorganic chemistry due to the targeting of mitochondria and the redox metabolism of the cells instead of DNA as commonly assumed for platinum and ruthenium complexes. Thus, a separate chapter is certainly warranted, but the position within the book is a bit strange.

The next sections of the book then switch from an element-wise treatment to a focus on certain applications of metal complexes, in particular for imaging. In Chapter 8, Aime et al. give a short introduction to the theory of magnetic resonance imaging (MRI) as well as the most important classes of contrast agents based on gadolinium(III) as well as manganese(II) complexes, but also briefly cover superparamagnetic iron oxide (SPIO) nanoparticles.

The focus of Chapter 9 written by Alberto is on metal-based radiopharmaceutical agents. The selection and production of radionucleotides for diagnostic imaging as well as therapeutic applications is discussed in a very insightful way and a table of the most important isotopes and their properties will aid in the selection of suitable systems. A very important aspect of diagnostic radioimaging is the selective enrichment of radioactive probes in specific tissues and thus concepts of labeling are also covered. After this tutorial introduction to the field, the rest of the chapter provides an element-by-element presentation of the most important radioisotopes and their complexes, including yttrium, rhenium, indium, gallium, and of course technetium.

A special problem of anticancer chemotherapy is the selective elimination of malignant cells from the body with minimal damage to healthy tissue. This is particularly important for brain tumors to minimize neuropathological side-effects of the highly cytotoxic agents needed to eradicate tumor cells, which, as in the case of glioblastomas, are often highly aggressive and metastatic. An interesting approach to target such malignant cells in the very sensitive brain tissue is a binary therapy, which requires both an internal and external component to exert its cytotoxic activity. A promising approach in this context is neutron capture therapy (NCT), which is discussed in Chapter 10 by Rendina and co-workers. Thermal neutrons can pass through tissue and then interact with isotopes showing high capture cross-sections. The neutron capture process leads to a nucleus in an excited state which then either decays to high-energy particles or returns to the ground state with emission of gamma radiation. The two most important nuclei are ^{10}B as well as ^{157}Gd, and key criteria for the development of such BNCT and GdNCT as well as some important classes of compounds are covered here.

In contrast to the other sections, which deal with artificial metal-based agents introduced to the body for diagnostic or therapeutic purpose, Orvig and Mawani, in Chapter 11, provide a very detailed account on diseases originating from misregulations in metal homeostasis, leading to either metal overload or deficiencies in essential metals. Of course, iron and copper metabolic diseases are treated in depth, but misregulated uptake or efflux of many other metals also has pathophysiological effects and is competently treated in this section.

In Chapter 12, Gasser and Metzler-Nolte then again take up the theme of targeting of specific molecular structures, also covered more generally in Chapter 2, but now with a special focus on metal-based enzyme inhibitors. In contrast to the traditional approach of medicinal inorganic chemistry, in which a certain class of compounds is synthesized and then tested on a number of cells lines followed by attempts to identify the underlying physiological mechanism of action as well as molecular target structures, a number of researchers have recently started to develop metal complexes which can specifically bind to the active site of particular enzymes which are shut off by these metalloinhibitors, allowing identification of the signaling and metabolic pathways in which they are involved. Such metal-based enzyme inhibitors require a very tight control of the stereochemistry of the usually octahedral complexes to ensure enzyme binding constants in the sub-nanomolar range. Different approaches to this nascent field are presented and illustrated with coordination and organometallic compounds capable of acting as protein kinase, proteasome, and cyclooxygenase inhibitors, among others. This is one of the first overviews of this highly promising field of research and will provide the reader with many stimulating ideas how to further advance this area of bioinorganic chemistry.

Luminescent metal complexes for bioimaging and diagnosis then are the topic of the final Chapter 13 by Reinhoudt et al. After a short summary of the relevant photophysical properties, this section mostly covers the usual ruthenium(II), iridium(III), rhenium(I), and platinum(II) compounds as well as lanthanide complexes and then concludes with a very short account on metal nanoparticles for luminescent detection.

A 17-page index completes the book, which allows one to easily identify more specific topics, although most chapters are short enough to allow quick browsing to find sections of interest. Quite pleasingly, most figures are drawn using a common template, giving the book a uniform look, which is not always the case with multi-author volumes, and the overall graphical quality is high, although a few of the color figures look a bit blurry. No serious misrepresentations could be found and the literature is up to date, with many references up to 2008

or even 2009. The only main criticism is the somewhat arbitrary sequence of some of the chapters and the rather enumerative character of the first, introductory chapter, which also duplicates much of the information given in the later sections. Here, unfortunately, historic developments, key concepts, and future challenges of bioinorganic medicinal chemistry, are not elaborated clearly enough, especially to the non-expert reader.

Now, who would benefit from reading this book or at least parts of it? For self-study by Bachelor or Master students of Chemistry and related subjects like Biology, Pharmacy, and Medicine, this volume requires too much background knowledge for easy access and thus this audience is better pointed to *Metals in Medicine* by J. C. Dabrowiak as an introductory text.

However, for the preparation of lectures and exercises, for example, lecturers will find many novel and inspiring examples to illustrate the main themes of research in bioinorganic and medicinal inorganic chemistry. In contrast to the somewhat older *Metallotherapeutic Drugs & Metal-based Diagnostic Agents* by Gielen and Tiekink with an element-by-element treatment, Bioinorganic Medicinal Chemistry is more focused on certain applications (e.g. anti-cancer, bio- and radioimaging) and concept than particular elements and also contains some very interesting general chapters on targeting of metal complexes as diagnostic and therapeutic agents as well as biological screening methods. Expert readers looking for an up-to-date overview of recent developments in their field of research as well as doctoral students with a certain background knowledge in bioinorganic chemistry entering this highly interdisciplinary and quickly advancing field are the main audience for this well-edited book and will benefit from the concise treatment as well as the many references to highly topical primary publications.

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