Ligand Design in Medicinal Inorganic Chemistry
Ligand Design in Medicinal Inorganic Chemistry

Edited by

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Tim Storr obtained his B.Sc. from the University of Victoria, Canada, and his Ph.D. in Medicinal Inorganic Chemistry from the University of British Columbia, Canada, in 2005 working with Professor Chris Orvig. He then pursued postdoctoral studies with Professor T. Daniel P. Stack at Stanford University studying metalloenzyme mimics. In 2008 he joined the faculty at Simon Fraser University, Canada, as an assistant professor where his bioinorganic chemistry research programme targets the development of new chemical tools to diagnose and treat disease. His research is funded by the Natural Sciences and Engineering Research Council and the Michael Smith Foundation for Health Research. Current research interests include metal overload disorders, Alzheimer’s disease, cancer, diagnostic imaging, site-selective therapies, and catalysis.
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Introduction to Ligand Design in Medicinal Inorganic Chemistry

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Medicinal inorganic chemistry continues to provide significant innovation in both diagnostic and therapeutic medicine. The field can be divided into two main categories: drugs that target metal ions in some form, and metal-based drugs in which the central metal ion is essential for the clinical application. Although the field of medicinal inorganic chemistry is not new, a better understanding of metal ion interactions in the body has enabled the development of many effective disease treatment strategies involving metal ions. The development of Cisplatin ($\text{cis} \cdot [\text{Pt(NH}_3)_2\text{Cl}_2]$) has played an instrumental role in bringing the field of medicinal inorganic chemistry into the mainstream [1]. Cisplatin and the second generation analog Carboplatin, shown in Figure 1.1, are the most commonly prescribed anticancer agents which greatly improve survival rates in ovarian, bladder, cervical, and testicular cancers [2].

However, as recently written by Norman and Hambley, “with the notable exception of platinum anticancer drugs, metal-based therapeutics occupy a relatively minor place in the organic dominated history of drug development [3].” Therefore, there is a broad scope for innovation in the field of medicinal inorganic chemistry! An inherent advantage of metal complexes lies in the accessibility of multiple oxidation states, overall charge, and geometries. However, these properties can become a disadvantage if not controlled in the biological application. Predicting the behavior of metal-based medicinal agents in vivo is a major challenge facing medicinal inorganic chemists today. The history and basic concepts of medicinal inorganic chemistry have been comprehensively reviewed [4–11]. The main goal of this book is to highlight the role of ligand design in the rapidly expanding field of medicinal inorganic chemistry [12–14]. Through a series of 14 chapters, expert researchers describe the importance of ligand design in medicinal inorganic chemistry.
Metal ions have an essential role in the human body by providing charge balance, facilitating electron transport, and catalyzing enzymatic transformations. For each application, the metal cation and the atoms immediately surrounding the metal cation (i.e., coordination sphere) can be tuned specifically. The type, number, and geometry of the ligands, commonly in the form of amino acid side-chains, ensure that the active site is maintained (Table 1.1).

Continued research into the uptake, transport, and utilization of metal ions in the body has enabled the development of many disease treatment strategies targeting metals. For example, the role of ligand design in essential metal overload disorders such as Wilson’s disease (Cu) and Hemochromatosis (Fe) is discussed by Delangle and co-workers in Chapter 11. In addition, the role of dysregulated metal ions in protein misfolding diseases of the brain, and the design of molecules targeting these processes, are discussed by Lim and co-workers in Chapter 10. Finally, the design of metal-binding molecules that inhibit the biological function of metalloproteins is discussed by Cohen and co-workers in Chapter 14 [16].

Table 1.1 A brief introduction to essential metal ions in the body and their functions [15]

<table>
<thead>
<tr>
<th>Metal ions</th>
<th>Coordination number, geometry, ligand preferences</th>
<th>Function</th>
</tr>
</thead>
<tbody>
<tr>
<td>Na⁺</td>
<td>6, octahedral, carboxylate/ether/hydroxyl</td>
<td>Charge balance, osmotic pressure, and nerve activity</td>
</tr>
<tr>
<td>Mg²⁺</td>
<td>6, octahedral, carboxylate/phosphate</td>
<td>Structural role in hydrolases, isomerases, and phosphate transfer</td>
</tr>
<tr>
<td>K⁺</td>
<td>6–8, flexible, carboxylate/ether/hydroxyl</td>
<td>Charge balance, osmotic pressure, and nerve activity</td>
</tr>
<tr>
<td>Ca²⁺</td>
<td>6–8, flexible, carbonyl/carboxylate/phosphate</td>
<td>Structural, charge balance, reaction initiator, and phosphate transfer</td>
</tr>
<tr>
<td>Cr³⁺</td>
<td>6, octahedral, oxygen-donors</td>
<td>Essential to carbohydrate/lipid metabolism</td>
</tr>
<tr>
<td>Mn²⁺/³⁺</td>
<td>6, tetragonal/octahedral, carboxylate/hydroxide/imidazole/phosphate</td>
<td>Structural role in oxidases</td>
</tr>
<tr>
<td>Fe²⁺/³⁺</td>
<td>4 or 6, tetrahedral or octahedral, carboxylate/oxygen/phenololate/thiolate/imidazole/pyrrole</td>
<td>Electron transfer in oxidases and oxygen binding/transport</td>
</tr>
<tr>
<td>Co²⁺/²⁺</td>
<td>4 or 6, tetrahedral or octahedral, carboxylate/imidazole/thioether/thiolate</td>
<td>Alkyl group transfer (B₉₁₂), oxidases</td>
</tr>
<tr>
<td>Cu²⁺</td>
<td>3–5, trigonal planar, tetrahedral, square planar, square pyramid, carboxylate/imidazole/thioether/thiolate</td>
<td>Electron transfer, oxidases, and hydroxylases</td>
</tr>
<tr>
<td>Zn²⁺</td>
<td>4 or 5, tetrahedral or square pyramid, carbonyl/carboxylate/imidazole/thiolate</td>
<td>Structure in zinc fingers, gene regulation, anhydrases, dehydrogenases, and peptidases</td>
</tr>
</tbody>
</table>
Natural systems provide much of the inspiration for the strategies employed by medicinal inorganic chemistry researchers. Thus, the design of active agents uses many of the same features present in biological systems to stabilize metal ions. The ligand(s) play a key role in determining the pharmacokinetic parameters of the metal-containing drug molecule allowing for tuning of a compound for the specific application. Basic inorganic chemistry concepts such as Hard Soft Acid Base (HSAB) Theory, kinetic inertness, and thermodynamic stability, can be used in the design process [17, 18]. Ligands can be purposefully chosen to limit complex dissociation and metal-associated toxicity in vivo in the presence of endogenous metal-binding molecules such as citrate, phosphate, bicarbonate, and biomolecules such as glutathione, transferrin, and albumin. Additional factors that must be considered include: matching the oxidation state and coordination preferences of the metal ion, kinetics of complex formation, water solubility, overall charge, and the pathway of excretion from the body. Depending on the application, a larger degree of importance may be placed on specific design features of the medicinal agent. For magnetic resonance imaging (MRI) contrast agents discussed by Bonnet and Tóth in Chapter 12, the Gd$^{3+}$ ion offers the best response and is incorporated into all but one of the commercially-approved agents. However, the high concentration used and known toxicity of the Gd$^{3+}$ ion in the body necessitates the use of ligands that confer kinetic inertness and high thermodynamic stability to the complex. High thermodynamic stability of Gd$^{3+}$ complexes, along with other lanthanides, is achieved with multidentate poly(amino)polycarboxylate ligands which form strong electrostatic interactions with the hard cation. Example ligands include the linear diethylenetriaminepentaacetic acid (DTPA) and macrocyclic 1,4,7,10-tetraazacyclododecane-1,4,7,10-tetraacetic acid (DOTA). The Gd$^{3+}$ complexes of both of these ligands have been approved for clinical use and are shown in Figure 1.2.

Many of the same important design features for MRI contrast agents are applicable to metal-based radio-pharmaceutical research as described by Ferreira and co-workers in Chapter 3. For metal-based radiopharmaceuticals, the low concentration of the radionuclide available in the ligand complexation step, as well as the short half-life of many radionuclides (e.g., $^{68}$Ga = 68 minutes), require careful consideration of the kinetics of complex formation. For the binding of metal ions in vivo, as described in Chapter 11 for metal overload disorders of Cu and Fe, ligand design needs to take into account the binding preferences of a specific oxidation state of the metal ion. As an example, in the Fe-overload disorder Hemochromatosis, the development of binding agents that stabilize the more kinetically-inert Fe$^{3+}$ oxidation state are of interest. A high affinity for Fe$^{3+}$ is necessary in order to compete with the iron transport protein, transferrin. An additional important design consideration is the Fe$^{3+}$/Fe$^{2+}$ redox potential of the resulting complex. A value below −300 mV (vs. the Normal Hydrogen Electrode (NHE)) is hypothesized to prevent redox-cycling in the presence of biological reducing agents, such as ascorbate and glutathione, and the possibility of generating reactive oxygen species (ROS) in vivo [19, 20]. However, the design of metal complexes that undergo redox processes under controlled conditions in the body has proven to be an effective targeting method in cancer diagnosis and therapy. Under certain conditions, the reducing environment of hypoxic tumor tissues [21] can be exploited for the

![Figure 1.2](image-url)  
**Figure 1.2**  Examples of gadolinium complexes used in MRI imaging (a) Gd-DTPA and (b) Gd-DOTA. See Chapter 12 for further details.
selective activation of metal-based diagnostics and therapeutics [22]. Examples include Ru-based anticancer agents (Chapter 15), PtIV complexes (Chapter 2), CoIII compounds [23, 24], and the radiopharmaceutical 64CuII-diacetyl-bis-N4-methylthiosemicarbazone (64CuATSM) (Chapters 3 and 7). The anticancer activity of the ferrocene-containing ferrocifens [25], and antimalarial activity of ferrocene-containing agents discussed in Chapter 8 [26], may in part be due to redox activation of the ferrocene unit and generation of ROS.

In addition to providing a stable complex, ligands can impart additional properties to metal ions. For example, ligand photosensitization of metal complexes can provide an emissive response useful for imaging and/or drug activation. Ligands are essential to the development of emissive metal complexes for biological applications. There has been significant interest in the development of both transition metal- (Chapter 4) and lanthanide- (Chapter 5) containing optical probes. In Chapters 4 and 5, the important design features of metal-based optical probes are described in detail. Optical probes, in general, permit the in vitro visualization of biological processes at the subcellular level, and have recently been reported for in vivo diagnostic applications [30, 31]. Properties such as biological stability, large Stokes shift (difference in energy between excitation and emission wavelengths), and long luminescence lifetimes of metal-based probes provide an improvement over organic fluorophores. In almost all cases, metal-containing optical probes depend on photophysical processes involving the ligand, and the majority of ligands used are conjugated heterocycles including bipyridine, phenanthroline, and phenylpyridines. These same planar aromatic heterocyclic ligands can also display DNA-intercalating ability, thereby providing a targeting feature to certain optical probes [32]. As discussed by Coogan in Chapter 4, transition metal optical probes containing d6 complexes (ReI, RuII, and IrIII) are the most commonly studied (Figure 1.4), and more recently d8 and d10 platinum and gold complexes have been reported. The combination of optical imaging and cytotoxicity in one agent is briefly described for both Pt (Chapter 2) and Au (Chapter 9) complexes. Lanthanide probes employ much of the same design features as MRI agents (thermodynamic stability and kinetic inertness), and in contrast to the transition metal optical probes, the emission is primarily metal-based (4f electrons), thus leading to sharp line-like emission spectra. The low extinction coefficients of lanthanide ions (f-f transitions are Laporte forbidden) necessitates the use of a sensitizing moiety, an organic absorber which can transfer energy to the lanthanide excited state. In the majority of cases, the sensitizer is either directly bound to the lanthanide ion, or attached to a chelating ligand that is bound to the lanthanide ion (Figure 1.4). As described by O’Neill and New in Chapter 5, the long luminescence lifetimes, and information rich spectra of lanthanide complexes, provide many opportunities in optical imaging research. Ligand photosensitization of metal complexes can be used in a number of pharmaceutical applications, where following excitation, the energy transfer can initiate ligand
Introduction to Ligand Design in Medicinal Inorganic Chemistry

Figure 1.4 Examples of photoactivated metal complexes: (a) An emissive ReI tricarbonyl complex [33]. (b) An emissive EuIII complex containing a sensitizer (in bold) for in vitro imaging [34]. (c) A Mn complex that releases NO under photoexcitation [35].

Dissociation leading to the release of bioactive agents. Energy transfer can also occur to exogenous molecules such as O2, which is the mechanism of activation in photodynamic therapy. In Chapter 13, Mascharak and co-workers describe the design features of metal complexes that are activated by light. Through ligand design, they show that photoactivation is controlled by the power, wavelength, and exposure time of the light. Specific examples include photoactivated toxicity and the release of small-molecule signaling agents such as NO and CO (Figure 1.4).

The targeting of a diagnostic and/or therapeutic agent in the body is essential to an accurate diagnosis as well as for limiting the off-target toxicity of the administered drug in therapeutic applications. In the case of Cisplatin, uptake is not specific to cancer cells and thus off-target toxicity is a major limiting factor, with less than 1% of the injected drug reaching its tumor DNA target [36]. Despite this drawback, Cisplatin is still an effective front-line treatment. A major research focus for medicinal chemists today is to improve the targeting of the medicinal agent and a large number of innovative ideas are presented in this book. We will only highlight a few specific examples here. Information on the uptake, transport, localization, and eventual excretion of a drug molecule is instrumental in the design of more effective agents. An interesting example is the longstanding (several thousand years!) application of Au in medicine. The emergence of specific thiol and selenol protein drug targets such as thioredoxin reductase, and the use of ligands to control cellular uptake and reactivity of the Au metal center, are excellently described by Berners-Price and Barnard in Chapter 9. In Chapter 7, Vieira and Beraldo detail the design of Schiff base-derived ligands in a number of disease applications. Many of the chapters describe the attachment of a biological targeting vector to a metal complex. Biological targeting vectors include, but are not limited to: carbohydrates, amino acids, peptides, antibodies, and active drug molecules. The distance between the targeting vector and the metal complex is an important design consideration. Mikata and Gottschaldt review the use of carbohydrate targeting ligands in Chapter 6. Appending a carbohydrate moiety to a metal complex has the ability to reduce toxicity, and improve solubility and molecular targeting of the metal-based drug via use of carbohydrate active transport pathways. In Chapter 8, Navarro and Biot describe the attachment of the known antimalarial Chloroquine (CQ), either pendent or directly bound to a metal complex, which affords a series of new leads that overcome the CQ-resistance of the malaria parasite (Figure 1.5). A major mechanism of drug transport in the blood is via binding to the hydrophobic pockets of the protein human serum albumin (HSA). Targeted HSA binding greatly enhances contrast for the commercially available blood pool imaging agent MS-325 (Chapter 12); a pendent lipophilic phosphine moiety is attached to the GdIII complex which interacts with HSA and slows the rotational correlation time (τR) of the complex (Figure 1.5). The development of a series of Ru anticancer agents that employ ligands designed to interact with HSA and improve targeting are described by Mu and Walshy in Chapter 15.
Metal complexes attached to peptide targeting vectors are of great interest in medicinal inorganic chemistry and the identification of new disease targets will lead to continual development in this area. A number of radiodiagnostic agents containing tumor-specific peptides attached to radiometal chelates are discussed by Ferreira and co-workers in Chapter 3. High target to background ratios provide non-invasive images of tumors and metastatic tissue, and also present the possibility of attaching therapeutic isotopes (e.g., $^{90}$Y and $^{153}$Sm) for treatment. Similar peptide targeting strategies are discussed for Pt (Chapter 2) and Au (Chapter 9) anticancer agents to take advantage of specific active transport pathways. The use of radiolabeled antibodies for tumor imaging and therapy is of significant interest. The extended plasma half-life of antibodies requires a long-lived isotope to obtain useful diagnostic images. The application of $^{89}$Zr (Chapter 3), and the use of desferrioxamine (DFO) as the metal chelate (a biological siderophore shown in Figure 1.6), in combination with antibodies such as Bevacizumab demonstrates the influence of medicinal inorganic chemistry in modern diagnostic imaging. Finally, the recent development of a CuI pro-ligand that is selectively activated in liver hepatocytes shows considerable promise as a Wilson’s disease treatment (Chapter 11) [39]. These compounds are decorated with carbohydrate residues that are recognized by the asialoglycoprotein receptor (ASGP-R), and once internalized, cleavage of disulfide bonds in the reducing intracellular medium releases the active chelator. Pro-chelator molecules also show considerable promise in binding dysregulated metals in neurodegenerative disease (Chapter 10) [40, 41].

The field of medicinal inorganic chemistry offers an important opportunity to expand our ability to diagnose and treat disease. Throughout this book, the authors have described the importance of ligand design in tailoring the properties of drug candidates to the specific application. Each individual chapter shares significant

Figure 1.6 Desferrioxamine (DFO) is a bacterial siderophore produced by the actinobacteria Streptomyces pilosus. DFO is used to treat acute iron poisoning (Chapter 11), and is also used as a radiometal chelate (Chapter 3)
insight into how ligand design is increasing our understanding of pathophysiology of disease, and providing a mechanism to increase the efficacy of drug molecules. We hope you enjoy each chapter as much as we have, and apply the concepts and insights within to your own research in medicinal inorganic chemistry.

References


2

Platinum-Based Anticancer Agents

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2.1 Introduction

The ligands of platinum anticancer complexes influence everything from the type of pharmaceutical formulation required, to the pharmacokinetics and the mode of cytotoxicity. The ligands determine the aqueous solubility of platinum complexes, which in turn determines the route of drug administration; for instance, oral versus intravenous. Once the platinum complex enters the circulation, its reactivity dictates the number of unwanted side-reactions with blood proteins, while the size, charge, lipophilicity and shape of the ligands influence the distribution of the complex throughout the body and the rate at which it is excreted. High molecular weight ligands are useful for trapping platinum complexes in tumour tissue; a phenomenon known as the enhanced permeability and retention (EPR) effect [1, 2], while charged ligands can be employed to enhance tumour penetration [3, 4]. Lipophilic ligands are useful for increasing cellular uptake [5, 6], while the shape of the ligands can be tailored to improve DNA affinity, facilitate binding with receptors on the surface of tumour cells, and inhibit enzymes involved in cancer progression. The ligands also determine the type of DNA-adduct that is formed, as well as the mode of cell-death that ensues. As a result, careful consideration must be exercised in the choice of ligands, in order to optimise the anticancer properties of novel platinum complexes.

2.2 The advent of platinum-based anticancer agents

The era of platinum-based chemotherapy dawned in the 1960s, following Barnett Rosenberg’s serendipitous discovery of the antiproliferative effects of cisplatin (1) [7]. Cisplatin was granted FDA approval in 1978, with its success paving the way for the regulatory approval of the second- and third-generation platinum
anticancer agents, carboplatin (2) and oxaliplatin (3) [8, 9] (Figure 2.1). Platinum drugs play a central role in cancer treatment and are used today in almost half of all chemotherapeutic regimes, often in combination with other anticancer agents [8, 10].

Since the discovery of the anticancer properties of cisplatin, a vast amount of research has been directed towards understanding its mode of action. To reach its biological target, DNA, cisplatin must travel through the bloodstream, in which the relatively high chloride concentration (≈100 mM) largely prevents aquation of the chlorido ligands [8, 9, 11, 12], although binding to blood proteins including human serum albumin and haemoglobin is known to occur [13–15]. Upon arrival at the tumour site, cellular uptake of cisplatin is achieved either by passive diffusion down a concentration gradient [11, 12], or by facilitated transport mechanisms, for instance, via the copper transporter-1 (CTR1) [16–19] or the organic cation transporters (OCTs) [20–22]. Once the drug enters cells, the lowered chloride ion concentration (3–20 mM) allows activation of the platinum complex by aquation of one or both of the chlorido ligands [11, 12]. In its activated form, cisplatin can bind to DNA, usually by forming crosslinks with adjacent purines on the same DNA strand, though crosslinks can also form between guanines separated by another base or between opposite strands [9, 23, 24]. These platinum-DNA adducts cause distortions in the DNA structure, including unwinding and bending, which can trigger apoptotic cell death [9, 24, 25]. Alternatively, the drug may react with intracellular components including glutathione, metallothionein, membrane phospholipids and cytoskeletal microfilaments [9, 11, 26]. Cisplatin can also be removed from tumour cells by the copper efflux transporters ATP7A and ATP7B and the GS-X efflux pumps, a family of organic anion transporters which are able to export platinum-glutathione adducts out of cells [17, 27–30]. The extracellular and intracellular promiscuity of cisplatin results in less than 1% of intravenously administered drug reaching its tumour DNA target [10].

Cisplatin has been used to treat many tumour types, including ovarian, bladder, head and neck, cervical and non-small-cell lung cancer, and is particularly useful for treating testicular cancer, for which it boasts an overall cure rate exceeding 90% [10, 25, 31]. There are, however, several limitations related to its clinical use. The leading drawback of the drug is its severe dose-limiting side-effects, which arise from its indiscriminate uptake by all rapidly dividing cells (including tumour cells but also, for instance, bone marrow cells), and the pressure on the kidneys to excrete the drug from the body [8]. Side-effects include nephrotoxicity, emetogenesis, neurotoxicity, myelosuppression and otorrhea [8, 10, 25]. Furthermore, numerous cancer types are able to develop resistance to cisplatin, by means of enhanced DNA adduct repair and tolerance, reduced cellular uptake and increased efflux, downregulation of cell-death pathways, and inactivation by proteins and thiols [8, 9, 11, 25]. Finally, cisplatin has been found to suffer from poor tumour penetration, with evidence suggesting that clinically effective doses of the drug are only delivered to tumour cells situated closest to blood vessels [32, 33].