CHAPTER 1

Organometallic Compounds in Biomedical Applications

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I. INTRODUCTION

The toxicity as well as therapeutic value of organometallics is well known. The introduction of metal ions within biological macromolecules such as proteins and nucleic acids is a continuing area of research. The appearance of metal-containing macromolecules in the human body is extensive and includes such metals as iron (transferrin, hemoglobin), molybdenum (xanthine oxidase), vanadium (hemovanadin), zinc (carbonic anhydrase), and copper (hepatocuprein). The use of organometallic medicinals is widespread. Some examples include merbromine (mercurochrome), meralein (mercury, antiseptic), silver sulfadizine (prophylactic treatment for severe burns), arsphenamine (arsenic, antimalarial), 4-ureidophenylarsonic acid (therapeutic for ameblasis, tryparsamide, and Gambian sleeping sickness), and antimony dimercaptosuccinate (schistosome). Table 1 contains a brief listing of additional metal-containing drugs.

Perhaps the earliest written record of the use of medicines is the "Ebers" papyrus, from about 1500 BC. This describes more than 800 "recipes," some of which contain substances today known to be toxic, including hemlock, aconite

Table 1 General Biological Uses for Metal-Containing Drugs

Metal	Medical Use
Au	Arthritis, gout
Ag	Antiseptic agent, prophylacetate
As, Sb	Bactericides
Bi	Skin injuries, diarrhea, alimentary diseases
Co	Vitamine B_{12}
Cu	Algicide, fungicide, insecticide
Ga	Antitumor agent
Hg	Antiseptic
Li	Manic depressoin
Mn	Fungicide, Parkinson's disease
Os	Antiarthritis
Pt, Pd	Antitumor agents
Rb	Substitute for K in muscular dystrophy; protective agent against adverse effects of heart drugs
Ru, Rh, Os	Experimental antitumor agents
Sn	Bactericide, fungicide
Ta, Si	Inert medical applications as gauzes, implants
Zn	Fungicide

(ancient Chinese arrow poison), opium, and metals, including lead, copper, and antimony.[1] Use of mercury in medicine in ancient Greece was described by Dioscorides, and by the Persian Ibn Sina of Avicenna (980–1036 AD), for use against lice and scabies. He also reported observations of chronic mercury toxicity.[2]

Arsenic is another metal known to the ancients with toxic as well as medicinal properties. The sulfides of arsenic, which were roasted, were described by Discorides in the first century AD as medicines as well as colors for artists. There is evidence that arsenic was used as a poison in Roman times.[3] Medieval alchemists were well aware of the poisonous nature of arsenic compounds, which were used in various recipes. Paracelsus, the Swiss physician, used arsenic compounds as medicinal agents.[4] Arsenic was widely used as a pesticide in the form of calcium arsenate following the turn of the 20th century.

Paracelsus understood the relationship between medicines and poisons as stated in the third of his 1536 Sieben Defensiones:[2] "What is not a poison? All things are poisons and nothing is without toxicity. Only the dose permits anything not to be poisonous. For example, every food and every drink is a poison if consumed in more than the usual amount; which proves the point." We might add the mode of delivery is also critical. For instance, water injected down the windpipe kills.

Metal-containing compounds which are toxic to fungi, bacteria, protozoa and other disease-causing agents can often be toxic to humans. Mercury toxicity has been known since ancient times. Romans, for example, used criminals in the cinnabar mines in Spain as the life expentancy of a miner was just 3 years.[5] Other examples of metals that were mined for a variety of uses include lead and arsenic. Egyptians were known to use lead back to 5000 BC, and mines in Spain date to about 2000 BC.[6] It has been suggested that the use of lead in making wine and other products, and the use of lead in pipes could have contributed to widespread lead poisoning in Roman times.[7]

Evidence for lead contamination in the environment from anthropogenic activities including mining, smelting, and combustion is historically preserved in various sites such as ice in Greenland, lake sediments and peat in Sweden, and elsewhere. Studies of such historical samples have shown, for example, that the $^{206}Pb/^{207}Pb$ ratios of about 1.17 in 2000 year-old corings are similar to ratios of the lead sulfide mined by the Greeks and Romans during this time period. By contrast, local northern sources such as those in Sweden that are uncontaminated by long-range atmospheric transport, exhibit a much higher ratio (about 1.53). In fact, these studies confirm that lead use and deposition greatly decreased following the decline of the Roman Empire.[8]

Although lead has been used since ancient times for medicinal purposes, its toxic properties were also understood. Thus, lead colic was reported by Hippocrates, and in about 50 AD, poisoning of lead workers was documented by Pliny. Ramazzini observed toxicity to potters working with lead in 1700 AD, but it was not until 1933 that Kehoe demonstrated wide exposure to lead in the environment. Lead produces adverse effects on children with respect to behavior and reduced IQ scores, even at very low levels.[7]

The use of metal and metalloid-containing polymers in biomedical applications is widespread. Polysiloxanes are the primary materials currently employed. Organotin polymers are also widely used and polyphosphazenes have been used. Chelated metals are widely employed in dental applications. Many others are waiting in the wings for use in biomedical applications including additional organotin polymers, ferrocene-containing polymers, as well as platinum polymers. Many more may emerge in the near future as signaled by the activity of small molecules containing metals as both drugs or essential sites for the biomedical activity. This brief chapter is intended to suggest potential areas where metal-containing macromolecules may play a significant role based on the study of such small metal-containing molecules. The use of small metal-containing molecules in biomedical applications was highlighted in a Chemical and Engineering News article called "The Bio Side of Organometallics," which reviewed a major meeting on this topic held in July 18–20, 2002, at ENSCP where 120 participants from 25 countries discussed this topic.

Areas covered in the other chapters of this volume will not be dealt with here. Instead, additional efforts will be described.

II. CASE FOR METAL-CONTAINING BIOACTIVE AGENTS

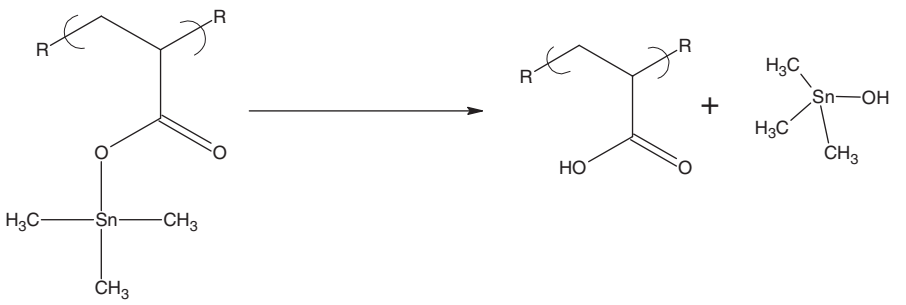
We have seen that metal- and metalloid-containing compounds exhibit a wide range of biological and biocidal activities, some of which have been employed in medicines and drugs. Polymers containing metal or metalloid functions become a natural extension of this effort. Just as organic compound drugs have been chemically bound to polymers or physically imbibed into polymer matrices in order to provide a variety of useful advantages, the same opportunities exists for using metal and metalloid species. The use of polymeric drugs provides many possible advantages; a few of them are described here:

1. Controlled release of the active agent either by diffusion from a matrix or hydrolytic/enzymatic cleavage from the polymer carrier. This allows a sustained and more steady delivery of the active agent within the body or from patches applied externally.
2. External application of a medicine for transdermal diffusion is possible for more volatile or water-soluble compounds.
3. The polymer can be tailored to modify the solubility of the active medicinal agent. Its hydrophobicity/hydrophilicity is dominated by the polymer carrier.
4. Proper design of molecular weight can greatly reduce the excretion rate, thereby increasing efficacy and reducing the required dosage. Control of chain length can also be employed to "isolate" or prevent movement of the polymer drug past barriers in the body such as the blood–brain barrier.
5. The polymer can enhance the concentration of the active agent in specific tissues or locations. Polymers containing attached specific binding recognition agents (e.g., antibodies, hormones) can bind to biological receptor sites. If that polymer

also has medicinal molecules attached, these active agents are now delivered to and concentrated in the targeted locations. This highly specific delivery to cells with the targeted receptors is but one end of the spectrum. Molecular weight and hydrophobic-hydrophilic partitioning effects can also be employed. Further, the large size of the polymer often allows preferential attachment to cell walls, again effectively increasing the delivery time and lowering toxic effects related to the kidney and renal system.

A. Tin-Containing Biocidal Polymers

Perhaps the best known use of metal-containing polymers to deliver toxic substances at controlled rates are the polymeric tin methacrylates that have been used extensively in antifouling marine coatings.[9] Organotins have had widespread application in biocidal compositions.[10] Trialkyltin derivatives are the most effective toxins against marine organisms that foul ship bottoms, ultimately leading to barnacle growth as the climax organisms after a complex multiorganism colonization process.[11] Specifically, tributyltin gave the best antifouling activity when readily hydrolyzed from a carboxylate function.[12,13] Therefore, a large number of multilayer coating systems were developed where tributyltin methacrylate monomer units were present that underwent hydrolysis, initially producing tributyltin hydroxide.[9,14] The released tin moieties killed or inhibited the organism succession needed to colonize the ship bottom surfaces, reducing fouling. Related systems containing triphenyltin, triphenyllead, tributyllead, organoarsenic compounds, and copper(I) oxide have been studied and used.



1 **2** **3**

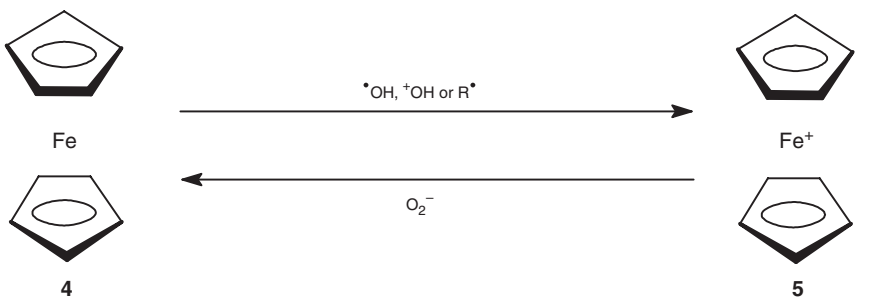
The use of biocidal antifouling coatings to store a toxic agent in large quantity and then deliver it more slowly at a location in which the toxicant is needed, suggests that polymers containing metals and metalloid functions, should become a fertile field for drug/pharmaceutical development and agricultural chemicals. An active agent might be released from the polymer or might function while in the polymeric form. Therefore, in the next example, we offer a rational for how the first synthetic organometallic compound prepared and characterized, ferrocene,[15–17] might serve as

a therapeutic agent when it is present in a polymer. In this case, however, a toxic agent would not be released. Instead, the iron center in ferrocene could function as a redox center to reduce the concentration of oxidants that cause cell damage via free-radical chemistry.

B. Ferrocene: A Therapeutic Role in Polymeric Systems?

The biochemistry of cancers is enormously complex, but it has generally been accepted[18–20] that free radicals play many important roles, notably in carcinogenesis and tumor promotion. Superoxide anion radical, hydrogen peroxide, and hydroxyl radical generation are formed during O_2 reduction in respiring cells. Protection is afforded by enzymes, such as superoxide dismutase, which converts superoxide ion into hydrogen peroxide and O_2. Catalase and glutathione peroxidase eliminate hydrogen peroxide, preventing Fenton reactions, which generate hydroxyl radicals.[21,22] Superoxide-generating promoters and reductions in superoxide dismuturase activity lead to increased superoxide levels in transformed cells.[22] Ultimately, radical species react at nuclear DNA causing replication errors during mitosis which is a causative factor in malignancy. Carcinogenic and metastatic processes are inhibited by antioxidants and free-radical scavengers.[18,22,23] Carcinostatic activity is exhibited by some metal complexes that serve as scavengers for superoxide.[19,24] Free-radical scavenger activity can be the operating mode of some anticancer drugs.[25]

Many metal-containing compounds are good reducing agents. For example, ferrocene is readily oxidized to stable ferrocenium by hydroxyl radicals or other radicals. These radicals are reduced (e.g., $^{\bullet}OH \rightarrow {}^{-}OH$). Furthermore, ferricenium is reduced by superoxide. Therefore, this redox activity can serve to remove both of these deleterious oxidants. This suggests that ferrocene might serve as a useful therapeutic center if its solubility, pharmocokinetic response, distribution in the body, and other required features could be suitably tailored. The use of polymer-bound ferrocene species could serve to tailor these requisite properties. Thus, water-soluble ferrocene-containing polymer conjugates have been synthesized for this purpose,[26–28] and water-soluble monomeric ferricenium salts were found to have powerful antineoplastic activity, curing cells under the Ehrlich ascites tumor testing protocol.[27,28] It seems likely that metal-containing polymers should be a rich source of potential future therapeutic agents.



C. Polymeric Moderation of OsO_4 Toxicity

Polymer-binding of highly toxic metal reagents can ameliorate the toxicity of potentially beneficial osmium compounds. Osmium carbohydrate polymers, called *osmarins,* have been synthesized[29] and proposed for use as active agents to treat arthritis.[30] This proposal was based on the use of osmium tetroxide for about 50 years to treat human arthritis, mostly in Europe.[31] This treatment is controversial because of the high toxicity of OsO_4. Solutions of OsO_4 are injected into the synovial space of diseased joints. The treatment is longlasting when successful according to Swiss scientists who examined 73 successfully treated patients.[32] Osmium-containing material remained in the joints for as long as 5 years, suggesting a long-term biological effect.[32] The use of the carbohydrate osmium polymers for this purpose was proposed[30] to produce the long-term beneficial effects of osmium deposits while avoiding trauma associated by unselective OsO_4 oxidations encountered after OsO_4 injections. The osmarin polymers are prepared by reacting $Os(OAc)_4$ with glucose.[29] Polydisperse, polyanionic spherical polymers are obtained with molecular weights from a few thousand to a few hundreds of thousands. They are thought to be carbohydrate-solubilized OsO_2 species. Unlike the highly toxic OsO_4, the osmarin polymers have low acute toxicities and does of 1 g/kg have been administered to mice with no mortality.[33] When injected into pig tarsal joints, these polymers bind to all of the tissue surfaces facing the synovial space but cause far less trauma than that observed by injecting OsO_4.

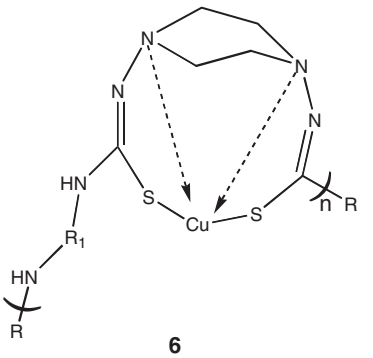
The tin, iron, and osmium examples discussed above allow one to imagine all sorts of possibilities for metal- and metalloid-containing polymers with biomedical applications. In the next section a series of selected biomedical applications of metal-bound polymers is reviewed. This is followed by a short review of some representative small molecules containing metals which have biomedical uses.

III. MISCELLANEOUS POLYMERS

A. Metal Chelation Polymers

As noted in Table 1, copper-containing materials have been utilized as algicides, fungicides, and insecticides. Numerous copper-containing polymers have been formed through the chelation of copper. Donaruma and coworkers described the use of poly(thiosemicarbazide) copper(II) complexes, **6**, as algicides and molluscicides.[34] They showed that this polymer released copper(II) slowly and demonstrated that the product could be used to construct reusable cartridges for schistosomaisis and algae control. Various R_1 groups were studied.

Numerous iron-containing polymers have been synthesized and studied for biomedical application. Here we will look at simple iron(II) chelating polymers developed for medical applications.



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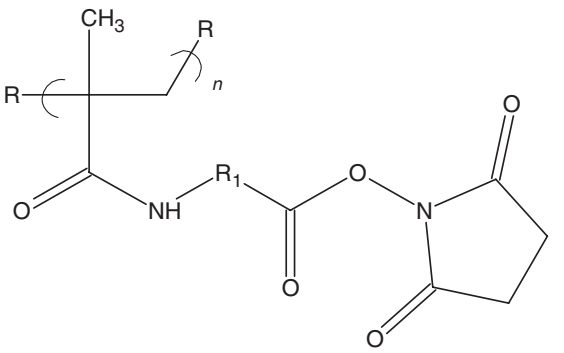
Medical interest in developing iron chelating drugs is due almost entirely to the potential use in removing iron from patients experiencing iron overload.[35–39] There are two major causes of iron overload. They include the over consumption and under removal of iron. The under removal of iron is generally encountered in a disease called β-*thalassemia*, better known as *Cooley's anemia*. Iron poisoning is a problem in small children caused by the inadvertent ingestion of iron-containing materials. Before the use of iron chelation therapy in the 1960s, such conditions were generally fatal. Today good treatments exist involving the use of powerful iron chelating agents. Cooley's anemia is a genetic disorder, rare in the United States but widespread in the Mediterranean area, the Middle East, India, and Southeast Asia. The disease is characterized by an inability to synthesize adequate amounts of the beta chain of hemoglobin. Because excess alpha chains cannot form soluble tetramers, precipitation occurs in red cell percursors leading to their death and to the anemia.

A number of naturally occurring iron chelators exist including desferrioxamine B, enterobactin, and ferrichrome.[40] Each of these bind the iron through various chelating groups, generally oxygen and nitrogen. Because of its low toxicity and high ability to chelate iron, desferrioxamine B (DFO), is now available for commercial use under the tradename of Desferal.[41] While DFO is effective in removing large amounts of iron rapidly, it has a short plasma residence time.

Research in the chelation of iron is sponsored by various Cooley's Anemia Foundations, the National Institute of Arthritis, Diabetes, and Digestive, and Kidney Diseases of the National Institutes of Health. Much of effort has been directly toward mimicking the naturally occurring siderophores such as desferrioxamine by inclusion of hydroxamic acids, catechols, and phenols into a variety of structures. This gives compounds that have vary high stability constants for iron but are nontoxic and active in the human body.

Winston and coworkers did extensive work in this area to develop polymer-containing materials that bind iron.[35–39] These studies illustrate the formation of metal-containing materials, not as a drug itself, but to study the effectiveness of the chelating agent as a potential drug for biomedical use.

Hydroxamic acid is the functional group responsible for binding the iron in DFO. It has been known since 1869.[40] The first hydroxamic acid polymer was made in 1946. A number of hydroxamic acid polymers with controlled spacing have been developed that effectively bind iron with iron binding log *K* values around 30. The structure of one of these is given below, where R_1 is the spacer.



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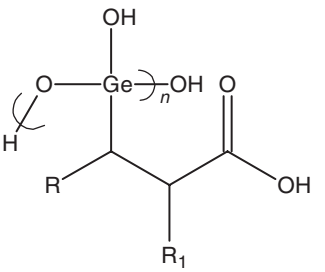
B. Condensation Polymers

A number of metal-containing polymers have been touted as potential anti-cancer agents. This volume contains reviews that describe the most common of these: platinum-, tin-, and ferrocene-containing polymers. However, other metal-containing polymers are also known. Norihiro[42] described the use of oligomeric organogermanium compounds with the following formula, where R and R_1 are H or lower alkyl and *n* is equal to or greater than 2. While the monomer is not active, the oligomer inhibits experimental tumor growths at dose levels of 50–200 mg/kg.



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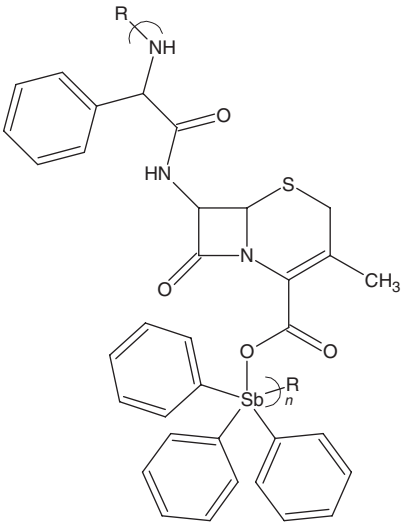
Carraher and coworkers[43] have synthesized a number of group VA-containing polymers that exhibit both anti-tumor and anti-bacterial actively. Polymers formed from reaction with triphenylantimony dichloride and thiopyrimidine exhibit good inhibition of Balb/3T3 cells at concentrations down to 10 μg/mL.

Products from triphenylantimony dichloride and cephalexin show good inhibition of Balb/3T3 cells to 2 μg/mL; polymers from triphenylarsenic dibromide and cephalexin exhibit cells to 50 μg/mL; and those from trimethylantimony dibromide and cephalexin show good inhibition to 15 μg/mL.[44] The structure for the triphenylantimony dichloride and cephalexin product is given below.



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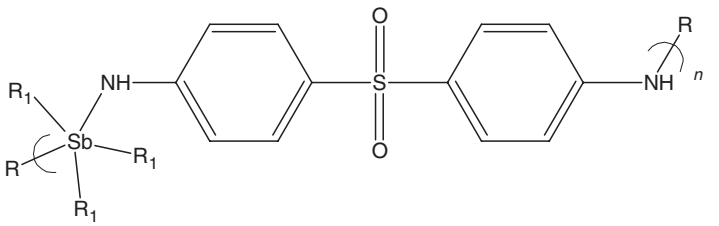
A number of antimony(V) polyamines were synthesized and biologically characterized as antibacterial agents.[45] The products inhibited a wide range of bacteria, including *Actinobacter calcoaceticus, Alcaligenes faecalis, Branhamella catarrhalis, Enterobacter aerogenes, Escherichia coli, Klebsiella pneumoniae, Neisseria mucosa, Psedomonas aeruginosa, Staphylococcus epidermis,* and *Staphylococcus aureaus*. These materials also effectively inhibited HeLa cells at concentrations of about 5 μg/mL. A sample structure is given below.[45]



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IV. SMALL-MOLECULE ANALOGS

There are many examples of current efforts where "small" organometallic compounds are being investigated for biomedical application. Following is a short description of some of these.

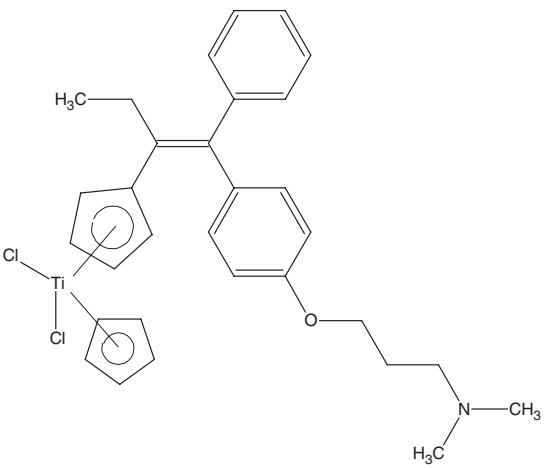
As shown in the present volume, metal-containing polymeric materials are being widely considered as critical agents in the war against cancer. In a similar manner, small molecule compounds are being investigated in the fight against cancer.

Jaouen, Top, Vessieres, and coworkers are utilizing organometallic compounds for treating breast cancer, the most common cancer among women, affecting about one in eight females.[46] The most widely employed drug employed in the treatment of breast cancer is tamoxifen.[47,48] While generally well tolerated, it has some drawbacks. After extensive use, resistance to the drug can develop. It also increases the risks of uterine cancer, blood clotting in the lungs, and is not as effective against hormone-independent tumors that account for about one-third of breast cancers.

The main function of tamoxifen is to block or interfere with the action of estradiol, one of a group of female hormones known as esterogens. Tamoxifen metabolizes forming hydroxytamoxifen that binds to an estrogen receptor preventing the cell from growing and dividing.

Jaouen and coworkers are investigating a number of cyclopentadienyl, Cp, metal complexes for tamoxifen-like activity. They initially focused on titanocene dichloride, Cp_2TiCl_2. While early results showed promise, the tamoxifen-titanocene derivative acted like an estrogen, promoting the growth of breast tumors rather than preventing their growth. The structure of one of these derivatives is given below.

In a similar study, ferrocene-substituted tamoxifens, "ferrocifens," exhibited good antiproliferative effects on several breast cancer cell lines.[49] These ferrocifens are the first drugs that show good activity against both the hormone-dependent and hormone-independent breast cancer cells.



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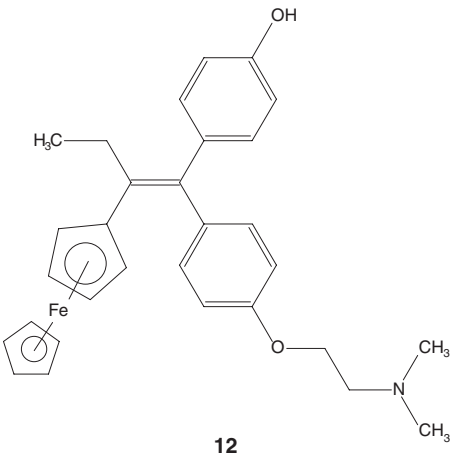
The hydroxyl derivative, hydroxyferrocifen, shown below, also inhibits cell growth in kidney cancer and ovarian cancer cell lines. Live animal tests in rats and mice show that some of the hydroferrocifen derivatives are less toxic than tamoxifen itself.



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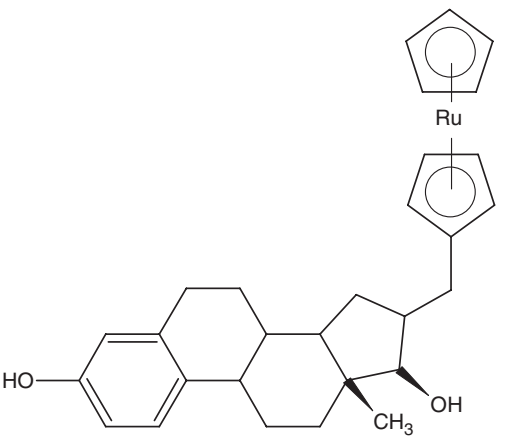
This group also synthesized and studied a series of Ru, W, and Co complexes of 17-estradiol.[50] These modified hormones showed good affinity for the binding at the estrogen receptor site. One of these compounds is illustrated below.

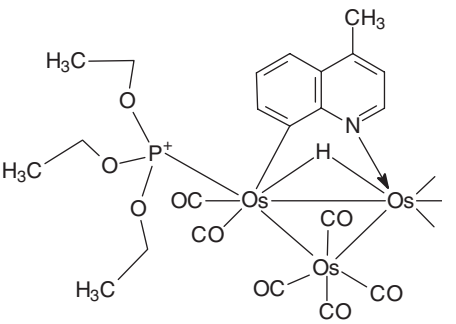


13

Oscella, Rosenberg, Hardcastle, and coworkers have been active in developing a number of metal-containing drugs containing such metals as Co, V, Ru, Pt, and Fe.[51] They have also been developing Os-containing drugs for the purpose of

specifically targeting telomerase. Telomerase is known to be involved in the growth of at least some cancers. For each cell cycle, the telomers that appear at the ends of chromosomes are shortened to ensure that after 50–70 replication cycles the cell ceases to divide and succumbs to programmed cell death or apoptosis. Telomerase allows tumor cells to circumvent this normal process by elongating the length of the telomer ends. In fact, one reason for the efficacy of cisplatin against testicular cancer is believed to be its ability to inhibit telomerase. Unfortunately, cisplatin is not specific to telomerase inhibition, which brings about the occurrence of undesired side effects.

It is important that the non-tumor-specific toxicity be as mild as possible. In search of such a drug, this research group settled on one class of osmium derivatives. These compounds have a nucleobase-like ligand and a phosphine or phosphite ligand capable of imparting water solubility. Both of these components are coordinated to a massive but chemically inert triosmium–nonacarbonylhydrido core. One of these structures is given below. These compounds differ from cisplatin since they do not alkylate DNA. Instead they interfere with the catalytic activity of the telomerase through their steric bulk. Some of these compounds exhibited good telomerase inhibition with little evidence of nonspecific cytotoxicity, suggesting that they interact directly with the enzyme. After several replication cycles, the cells died.



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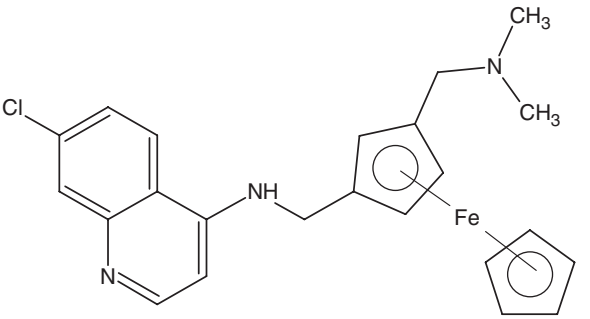
Metal-containing compounds are also being used as selective toxins. Brocard and coworkers have been studying ways to combat the malaria parasite, *Plasmodium* falciparum.[52] While there are drugs such as chloroquine that are able to inhibit the malaria parasite, resistance to these drugs is increasing. Since these parasites need blood, a strategy was worked out that combined the poison, chloroquine, with a bait, ferrocene that contains the iron necessary to produce hemoglobin. The compound called *ferroquine*, **15**, shown below, is much more potent than chloroquine at inhibiting the parasite in mice. It is active against both chloroquine-sensitive and chloroquine-resistant strains of *Plasmodium*. It is also safe and nonmutagenic.



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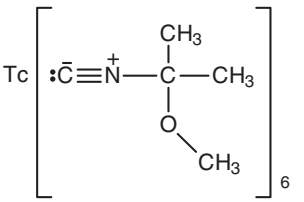
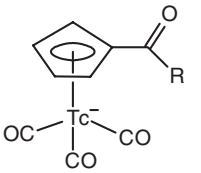
Metal-containing compounds are also used in other biomedical applications, independent of any biological response. Technetium-99m sestamibi, a hexakis(alkyl isocyanide) complex of ^{99}Tc, is one of the most important myocardial imaging agents. It is sold under its tradename of Cardiolite. Its structure, **16**, is given below, where only two of the six connecting ligands are given.



16

Half-sandwich metal-containing compounds are being studied for use in the radiopharmaceutical industry.[53,54] They are made from cyclopentadiene attached to a targeting biomolecule such as a tumor-specific peptide or a small molecule that binds to a central nervous system receptor. One of these, **17**, is depicted below. The half-sandwich complex is robust and lipophilic. Hopefully it will ferry the radioactive label across the blood-brain barrier. Again, emphasizing Tc, Alberto and coworkers have made a number of Tc compounds as possible replacements for Cardiolite. They have also been looking at Tc-containing materials as possible anticancer agents. One such representative structure is **17**. The use of ^{99}Tc in diagnostic medicine takes advantage of its gamma-ray emission. In about 20% of the decompositions, the metastable nucleus decays by internal conversion leading to the ejection of inner and outer-shell electrons that may be used for cancer therapeutic purposes if the radionuclide is near the DNA strand. Current efforts are aimed at looking at binding such to compounds with the DNA bases.



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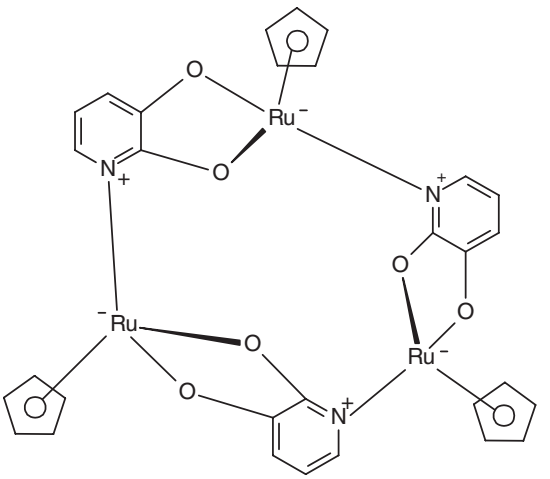
Metal-containing compounds are also being investigated as analytical tools in the biomedical arena. For instance, there is a need to develop quick ways to test for lithium. Lithium carbonate is an important drug in the treatment of bipolar disorder. The therapeutically useful range of lithium concentration in the blood is narrow, so monitoring is important. It is currently done using atomic emission spectroscopy, a time-intensive and costly technique. There are many researchers looking at this problem, and some of them are using metal-containing compounds as the sensing agents. Severin and coworkers are looking at a variety of Ru-, Rh-, and Ir-containing macrocyclic lithium receptors.[55] One such cage structure is depicted below. The oxygen-rich inner core tightly bonds the lithium ion. The group is able to selectively bind lithium ion from aqueous solutions even in the presence of many other metal ions, including solutions saturated with the sodium ion.



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Along with their applications as analytical tools and for complexation within caged arrangements, metals are also being incorporated as the essential sites within a number of caged compounds for biomedical uses. Here, we will briefly describe one of these opportunities.

While MRI (magnetic resonance imaging) provides good imaging resolution, it often has a limited sensitivity. To increase the sensitivity, novel materials that have stronger proton relaxivity and higher MR signal enhancement at low concentration are being studied. Gadolinium chelate compounds are among the most widely employed magnetic resonance imaging, MRI, contrast agents.[56–59] They have been used to assist the assessment of abnormalities such as brain tumors and hepatic carcinoma.

Water-soluble multihydroxyl lanthanoid endohedral metallofulleronols have been synthesized and characterized for use as MRI contrast agents.[60] Endohedral metallofullerenes have been studied since the early 1990s.[61–63] One of the more important and novel electronic properties of these metallofullerenes is the so-called intrafullerene electron transfer from the encaged metal atoms to fullerene cages.[61–63] This allows their use as MRI contrast agents. The most widely studied of these compounds are the Gd endohedral metallofulleronols.[60] Preliminary studies are promising.[60] These materials have high longitudinal and transverse relaxivities for water protons, significantly higher than for corresponding lanthanoid chelate complexes. The large longitudinal relaxivity value is ascribed to the dipole–dipole relaxation together with a substantial decrease in the overall molecular rotational motion. The large transverse relaxivity is attributed to the so-called Curie spin relaxation.

V. SUMMARY

In summary, this chapter intends to convince the reader that metal-containing compounds, both small and large molecules, form the basis for wide-ranging, selective, and exciting contributions to biomedicine. Scientists might well view activities achieved with small-molecule metal-containing compounds as models for analogous polymer-containing materials that may have the advantages of being polymeric. These advantages might include restrictive movement, controlled release, modified solubilities, better specificity, greater stability, wider design of molecular capabilities, slower excretion rates, and multiple attachments. In the chapters that follow in this volume these potential advantages and opportunities are expressed in greater detail.

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