

# **METAL COMPLEXES:** ENVIRONMENTAL AND BIOMEDICAL APPLICATIONS



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**Bentham Books**

# **Metal Complexes: Environmental and Biomedical Applications**

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## **O gvnE qo r ngz gu' Gpxlt qpo gpwnt pf 'Dkqo gf lecnCr r nccv kpu**

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ISBN (Online): 978-981-5238-72-3

ISBN (Print): 978-981-5238-73-0

ISBN (Paperback): 978-981-5238-74-7

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First published in 2024.

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## PREFACE

A century ago, Alfred Werner won the Nobel Prize in chemistry for proposing the octahedral configuration of transition metal complexes and developing the foundation for modern coordination chemistry. His revolutionary research work was of significant importance for the development of the chemistry of metal complexes, which has diminished the border between organic and inorganic chemistry because it is the chemistry of organic ligands and inorganic metal ions. Metal complexes are being utilized in many aspects of human life due to their interesting and unique properties. Today, we find a significant increasing interest in the design of metal complexes for different applications. Some of these are used in multifarious fields of biomedical, energy, and environmental protection and are keenly observed among scientific communities across the globe. Metal complexes play major roles in many subject areas, including biochemistry, therapeutics, diagnosis, catalysis, sensing, and energy conversion. The reason and motivation to propose this book are to design new research plans for graduate students with their basic understanding of coordination chemistry during their undergraduate study.

Chapter 1 discusses the general oxidation states of various metal ions and the introduction to coordination complexes, followed by a discussion on the use of coordination compounds, their syntheses, and their characterization. Chapter 2 discusses the metal complexes synthesized from Schiff bases and N-heterocyclic carbenes. In Chapter 3, the cage metal complexes and their applications are described. Chapters 4 and 5 describe the metal complexes that are used in therapeutics and diagnostics. The application of metal complexes in solar energy conversion is discussed in Chapter 6. Chapter 7 discusses the use of metal complexes in analytical chemistry, and Chapter 8 discusses the use of metal complexes as catalysts in a variety of organic reactions. Chapter 9 discusses the anti-bacterial and anti-fungal applications of metal complexes, and Chapter 10 discusses the metal complexes used as sensors.

This book is intended for undergraduate and graduate students, instructors at the graduate level teaching related coursework, and those working in the diverse fields of biochemistry, biology, organic, inorganic, and bio-inorganic chemistry sciences. The text can prove beneficial for researchers, investigators, and scientists whose works involve organic chemistry, analytical chemistry, and inorganic chemistry, as well as those who are working on radiopharmaceuticals. It can serve as a reference book for P.G. and Ph.D.-level research scholars. All academic research libraries will benefit from having a copy of the book as a reference manual as well.

The writer's own teaching and research experience of over one decade has played a crucial role in designing and writing the book.

Suggestions for improvement of the contents are most welcome from the students and research fraternity, which can be incorporated in future editions.

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**CHAPTER 1****Introduction to Metal Complexes: A Special Reference to Oxidation States**

**Abstract:** There are 90 elements on the earth's crust. Among these, 81 are life supporting and the remaining 9 are radioactive in nature. The human body consists of nearly 3% of metals. Transition metals having partially filled d-subshell can easily accept and donate electrons and hence achieve variable oxidation state. These variable oxidation states enable the modulation of variable redox systems, which are available in biological systems. They can also interact with a wide range of negatively charged compounds. The aforementioned properties of transition metals have sparked the creation of metal-based drug development that holds great promise for medicinal use. Metal-based drugs (metallo drugs) are now used in theranostics, *i.e.*, therapy and diagnosis. Metal-based drugs like oxaliplatin, carboplatin, and cisplatin are being used in the treatment of cancer. Moreover, transition metal-based drugs are also used to treat cardiovascular diseases, inflammation, rheumatoid arthritis, ulcer, diabetes etc. In this chapter, various oxidation states of transition metals of different series of the periodic table are briefly discussed, along with their application in the field of medical science.

**Keywords:** Oxidation state, transition metal, biological activity, metallo drugs, medical application.

**INTRODUCTION**

In the biological system, metal ions have an essential role, such as in disease therapy and diagnosis, which is known as medicinal inorganic chemistry [1]. In the field of bioinorganic chemistry, metal ion-bound components or metal ions are introduced into the biological system for treating a wide range of diseases. Metal has the property of losing electrons easily to form cations that dissolve in biological fluids. Metals exhibit their biological activity in positively charged forms. Proteins and DNA are examples of biological substances that are rich in electrons, whereas metal ions lack electrons. The attractive force between these two opposite charges enables metal ions to interact and bind with biological moieties. A similar concept applies to the affinity of metal ions for other tiny ions and necessary components of life, such as oxygen. Metal plays a wide range of activities, like shuttling electrons and transporting oxygen to different parts of the body. An iron-containing protein named hemoglobin binds with oxygen

molecules and transports them to tissues of the body. In a similar manner, the skeletal framework of the human body is made up of minerals that contain calcium. Metals like Mn, Fe, Zn, and Cu are integrated into catalytic proteins like metalloenzymes, facilitating the chemical reactions necessary for life [2]. In clinical applications, metal complexes are already being used, and further research is encouraged for novel drug development based on metals to be used as anticancer, radio-sensitizing, anti-diabetes, anti-HIV [3], antiparasitic, antiviral, antibacterial, and antibiotic agents. The unique benefit offered by transition metal complexes is their ability to bind with DNA. Transition metal sites are attractive components for nucleic acid reversible identification as they show perfect coordination stereochemistry. Additionally, they exhibit distinct photophysical and electrochemical characteristics, hence enhancing the functionality of the binding agents [4]. Ru and Pt ions, among others, are considered coordination sites for efficient anticancer agents [5 - 7]. There is a great need for the production of cost-effective first-row transition metal compounds as effective DNA binding agents having low cytotoxicity [8 - 10]. Therefore, the focus is generally on studies concerned with some biological application of easily available and cheaper transition metal coordination compounds of the first row, such as Co (II), Fe (II), Mn (II), Cr (III), V(II), and V(IV). These metal ions are also important for the intracellular biological environment of living things. Transition metal-based complexes are important for photochemistry, material production, biological systems, and catalysis. A range of magnetic, optical, and chemical properties are also displayed by them.

## **OXIDATION STATE CONCEPT**

The oxidation state of a transition metal in a complex refers to the left charge after all the ligands are eliminated. Further, the electron bonding pair between the ligands and the central metal ion is exclusively assigned to the bonding partner having more electronegativity, generally ligands [11]. This explanation is more practical in the case of ionic bonding. During redox-active ligand involvement and covalent bonding, the identification of the formal oxidation state is quite complicated, and the assigned oxidation state essentially differs from the actual distribution of electronic charge between the ligand and the metal. Therefore, strongly electronegative ligands like oxygen and fluorine are considered, and those examples are avoided where metal bonding occurs and redox-active ligands are present [12]. It is to be confirmed that the partial computed charges derived from the population analysis should not be compared equally with the formal oxidation number unless the case is the most ionic system [13].

### 3D TRANSITION SERIES ELEMENTS

#### Chromium (Cr)

Chromium is the first metal in this series, possessing a wide range of oxidation states from -2 to +6. Several oxyfluorides and oxo complexes are known in oxidation state (VI) for the binary oxides of Cr (VI). Matrix separation of  $\text{CrF}_6$  is also reported in the literature [14 - 16]. DFT and quantum chemical calculation are evident in the octahedral geometry of  $\text{CrF}_6$  [17].

#### Manganese (Mn)

Seven is the highest attainable oxidation state by manganese and is shown by many oxyfluorides, permanganate ions, and binary oxides.  $\text{MnF}_4$  is the highest oxidation state of manganese known for fluorides [18, 19]. Fluoro manganate complexes exist like  $(\text{XeF}_5)_2\text{MnF}_6(\text{Cr})$  with variable oxidation states [20]. There are experimental attempts and speculation for the preparation of manganese fluorides with higher oxidation states such as  $[\text{MnF}_6]^-$  or  $\text{MnF}_5$ .

#### Iron (Fe)

Experimentally, Fe (VI) is the highest attainable oxidation state in the form of the ion  $[\text{FeO}_4]^{2-}$  and nitride. Here, the central metal ion is hexa-coordinated in the complex [21]. X-ray absorption and Mossbauer spectroscopy are used for the characterization of the latter complex. The octahedral structure with 157 pm bond length in FeN at the terminal position is also supported by DFT calculation [22]. Fe (VI) system in  $\text{FeO}_4$  is confirmed by the low-temperature matrix isolation-IR spectroscopy in addition to the quantum-chemical calculations [23 - 25]. A single stretching band is not seen in the  $\text{FeO}_4$  tetrahedral molecule. Moreover, the CCSD(T) and B3LYP calculations confirm the higher stability of the peroxide complexes [25 - 27]. Oxo complexes are more stable than the binary fluorides. The experimentally characterized iron fluoride with the highest oxidation state is  $\text{FeF}_3$ . The fluoride compound  $\text{FeF}_4$  was reported in 2003 by FTIR spectroscopy and Knudsen effusion spectrometry [28]. A hexafluoro ferrate compound  $\text{Cs}_2\text{FeF}_6$  was reported, which was synthesized in the presence of high pressure and temperature [29].

#### Cobalt (Co)

The highest oxidation state of cobalt is V. A tetrafluoride complex of cobalt,  $[\text{CoF}_4]^+$ , is isolated and characterized by mass spectrometry in the gas phase. It is formed from  $\text{TbF}_4$  and  $\text{CoF}_3$  [30, 31]. The highest attainable oxidation state is IV in

## CHAPTER 2

## Synthesis of Metal Complexes from N-Heterocyclic Carbene and Schiff Base Ligands

**Abstract:** The synthesis of transition metal complexes from N-heterocyclic carbene and Schiff base ligands is discussed in this chapter. A few basic characteristics of water-soluble, N-heterocyclic carbene-based complexes are also described. The increased hydrophilicity of these water-soluble metal complex-based catalysts improves their applicability. Though research based on carbon-carbon coupling reactions is dominating, recent studies demonstrate that water-soluble N-heterocyclic carbene-based complexes can be utilized in the hydrocyanation and metathesis reactions. Compounds formed by the condensation of active carbonyl compounds and primary amines are called Schiff bases.  $RR'C=NR''$  is the general structure of Schiff bases, where  $R''$ ,  $R'$  and  $R$  are hydroxyaryl, hydroxyalkyl, cyclohexyl, alkyl, etc. In this chapter, the synthesis of metal complexes from N-heterocyclic carbenes and the synthesis of Schiff base complexes by ligand exchange, metal exchange, amine exchange, coordinated secondary amine oxidation, in situ methods, and direct synthesis methods are described.

**Keywords:** Catalysis, Metal complexes, N-heterocyclic carbene, Schiff base, Water soluble.

### INTRODUCTION

Water is referred to as the universal solvent because it can dissolve a wide range of substances as compared to any other solvents. It is the most readily available and environmentally friendly solvent for use in the reaction media. The use of water as a solvent is quite interesting for the commercial chemical reaction industry as well as for traditional green chemistry ideas [1]. Replacing volatile organic solvents with water displays economic potentiality in commercial chemical industries. Furthermore, because volatile organic solvents are flammable, explosive, and carcinogenic, they should be handled carefully as they are associated with a number of health risks. The utilization of water has certain disadvantages, like requirements of purification of water and high specific heat capacity, which causes problems in quick cooling, heating, and high distillation energy of water. In addition to its abundance, water also exhibits unique chemical selectivity and reactivity owing to its unique characteristics, such as high

dielectric constant and capability of solvation of polar compounds and salts. According to the principles of green chemistry, a high E-factor (amount of waste generated/kg of final product) and high atom economy are associated with homogeneous catalysts. But, in this case, the recycling of the catalyst is very costly [2, 3].

The use of homogeneous catalysts, which are soluble in water in multi-phase or aqueous medium [4], because a majority of components exhibit low solubility in water, can solve this problem and explore effective methods of chemical reaction. Hence, commercial homogeneous catalysis with water as a solvent is performed on a wide scale, for example, propylene hydroformylation by Shell Higher Olefins Process or Rhne-Poulenc/Ruhrchemie process catalyzed by rhodium (Rh) [5, 6]. The utilization of the N-heterocyclic carbene (NHC) ligand exhibits interesting characteristics like complex stability and high electron donation.

Transition metal complexes based on NHCs are reported in the literature, but there are no reports regarding their commercial application [7]. Substituents in NHCs are applied to influence the electronic and steric characteristics of carbene ligands and to provide stability [8, 9]. Significantly, the substituents are used in the NHCs to enhance the stability through chelate effects [10, 11], chirality induction [12 - 14], and donor strength [15, 16]. In this book chapter, a few examples of metal complexes based on N-heterocyclic carbene, which are soluble in water, are briefly highlighted.

Currently, infectious diseases are spreading and becoming more prevalent globally. This dramatic rise of infectious diseases is harmful both for the world economy and public health. There is a requirement to generate and develop active and advanced drug components. In this context, the application of Schiff bases and their derivatives pharmacologically is valuable. The carbonyl and primary amine condensation products are called Schiff bases. In the year 1864, Schiff bases were reported first by a German chemist, Hugo Schiff [17]. The general structural property of Schiff bases is an azomethine group, which consists of substituents heterocyclic, aryl, cycloalkyl, and alkyl groups. The significant application of metal complexes based on Schiff bases is seen in the material science, biomedical [18], supramolecular chemistry, and bioinorganic chemistry sectors. These complexes are also used as stereospecific active catalysts in transformation and hydrolysis reactions in organic and inorganic chemistry, oxidation, and reduction. Metal bonding with ligands generally takes place by using heteroatoms like oxygen, sulfur and nitrogen. Different types of bonding between metal and ligands are shown in Fig. (1). Metal complexes based on Schiff bases are applied in pharmaceutical, polymerization, and dyes and pigments industries. As a biologically active component, Schiff bases exhibit



versatile pharmacological properties. 2-thiophene and 2-aminobenzoic acid-based Schiff base metal complexes are associated with effective antibacterial properties, which are briefly described in this chapter.

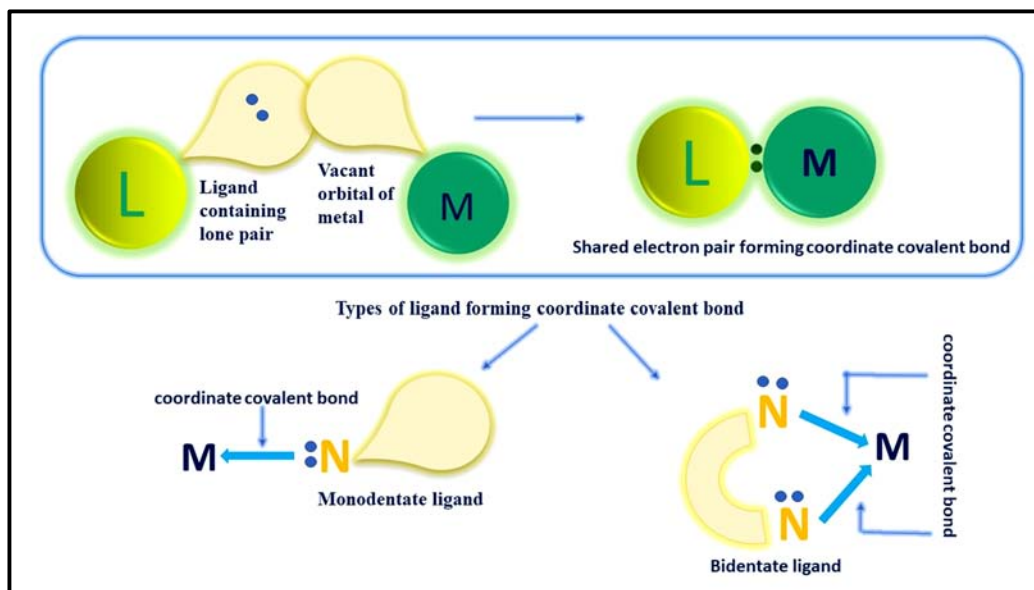


Fig. (1). Mechanism of metal-ligand bonding interaction.

## METAL COMPLEX SYNTHESIS BY WATER-SOLUBLE POTENTIAL N-HETEROCYCLIC CARBENE (NHCS)

The common precursors for N-heterocyclic carbene are salts of azolium, which are soluble in water. They are used as ionic liquids [19, 20] or as organocatalysts [21] in their ionic form. For ionic liquids, it is highly essential that they are immiscible with non-polar solvents, which enable the separation of products in an environment-friendly manner. Regularly utilized N-heterocyclic carbene featured with aromatic or aliphatic substituents increases the hydrophobic characteristics instead of the solubility of water. The synthesis of the ligands by following different paths is discussed here. All the discussed ligands are identified as perfect substrates for the synthesis of N-heterocyclic carbene-based metal complexes.

### Metal Complex Functionalized with Ester or Carboxylate/carbonate

In 1997, the first N-heterocyclic carbene-based complex was reported. In this carbene ligand, two nitrogen-bound carboxylate groups are present [22]. Imidazolium salts are synthesized by introducing ethoxycarbonyl ethyl ester groups. A water-soluble metal complex of Rhodium (Rh) with this ligand was synthesized. The ester group present in this complex undergoes characteristic

## Biomedical Applications of Clathrochelates

**Abstract:** Many different applications for coordination compounds can be found in human life, as they possess numerous interesting properties. Metal complexes consist of a central metal atom or ion known as a coordination center and binding molecules or ions in the surrounding environment called ligands. Metal ions have special qualities that can be used in medicinal inorganic chemistry to create novel medications. Drugs containing metals are useful in many medical applications, such as diagnosis and treatment. Here, we have covered the uses of metal complexes, particularly those involving enclosed metal ions, or cage metal complexes, in the biochemical and medical industries.

**Keywords:** Clathrochelates, Encapsulation, Macrocyclic, Nucleic acid, Radiotherapy.

### INTRODUCTION

Metal complexes, also known as coordination complexes, basically consist of two parts. One is the central metal atom or ion called the coordination center, and the other is the surrounding array of bound molecules or ions, which are referred to as ligands or complexing agents. Coordination refers to the “coordinate covalent bonds” between the ligands and the central metal atom. When metal ions are encapsulated within a three-dimensional cage of macrobicyclic ligand, clathrochelate or cage metal complexes are formed. Cage macrobicyclic complexes are reported as a novel group of compounds having unique physicochemical, physical, and chemical characteristics [1]. Such compounds are the focus of biochemistry and chemistry research due to their unique characteristics of a metal ion, which is encapsulated in a macro polycyclic ligand cavity and isolated from external conditions. The presence of such a complex is integrated with properties like thermodynamics, kinetics, the ability to form molecular structures that are ordered, the ability to exhibit redox reversible reactions, low toxicity, intense coloration, and photo-chemical stabilities. These properties allow clathrochelates to be used as electron carriers, redox reaction catalysts, biologically active species, luminescent probes, dyes, and functional materials [2]. Due to their unique metal cage complex structure, clathrochelates are an attractive research topic in electrochemistry, magnetochemistry, and

photochemistry. The metal cage complex entirely isolates the metal ions from the surrounding environment [3]. The use of these complexes in bioinorganic chemistry is attractive as they provide active sites for model siderochromes and enzymes. Metal cage complexes or clathrochelates are distinct cage compounds with rigidity that are self-assembled selectively from precursors, which are very simple in the presence of mild factors [4]. These factors enable them to act as potential molecular scaffolds for supramolecular, polytopic molecular, and polyfunctional systems synthesis [5, 6]. In addition to the membrane support of metal ions, they are utilized in antioxidants, antiparasitic detergents, anthelmintics, pharmaceuticals, antidotes, MRI imaging agents, and metal ion therapeutics. This chapter attempts to briefly discuss the applications of clathrochelates in medical and biochemical areas.

### **Application of Clathrochelates in Animal and Human Diagnostics and Therapy**

Owing to the unique characteristics of metal cage complexes, there is a possible opportunity for their application in numerous disease diagnostics and therapies. Initially, encapsulated metal ions are separated from their surroundings *i.e.*, from the properties like chemical (thermodynamic and kinetic) and photostability. Anaemia is one of the most common non-contagious diseases of pigs. Drugs with the active substance iron (IV) clathrochelate are used as antianemia drugs [7]. A wide variety of research areas are opened up by the functionalized cage complexes, which enable the delivery of target pharmaceutical and radiotherapeutic agents to specific sites in the living organisms.

### **APPLICATIONS OF NUCLEAR MAGNETIC RESONANCE PARAMAGNETIC PROBES AND CLATHROCHELATES IN MAGNETIC RESONANCE IMAGING**

Magnetic Resonance Imaging (MRI) and Nuclear Magnetic Resonance (NMR) are considered to be significant technologies for the study of biological systems [8]. Nuclear magnetic resonance spectroscopy is the principal source of structural information. Despite its limitations due to the size of the biomacromolecule under investigation, it is still able to determine native conformation in solution [9]. The accuracy of the structural information can be improved by using paramagnetic probes. In 1992, the first report was published on the utilization of metal cage complexes as relaxation agents [10]. Although complexes with regular 3D transition metal bear residual dipolar couplings [11], they are not commonly used as shift agents due to their physical instability and lower magnetic anisotropy, which result in a lower alignment ability and shift of smaller paramagnetic pseudo contacts. Metal cage complexes remove the hindrance caused by non-existent

magnetic anisotropy in iron(II) diamagnetic metal cages, unwanted small coordination for Co(II) low spin complexes, or chemical stability, which prevents them from being utilized as a shifting agent [12]. In recent times, high-spin metal cage complexes based on tris dioximate Co(II) have been reported with trigonal pyramidal geometry [13]. The NMR spectra display extremely large paramagnetic shifts and magnetic susceptibility anisotropy. Moreover, its corresponding cage complexes based on Co(II) trispyrazoloximate pseudoclathrochelate display even larger magnetic anisotropy [14]. The estimated value crossed the value of lanthanide-based paramagnetic tags [15]. These data provide support for the use of metal cage complexes based on transition metals as new contrast agents and paramagnetic labels in biomolecular MRI and NMR. Paramagnetic metal cage complexes can be covalently bonded to proteins by substituting nucleophiles directly. Chlorine atoms ribbed with derivatives of cysteine can generate thiolates in situ [16]. Metal cage complexes with paramagnetic  $Mn^{2+}$  and  $Fe^{3+}$  ions are applied for magnetic resonance tomography as imaging agents [17]. Mn(II) diaminosarcophaginate-based complexes show enhanced relaxation efficiency for protons of water due to their bonding with proteins, which leads to faster translational and rotational correlation times [17]. Researchers can use this platform to investigate parts of living organisms that are rich in proteins.

### **CLATHEROCHELATES BASED ON BORON AND THEIR APPLICATION**

Higher functionalized boron hydrides and boron clusters are robust in chemical scenarios and have low toxicity. Dodecahydro-closo-dodecaborate and its anion derivatives are reported to be radiopharmaceutical precursors that are boron-rich. Additionally, their derivatives are being studied as potential targets of  $^{10}B$ -NCT. This involves a thermal neutron nuclear reaction with  $^{10}B$  stable isotopes. Boron-enriched targets possess certain characteristics necessary for successful treatment with  $^{10}B$ -NCT. A principal obstacle is targeted delivery to the cell having tumor, which permits a lower required dose for therapeutic treatment effectively, thereby protecting the organism from intoxication. Metal cage complexes as molecular scaffolds based on Fe(II) trisdioximate are subjected to ribbed functionalization [18, 19] for providing polytopic and polyfunctional hybrid closo-borato-clathrochelates.

### **RADIOACTIVE CLATHROCHELATE COMPLEX FOR DIAGNOSTICS AND RADIOTHERAPY**

Radionuclides are utilized widely in numerous sectors of medicine as radiopharmaceuticals. Radionuclides are classified based on their therapeutic and diagnostic uses [20]. In Fig. (1), the application of some clathrochelates in

## Application of Metal Complexes in Therapeutics

**Abstract:** The development of therapeutics based on metals has been accelerated owing to the advanced activities of metal ions and their effective role in the field of biology. Therapeutics refers to the branch of science that deals with the treatment of diseases and the action of remedial agents. Metals are vital cellular substances opted by surroundings for numerous activities in various fundamental biochemical functions in living beings. The application of metals and their derivatives for clinical purposes has been practiced for a long time. A well-known drug based on metal, cisplatin, is universally utilized for the treatment of cancer, which chiefly aims at the retardation of genitourinary tumors like testicular cancer. However, drug resistance and certain side effects have restricted the applications of this drug in the medical field. With growing developments in the sector of inorganic chemistry, transition metals play a crucial role as therapeutic agents. Inorganic chemists have enabled the development of numerous transition metal-based complexes linked with required organic ligands, which are applied as therapeutics. This chapter throws light on the drugs based on metal complexes and their applications as therapeutic agents.

**Keywords:** Metal complexes, Metal-based drugs, Medicinal chemistry, Therapeutic applications.

### INTRODUCTION

Metal ions are essential for humans. Deficiency of some metal ions like copper, iron, and zinc can cause various diseases like heart disease, pernicious anemia, growth retardation, *etc* [1 - 3]. Metal ions are required for their applications in medicine and diagnosis. Metals, owing to their reactivity in the presence of organic agents, tunable coordination modes, and redox activity, are potential candidates for biological applications [4]. However, the activity of metals needs strict regulation, and an imbalance in the metal ion concentration can lead to different pathological disorders. In our environment, a large number of biological systems extensively utilize metal ions like Cu, Fe, and Zn, which have important functions that are essential for the normal functioning of living beings [5, 6]. Transition metals like Cu, Fe and Mn are associated with various biological functions such as structure building, catalysis, and electron transfer and also act as active sites of enzymes and proteins [7]. Irregularities in a few of these metals in the usual biochemical processes reflect the growth of different pathological

malfunctions such as cancer [8]. “Trace metals” are required for a number of biological cellular processes in minute but tightly controlled concentrations. A number of researchers have demonstrated significant progress in the use of coordination metal complexes in medicine to treat fatal human diseases. Transition metals show variable oxidation states and can react with some negatively charged molecules. These qualities of transition metals lead to the creation of metal-based drugs for possible pathological applications and unique therapeutic strategies. Advancement in inorganic chemistry opens the door for the application of metal complexes as a therapeutic system. The utilization of coordination metal complexes as therapeutic agents has increased with time. Metal complexes provide diverse activities like anti-diabetic, anti-infective and anti-inflammatory activities [9]. The development of metal complexes based on transition elements in medicine is a constant source of endeavor. Despite their numerous drawbacks and adverse effects, transition metal complexes are nevertheless routinely utilized in clinical treatments and as chemotherapeutic systems [10].

### APPLICATION OF METALS IN MEDICINE

Drugs consisting of metals play a vital role in certain clinical applications that include both diagnosis and treatment [11]. In Fig. (1), the structure of a few metal complexes is demonstrated, which are currently applied for medical purposes [12]. Some of them are as follows:

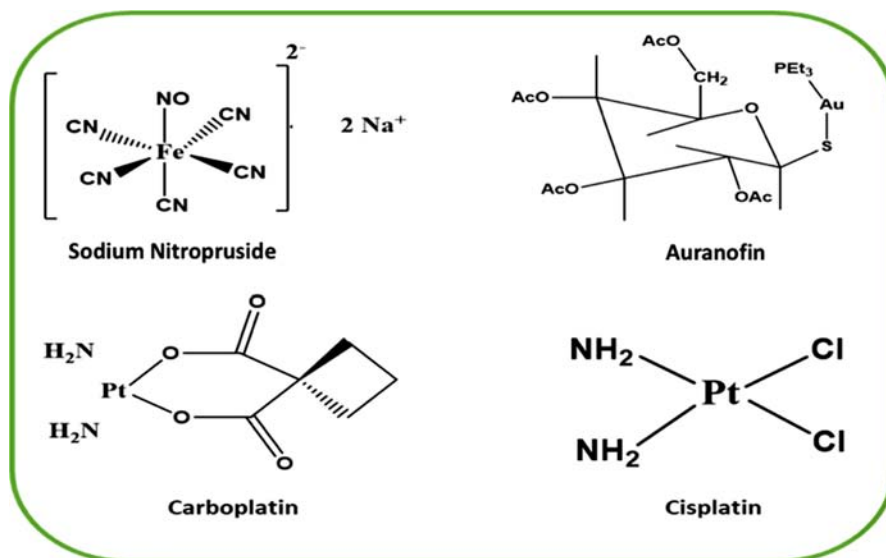


Fig. (1). Structure of different metal complexes used in therapeutics.

- Mercury: It is used as a diuretic and antiseptic [13].
- Manganese and Gadolinium: They are used in magnetic resonance imaging [14].
- Barium: It is used for X-ray diagnosis [15].
- Iron, Vanadium, Titanium and Platinum: Cis-diamine dichloro platinum, iron, vanadium and titanium react with DNA of tumor cells for cancer treatment [16].
- Bismuth: Bismuth subsalicylate is used for the treatment of acidity [17].
- Lanthanum: Lanthanum carbonate is used for the treatment of chronic kidney diseases, and its trade name is Fosrenol [18].
- Copper, Silver, and Gold: These metals with phosphine ligands are used as anti-cancer agents [19].
- Silver is used for the treatment of burn sites and the prevention of infection [20].
- Zinc in the metallic form is used for healing wounds, and in the cationic form ( $Zn^{2+}$ ), it is used for the treatment of Herpes virus [21].
- Lithium: Lithium carbonate is used for the treatment of prophylaxis of maniac depression behavior [22].
- Gold: Complexes of gold are utilized for the treatment of rheumatoid arthritis. Gold complexes interact with the albumin protein and thereby get absorbed by immune cells. Thus, they accelerate anti-mitochondrial effects [23].
- Platinum is used for the treatment of neck and head tumors. These metal complexes are believed to cross-link DNAs in cancerous cells [24].

The structure of a few metal complexes that are applied for medical purposes is given below [12].

### **CHARACTERISTICS OF METAL COMPLEXES**

Metals are capable of linking with ligands in 3D configuration, which enables group functionalization leading to defined molecular targets [25].

- Partially filled d-shells: The magnetic and electronic properties of transition metal complexes are influenced by the variable number of f-shell (for lanthanides) and d-shell (for transition metals) electrons [26].
- Redox activity: Transition metal shows reduction and oxidation reaction [26].

## Applications of Metal Complexes in Diagnosis

**Abstract:** This chapter summarizes some metal complexes that have been used in recent years to diagnose disease states. Gamma scintigraphy, positron emission tomography (PET), and magnetic resonance imaging (MRI) are discussed as diagnostic imaging modalities. With the three imaging modalities, metal complexes are used to image a variety of diseases, including heart disease, brain tumors, and cancer. It has been shown that many different radiometals can be used in the synthesis of coordination compounds for gamma scintigraphy and PET, and each of these will be discussed separately. Besides that, metal complex chemistry encompasses an extensive area of study that analyzes radiometals. The development of coordination compounds for MRI enhancement and radiopharmaceuticals, particularly those that have been used *in vivo* in the case of humans, are described. Essentially, this chapter aims to show that coordination chemistry has made significant progress toward the development of diagnostic imaging agents as a whole.

**Keywords:** Diagnostic imaging agents, MRI, Metal complexes, PET, SPECT.

### INTRODUCTION

Metal complexes are widely used for diagnosis and medical imaging of diseases. In MRI, metal complexes can act as contrast agents, and their emitted radiation can be utilized for radioisotope imaging [1]. Metal-based complexes are utilized for the treatment of diseases like arthritis and cancer. A wide variety of radiometal complexes for imaging study and treatment can be derived from nuclear medicine and can provide a virtual picture of various vital organs. A recent advancement in instrumentation and technology has enabled nuclear medicine to become an integral part of patient treatment and an important therapeutic and diagnostic tool [2]. In 1946, Sam Seidlin *et al.* described nuclear medicine in the Journal of the American Medical Association for the first time. I-131 (iodine) was successfully applied for the treatment of advanced thyroid cancer, as reported by Seidlin [3]. Nuclear medicine had gained much popularity since 1959 when scientists began to research and understand how to use radionuclides to monitor biochemical processes. The Argonne National Laboratory developed  $^{99m}\text{Tc}$  radiotracers in 1964. Currently, this radiotracer is widely used for diagnostic imaging [4]. It is reported that paramagnetic metal complexes can increase the contrast of MRI. Different radio metals and complexes based on them can be used in PET and



gamma scintigraphy. There are many types of non-radioactive metal complexes that are used as contrast agents during MRI. This chapter aims to present the latest developments in the use of metal complexes for MRI, PET, and gamma scintigraphy.

## METAL COMPLEXES PROPERTIES

The formation of imaging agents based on metal complexes requires a correlation of *in vivo* behavior with coordination chemistry. In addition to lipophilicity, charge, stereochemistry, stability, and redox properties are the factors that should also be considered [5]. Depending on the target tissue or organ, the required properties of the metal complexes differ. For example, neutral compounds cross the blood-brain barrier, positively charged ions accumulate inside the heart, and negatively charged compounds are released from the kidney [6]. In general, lipophilic complexes have more uptake in fatty tissues or the liver [7, 8]. To direct complexes to specific receptors, stereochemistry is highly essential. Besides this, one more essential factor is the stability of complexes. Thermodynamic stability of non-radioactive metal complexes can assist in predicting the *in vivo* behavior but cannot determine the *in vivo* stability [1].

## MODES OF DIAGNOSIS

Imaging techniques used in radiology include gamma scintigraphy, PET scans, and MRIs [1]. A nuclide containing radiopharmaceutical emitting gamma radiation as well as single photon emission computed tomography is required for gamma scintigraphy, along with a gamma camera that takes the image of the patient who has been injected with the radiopharmaceutical that emits gamma radiation. PET needs a labeled radiopharmaceutical containing radionuclide, which emits positron *i.e.*, ( $\beta^+$ ), along with a PET camera for capturing the image of the patient. The decay of the positron releases two photons of 511 keV. A PET scanner consists of detectors in a circular array for the detection of those photons specifically that are released in the opposite direction.

Metal complexes are utilized in all three forms of the imaging model, but among all, gamma scintigraphy is widely applied. For PET and gamma scintigraphy, metal radionuclide-labeled radiopharmaceuticals are administered to patients for the diagnosis of diseases like neurological disorders, cardiological disorders, liver and kidney abnormalities, infections and cancer. MRI provides anatomical information but has proven to be extremely accurate in the last few years [1].

## RADIOMETALS REQUIREMENTS FOR IMAGING

There are a few significant points to consider when designing radiopharmaceuticals based on radiometals.

- A radiopharmaceutical's half-life depends on how long it takes to reach its target site. The half-life period of radiometals needs to be long enough for diagnostic imaging and short enough to limit the drug dose to patients [9, 10]. For gamma scintigraphy and PET, the half-lives of the radiometals present in coordination complex-based radiopharmaceuticals range from ten minutes, like ( $^{62}\text{Cu}$ ), to a number of days like  $^{67}\text{Ga}$  [11 - 13]. The radiopharmaceutical should have a shorter half-life when targeting the brain or heart because it reaches the target quickly, whereas tumor-targeted radiopharmaceutical needs a longer half-life because it takes a long time to reach the target [14 - 17].
- Cost and mode of decay: The most common imaging modality in nuclear medicine is gamma scintigraphy, as most radionuclides decay by gamma emission [18, 19]. In the case of PET imaging, positron emission is required for decaying radionuclides [1]. The energy of the gamma photons is essential, and most gamma cameras are designed for capturing specific energy falling in the range of 100 to 200 keV [1]. A quality image cannot be obtained with radionuclide decaying with energies higher or lower than gamma energies within this range.
- Isotope availability

## RADIONUCLIDES PRODUCTION

Nuclear reactors are used to create radiometals that are used as radiopharmaceuticals for gamma scintigraphy or PET. Among them, the most significant one is  $^{99}\text{Mo}$ , which is used to generate  $^{99\text{m}}\text{Tc}$  [20]. As a nuclear reactor can produce large quantities of isotopes at a time, these isotopes are generally affordable. Moreover, other radiometals that are produced from cyclotrons or accelerators are very expensive because from an accelerator or cyclotron, only one isotope can be produced at a single time [21]. Gamma and positron-emitting metal-based radionuclides are shown in Figs. (1 and 2), respectively [1].

## METAL-BASED RADIOPHARMACEUTICALS

### Technetium

Segre and Perrier discovered the longest-living isotope of  $^{99}\text{Tc}$ , among other transition metals, after which  $^{99\text{m}}\text{Tc}$  began to dominate the sector of diagnostic nuclear medicine [1, 22]. Tc radiopharmaceutical is generally applied to take

## Metal Complexes used as Energy Materials

**Abstract:** The globe is currently dealing with an energy crisis, which is very concerning. While energy accessibility and availability have a significant impact on human well-being, the world's dependence on alternative energy sources is growing as a result of the ongoing depletion of fossil fuels. Scientists are developing other sustainable energy sources so that we can meet future energy needs and live in a cleaner environment. In the natural environment, excitation energy transfer is the principal procedure for the light-harvesting procedure. In recent years, transition metal complexes have been used in many applications, such as electroluminescent materials, photoinduced energy transfer materials, energy storage materials, and organic photovoltaic materials. Additionally, these materials provide the potential to behave as carbon sinks, hence providing a chance for more storage materials that are sustainable. For years, the electrochemical behavior of transition metal complexes has been explored in devices that store energy, such as redox flow batteries, supercapacitor electrodes, sodium-ion batteries, and lithium-ion batteries. In this chapter, various transition metals and other metal complexes that are utilized as energy materials are highlighted.

**Keywords:** Energy materials, Electroluminescent, Lanthanum metal complexes, Schiff base, Transition metal complexes.

### INTRODUCTION

To fulfill the demands of the future, an energy material with great performance and efficiency is absolutely necessary [1]. From small button cell batteries to heavy supercapacitors, efficient energy materials have been extensively used. In response to the growing need for energy storage devices, researchers have been exploring, characterizing, and synthesizing materials with high energy storage capabilities. To date, rigorous research has been done on improving and investigating various techniques of storing and converting energy, such as flow batteries, supercapacitors, batteries, and phase change materials [2]. Several studies have involved the synthesis and characterization of numerous materials as well as the development of methods to enhance electrochemical activity by combining other materials in different chemical compositions [3]. In addition to sustainability, energy storage materials must be durable [4]. Among the transition metal oxalates, oxalate anions, which are linked to metal atoms through oxygen

atoms, are efficient energy-storing materials. These are either synthesized artificially or from carbon dioxide by a process called biosynthesis [5]. This shows the need to utilize transition metal oxalates as a method of carbon storage. When carbon dioxide is reduced to  $C_2O_4$  using energy from a source with low carbon emissions, then transition metal oxalates reduce carbon dioxide from the atmosphere significantly [6]. The exploitation of fossil fuels by human activities has incurred a heavy burden on the environment, and as a result, the establishment of an era that was before industrialization is next to impossible [7]. To solve this issue, sustainability is highly required. The utilization of new techniques to produce renewable energy as supplements to conventional energy need to be planned. Renewable sources of energy can provide energy with minimal or no emissions of greenhouse gases and air pollutants [8]. Solar energy conversion systems, among other renewable sources of energy, have attracted researchers and engineers owing to the large availability of solar radiation [9]. The surface of the earth gets electromagnetic radiation of 120000 TW *via* sun rays and will keep getting this amount until the existence of the Sun [10]. In the year 1839, A.E. Becquerel was the first to identify the photovoltaic effect [11]. This type of device produces electrical energy without any other emission from solar energy [12]. Solar photovoltaic devices, from a single hour of generation of electricity, can cause a reduction in emissions of carbon dioxide by one thousand tons [13]. The development of hybrid materials, organic and inorganic materials, has led to many advances in devices with advancements in photovoltaics [14]. In comparison to inorganic photovoltaic devices, organic photovoltaic devices are less toxic and economical and can be easily reproduced [15]. Moreover, metal complexes based on Schiff bases having optoelectronic characteristics can also be applied as photovoltaic materials owing to their easier production, cost-effectiveness, electrical conductivity, non-toxicity, and biodegradability [16]. In this chapter, various metal complexes utilized as energy materials are briefly discussed.

### **LANTHANIDE METAL COMPLEX AS ELECTROLUMINESCENT MATERIAL**

Organic light-emitting diodes generally contain metallic layers and multiple organic layers on a glass plate that is covered with an ITO [17]. Various types of techniques are utilized for the deposition of this layer, like spin casting from solutions, Langmuir-Blodgett deposition, thermal evaporation, and plasma deposition [18]. Within the operating environment, all layers remain chemically stable and photooxidation or oxidation-resistant [19]. Furthermore, the optical characteristics of each layer should be taken into account when designing device structures. The output of light with higher efficiency requires layers of the device to be highly transparent for the radiation that is emitted [20]. Electroluminescent devices consist of multiple layers or single-layer structures except for cathode or

anode [21]. For injection and charge transfer improvement, additional layers are integrated with an organic light-emitting diode in place of a single-layer structure [22]. A device with multiple layers contains a cathode, electron transport layer, emission layer, hole transport layer, and anode [23]. Hole transport layers majorly enable hole transportation within the highest occupied molecular orbital (HOMO) level and within the lowest unoccupied molecular orbital (LUMO) electrons, which might be transported by a lesser degree [24]. Hence, the hole transport layer material possesses high mobility of the hole [25]. Moreover, such materials should have the property of low ionization potential, which can assist them in efficiently injecting holes out of the anode [26]. In comparison to the emission layer, the excitation energy level should be higher for the hole transport layer for the confinement of excitons in the emission layer.

Eu complex first exhibited red electroluminescence by utilizing a complex of  $\text{Eu}^{3+}$ , *i.e.*,  $\text{Eu}(\text{TTA})_3$  (TTA = thenoyltrifluoroacetone) [27]. Using a close space sublimation method, it was demonstrated that light-emitting diodes are composed of organic materials [28]. On utilizing complex  $\text{Eu}(\text{DBM})_3(\text{phen})$  (DBM: dibenzoylmethide; phen: 1,10-phenanthroline) as an emitting material, red electroluminescence was reported to be comparatively brighter [29]. With the addition of phenanthroline as a ligand, the coordination number of Eu ion is saturated, and the stability, volatility, and intensity of fluorescence of the Eu complex are improved [30]. Sharp emission bands are observed in the spectrum of electroluminescence of the Eu complex [31]. Additionally, platinum-based complexes present unique photophysical properties in which they can form excimer emission in which a single emitter produces broad white light emission and also narrow band emission in which a rigid, tetradentate molecular structure can produce narrow light emission in selected cases [32].

By vacuum co-deposition, Eu chelate complexes are formed, and their application to organic light-emitting diodes is studied by researchers [33]. Er and Yb are utilized in optoelectronic devices as active elements owing to their transitions in intra 4f at 1530 - 1560 nm [34]. At 1530 nm, Er ion infrared emission is interesting, particularly for optical fiber communication, owing to the emission of high bandwidth capacity and narrow line width at room temperature. A neodymium-based organic complex as an organic light-emitting diode was reported by O'Riordan and co-workers [35]. Klink and team produced Nd complex functionalized with lissamine [36]. A similar Nd complex functionalized with lissamine was produced at 890nm, as reported by Slooff and team [37]. An organic light-emitting diode containing Er was fabricated by Curry and Gillin [38]. The emitting material here was Er-tris(8-hydroxyquinoline) complex. Owing to the 4f transition of  $\text{Er}^{3+}$  ion at room temperature, sharp emission was observed at 1540 nm. An infrared emitter based on Er,  $\text{Er}(\text{acac})_3(\text{phen})$  complex was

## Metal Complexes used in Analytical Chemistry: A Special Focus on the Detection and Determination of Metal Ions

**Abstract:** Analytical chemistry is used to detect the analytes by using various analysis methods. Quantitative and qualitative analysis can be done using this approach. Coordination compounds play a key role in our environment. They are used in almost every branch of the biomedical field. An overview of the applications of metal complexes in analytical chemistry is provided. This topic covers different types of complexes and the ways they are used for analysis purposes. Some miscellaneous applications in analytical chemistry are also covered in this chapter. Moreover, different types of precipitants, volumetric reagents, indicators, and solvent extraction reagents are also included in this chapter.

**Keywords:** Analysis, Analytical chemistry, Metal ion, Metal complex, Method, Precipitant.

### INTRODUCTION

In analytical chemistry, information about the composition and structure of matter is obtained, analyzed, and communicated. The development and application of novel reagents and processes for the identification of trace elements in our surroundings are the focus of contemporary analytical chemistry. It also involves ensuring the safety and quality of food, pharmaceuticals, and water to diagnose diseases. Recently, various analytical methods like chemical tests, flame tests, gravimetric analysis, and volumetric analysis can be used to determine the analytes. Modern analytical chemistry is dominated by instrumental analysis, which includes spectroscopy, mass spectrometry, thermal analysis, electrochemical analysis, separation techniques, hybrid techniques, *etc.* Almost all branches of analytical chemistry use metal complexes. The unique factors of metal complexes, like ligand field stabilization reaction kinetics, conformational changes, *etc.*, enhance their importance in analytical fields, which include gravimetric and titrimetric analysis for liquid-liquid extraction and various types of chromatography. Generally, to determine the trace metals, spectrometry techniques are used, while the electroanalytical methods are recognized as a

powerful technique for the multi-element determination at the trace and ultra-trace level. Dyes are used as titration indicators in analytical chemistry due to the presence of chromophores and auxochromes. This chapter briefly surveys the many different uses of these compounds .

## **INTRODUCTION OF METAL IONS FROM VARIOUS SOURCES IN THE ENVIRONMENT**

Metal ions play a key role in our environment. In plants, animals, and humans, metal ions play an essential role in maintaining longevity.

### **Alkaline Earth Metal**

Due to high electrical and thermal conductivity, the alloy of Beryllium (Be) with copper or nickel is used to make gyroscopes, springs, spot-welding electrodes, *etc.* Other beryllium alloys are used as structural materials for high-speed aircraft, missiles, spacecraft, and communication satellites. Beryllium is also used in nuclear reactors as a reflector or moderator of neutrons. Beryllium and its compounds are poisonous and carcinogenic. The inhalation of beryllium dust or fumes can cause berylliosis, an incurable inflammatory condition of the lungs.

### **Transition Element**

Cobalt (Co), nickel (Ni), and chromium (Cr) are used in prostheses due to their high mechanical stability and superior biological compatibility. Radioactive cobalt-60 is used to treat cancer and preserve food. One of the most abundant elements in the earth's crust, titanium (Ti), is widely used in the cosmetic industry due to its bioactive properties. Both Copper (Cu) and zinc (Zn) are essential for plant growth and are needed for improving crop productivity. Zinc (Zn) cations and Zn complexes are also anti-/pro-oxidants and antimicrobials.

Aluminum (Al) and its ionic form,  $Al^{3+}$ , can be toxic to plants growing in acidic soils (pH 5.5), limiting production by negatively affecting root growth, nutrient uptake, and other metabolic processes. Cadmium (Cd) was used to electroplate steel and protect critical components of airplanes and oil platforms from corrosion. Cd absorbs neutrons; therefore, it is used in rods in nuclear reactors to control atomic fission. Cd, when present at high concentrations in soil, is toxic to all organisms. The toxicity of Cd causes birth defects and cancer.

Gold (Au) nanoparticles are used as industrial catalysts. The illegal extraction of gold and silver is commonly associated with mercury (Hg), a toxic metal that poisons the environment. Indium (In) is used to make indium tin oxide (ITO), which is an important part of touch screens, flatscreen TVs, and solar panels as it

conducts electricity, bonds strongly to glass, and is transparent. Indium nitride, phosphide, and antimonide are semiconductors used in transistors and microchips because of their low friction. Indium has also been used to coat ball bearings in Formula 1 racing cars. It has no known biological role as it is toxic. It can affect the development of an embryo if more than a few milligrams are consumed. The use of thallium (Th) is limited as it is a toxic element. Th oxide is used to produce special glass with a high index of refraction.

### **Metalloid**

Electronics companies use antimony (Sb) to produce some semiconductor devices, such as infrared detectors, diodes, and flame-retardant materials. Other materials such as paints, enamels, glass, and pottery are also produced. An alloy of lead and antimony is used to make batteries and cable insulation. It has no biological role as it is toxic in nature.

The benefits of metal ions are also accompanied by some drawbacks. So, to utilize metal ions for our benefit and to overcome the limitations of metal ions, it is necessary to detect the metal ions. In the following sections, we have summarized various detection methods used to detect metal ions.

## **ANALYTICAL METHODS FOR THE DETECTION OF METAL IONS**

### **Precipitation Analysis**

Precipitation analysis is a technique used for the separation of ions in an aqueous solution by using a reagent that precipitates one or more of the ions while leaving other ions in the solution. The determination of inorganic cations and anions by precipitation is accomplished by the use of coordination compounds in analytical chemistry. Here, we look for a few properties, including low solubility in water, freedom from precipitating or sticking, good filtering ability, stability to the stages of washing and drying without changing weight too much, and reproducing features like composition with Tschugaeff's dimethylglyoxime [1].

### ***Reagents for the Detection of Metal Ions***

This analysis can be explained by several examples of reagents, which include:

1,10-Phenanthroline, also known as phenanthroline, gives a dark red color to ferrous. It can be used to detect and measure the color of iron; the resulting complex is shown in Table 3.  $\text{Iron(1,10-Phenanthroline)}_3$  is stable in acidic medium. It is also suitable to trace color measurements of iron and to estimate iron in wine, leather and other biological materials.



## Metal Complexes in Catalysis

**Abstract:** For a long time, research based on versatile novel catalysis processes utilizing coordination compounds and transition metal ions has witnessed many significant discoveries and developments. This chapter presents new directions and themes for the development of coordination compound-based catalysts in the future. This fundamental field comprises both homogeneous and heterogeneous systems, including a variety of reactions. These types of catalysts exhibit the activation of saturated inert molecules like hydrogen and also involve a wide range of addition reactions like Ziegler-Natta type polymerization, acetylene hydration, carbonylation and annulation reaction, isomerization, hydrogen peroxide decomposition, hydrosilylation, allylic alkylation, hydrocyanation process, hydrogenation reaction, hydroformylation reaction, olefins catalytic oxidation, olefins hydrogenation, *etc.* The aim of this chapter is to discuss a few applications of catalysts based on transition metal compounds.

**Keywords:** Catalysis, Enantioselectivity, Schiff base complexes, Transition metal.

### INTRODUCTION

Coordination complexes based on transition metals have significant catalytic activity in a wide range of biological, heterogeneous and homogeneous reactions like unsaturated molecules *i.e.*, isomerization of olefins and addition reaction, reactions of saturated molecules like hydrogen, substitution reactions, hydrolytic reactions, and oxidation-reduction processes [1 - 4]. This unique, versatile catalytic activity is supported by certain factors, including:

- By coordinating with ligands, transition metals can stabilize a wide range of ligands, including alkyl groups and hydrogen. Hydrogen is a versatile ligand like allyl groups, polyenes, acetylenes, olefins, *etc* [5].
- Transition metal-based complexes are comparatively stable and reactive, especially low spin  $d^8$  and  $d^7$  complexes, owing to their structural and electronic characteristics, which show high intensity of reactivity nearly associated with carbanions, carbenes, free radicals or reactive intermediates.

Transition metal-based catalysts have been recognized as crucial instruments in the most recent developments in synthetic organic chemistry because of their potent ability to change a broad variety of molecules [6]. Chemistry has greatly enhanced with the development of supporting ligands, and this has an impact on the stability and reactivity of metal complexes in the coordination environment. Many organic compounds like carbenes, ethers, amines, and phosphines are applied as supportive ligands for organic elements of p-block in the periodic table [7]. With the arrival of N-heterocyclic carbenes in the year 1991, they have been used as strong sigma donors for several transition metals, enabling novel molecular modifications and effective catalysis [8]. For researchers, it is a challenging task to create new supporting ligands that offer distinct steric and electronic environments and molecular functionalities to expand the chemistry of catalysts based on transition metals. Nowadays, metalloids and main group metals have emerged as novel categories of supportive ligands for transition metals. Unlike organic ligands, these types of complexes exhibit symbolic coordination and electronic characteristics arising from low electro-negativity and Lewis acidity. The cooperative reactivity and redox activity of these complexes are fascinating. They carry high potential for the exploration of novel reactivity of catalysts based on transition metal for effective molecular modifications. The bond between the metalloid element and transition metal is generally not stable and difficult to form, even though it is a coordination or covalent bond. Hence, the formation of such novel complexes, which are easily accessible and associated with unique catalysis and desirable stability, is a challenging task. However, due to the diversified applications of metal complexes, they need to be explored. Some of the applications of metal complexes are shown in Fig. (1).

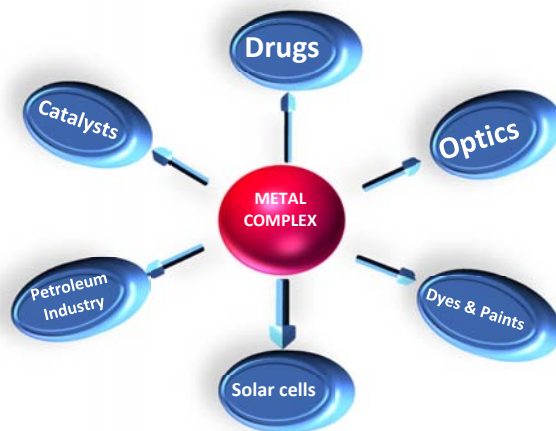
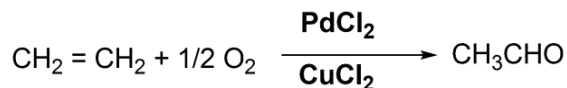


Fig. (1). Some applications of metal complexes.

## OXIDATION PROCESSES

### Wacker Process

Hoechst and Wacker cooperatively developed the Wacker process. The process involves the oxidation of ethylene with palladium chloride as a catalyst to form acetaldehyde [9], as shown below. On an industrial scale, this reaction was recognized as the first homogeneous catalysis associated with organopalladium chemistry [10].



Wacker process [9]

### Olefins Epoxidation Reaction Mo(VI) Complex Catalyst

Epoxides are the oxidation product of olefins. They are heterocyclic compounds made up of three atoms of oxygen and two atoms of carbon. This kind of material has a highly reactive nature. They involve the reaction of ring opening and closing accompanied by nucleophile attachment. These types of reactions are utilized for the formation of medications like steroids, antibiotics, and hypertension. In the process of olefins epoxidation, the most commonly utilized oxidant is hydrogen peroxide. Epoxide synthesis can be accomplished in several ways, but the most famous is propene epoxidation. It is reported that the production of propene oxide is approximately six million tons per year.

### Olefins Epoxidation Asymmetrically in the Presence of Oxidant Hydroperoxide and Titanium Complex

Complexes based on salen ligand and titanium have solved the everlasting problem associated with catalysis processes of homogeneous epoxidation by the selective oxidation of nonconjugated terminal olefins by hydrogen peroxide. For unfunctionalized olefins, epoxidation enantioselective titanium complex along with ligand salen consisting of phenyl substituents at C3' and C3 position is an effective catalyst in the presence of hydrogen peroxide in an aqueous medium [11]. Additionally, the epoxidation process was stereospecific. Research on the application of organometallic catalysts for the process of asymmetrical epoxidation was conducted by Sharpless [12]. Epoxidation of allyl alcohol takes place in the presence of oxidants tert-butyl hydroperoxide, derivatives of tartaric acid, and tetravalent titanium isopropoxide [12].

## Antibacterial and Antifungal Applications of Metal Complexes

**Abstract:** Metal ions have an extremely important role in preserving the longevity of living organisms. Humans can suffer from a variety of health issues when particular metal ions are deficient, including growth retardation from a zinc deficiency in the diet, pernicious anemia from an iron deficiency, and infantile heart disease from a copper deficiency. Antibiotic resistance is becoming more severe every day, posing a growing risk to public health. The creation of innovative medications with improved efficacy and new mechanisms of action is urgently needed in this situation. Inorganic compounds, specifically metal complexes, have a significant role in novel metal-based drug development. Owing to the inclination of the scientific community towards designing new metal complexes as diagnostic agents and drugs, a new branch of chemistry was developed, which is known as inorganic medicinal chemistry. In this chapter, metal complexes used as anti-fungal and anti-bacterial agents are discussed.

**Keywords:** Antifungal, Antibacterial, Antibiotics, Medicinal chemistry, Metallo drug.

### INTRODUCTION

Metal ions have an important part in biological processes and are related to applications in inorganic chemistry for disease diagnosis and treatment [1]. In the field of bioinorganic chemistry, components of metal ion binding or the introduction of metal ions into a biological process for treating diseases is one of the important areas of research [2]. Biomolecules such as DNA and protein are electron-rich, while metal ions are electron deficient. Owing to the electrostatic attractive force between the charges, metal ions prefer to interact and bind with the biomolecules [3]. The same theory is used to explain the affinity of metal ions towards small ions and molecules like oxygen, which are essential for the survival of living organisms. The metal complexes carry out a variety of tasks, including catalysis, electron shuttling, and oxygen transport. For instance, iron present in the hemoglobin binds to oxygen and transports oxygen to different tissues of the body. In a similar manner, minerals containing calcium are the basis of the structural framework of living organisms. Metalloenzymes and proteins

containing metals such as iron (Fe), zinc (Zn), copper (Cu), and manganese (Mn) facilitate a variety of chemical reactions necessary for life.

Metal complexes are also known as an efficient choice for antifungal and antibacterial agents. Significant improvement in the antimicrobial resistance of microorganisms towards generic medicines is a subject of significant concern [4]. Antimicrobial-resistant bacteria can be effectively combated by metal and metal-based antimicrobial compounds. In contrast to organic antibiotics, which act on specific targets on biochemical pathways like replication, transcription, translation, and enzymatic reaction, metals are reported to target multiple cellular sites such as cellular membrane, genetic material, and reactive oxygen species-mediated cellular pleiotropic effects on microbial cells [5].

Elements showing antifungal or antibacterial properties are shown in Fig. (1) below.

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Fig. (1). Periodic table of elements showing antifungal/antibacterial characteristics.

In the last few years, clinical scientists have started developing novel transition metal-based antimicrobial and antifungal drugs with remarkable success and great promise. In this chapter, an overview of the activities of metal complexes against various fungi and bacteria is presented.

## CHROMIUM COMPLEXES

Chromium complexes based on Schiff base are investigated due to their antimicrobial effect, but the significance is not high. Chromium (III) complexes were applied against *P. aeruginosa* (Gram-negative), *E. Coli*, and *S. Aureus* (Gram-positive) bacterial strains, but their activities were slower in comparison to

ampicillin, which is a standard drug. There are certain reports on Fe (III) and Cr (III) Schiff base complexes based on thiophene. Antimicrobial activities of the synthesized complexes were checked against strains of bacteria like *E. Coli* and *B. Subtilis*, as well as against strains of fungi like *C. albicans* and *Saccharomyces cerevisiae*. It is suggested from the phenomenon that metal ion polarity is decreased by the overlap of ligand and metal orbitals, as a result of which the positive charge of the metal ion is partially shared with the donor groups, and also electron delocalization occurs over the whole molecule [6 - 12]. There are some reports on the antimicrobial activities of chromium (III) complexes [13].

### **MOLYBDENUM COMPLEXES**

Few investigations on the antimicrobial properties of metal complexes based on molybdenum have been reported. A series of molybdenum (VI) complexes demonstrated antifungal properties against *A. niger* and *A. flavus* and antibacterial properties against *K. pneumoniae*, *S. aureus*, and *P. aeruginosa*. The final outcome was that these compounds' activities against bacteria strains were found to be similar to ampicillin and also active against *K. pneumoniae* and *P. aeruginosa* [14 - 20].

### **MANGANESE COMPLEXES**

Several manganese complexes have been synthesized by using manganese chloride with antibacterial drugs such as oxolinic acid, 1,10-phenanthroline, and enrofloxacin as ligands [21 - 23]. These complexes are active against two gram-negative bacterial strains, *E. Coli* and *X. campestris*, and three gram-positive bacterial strain complexes, *S. aureus*, *B. cereus* and *B. subtilis*. As compared to the traditional drugs, ciprofloxacin complexes displayed effective activities against the gram-positive bacterial strains *S. Mutans* and *S. Aureus* and gram-negative bacterial strains *V. harveyi*, *V. cholerae*, *V. alginolyticus*, *P. aeruginosa*, and *K. pneumoniae*. There are certain reports based on the antiparasitic and antibacterial effect of complexes based on Mn(I) tricarbonyl with clotrimazole, miconazole and ketoconazole ligands [24, 25]. These manganese complexes were used against gram-negative bacterial strains such as *Y. pestis*, *Y. pseudotuberculosis*, *P.aeruginosa*, and *E.coli* and gram-positive bacterial strains such as *E.faecium*, *E.faekalis*, *S.aureus* and *S.epidermidis*. Luteolin complexation with Mn(II) was performed to form the Mn(IV) complex. The complex and ligand were applied against various microbial strains like *P. aeruginosa*, *L. monocytogenes*, *S. aureus* and *E. Coli*. Carbonyl complexes based on manganese-containing isocyanide ligands were reported to be applied against *E. Coli* [26 - 31].

## Metal Complexes as Sensors to Detect Analytes

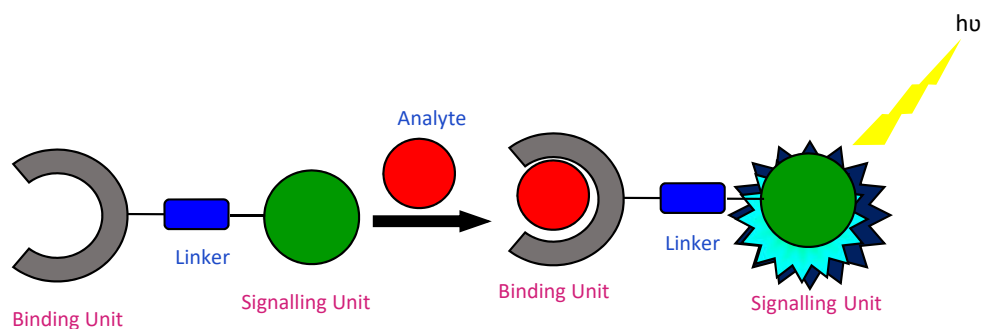
**Abstract:** Luminescent molecular chemosensors are designed in a way that sensing arises due to the binding of the analytes to the receptors. Here, the analyte binds to the metal-based receptor as a ligand. Researchers all around the world have been working to build these chemosensors to detect various analytes. These are used in many different disciplines, including biology, physiology, chemistry, and environmental science. Following the receptor-analyte engagement, an intercomponent process such as energy transfer or electron transfer occurs, which specifically modifies luminophore release and signals the recognition event. Because of their low detection limit and ease of use, the fluorescence probes are recognized as performing unique detection methods. This chapter discusses metal complex sensors for cation and anion detection.

**Keywords:** Anion sensing, Cation sensing, Luminescence, Metal complexes, Phosphorescence.

### INTRODUCTION

Chemosensors have attracted a great deal of interest in scientific communities owing to their diversified application in the fields of environmental science, medicine, biology and chemistry [1, 2]. Among the sensors, fluorescent probe chemosensors have earned attraction because of their versatility, cost-effectiveness, sensitivity, high selectivity and ease of synthesis [2, 3]. Apart from organic fluorescent probes, the synthesis and design of the metalloreceptors are also in trend because of their selectivity towards anions and cations [4]. Among metals, platinum-based luminescent complexes are often studied because of their unique photophysical characteristics [5]. The development and design of luminescent chemosensors based on transition metal complexes depend on their attractive photophysical characteristics like large Stokes shifts, high luminescence quantum yields, and long lifetime [6 - 9]. Furthermore, the ligands' luminescence properties and chemosensory nature can be altered by slight structural alterations. For metal ion sensing to be implemented, one must have a thorough understanding of host-guest chemistry as well as an interest in chemical and biological sensing. There are a number of reports based on the utilization of transition metal complexes for the chemosensing of metal ions having Pt(II), Ir(III), Re(I), and Ru(II)-based complexes. The literature has also revealed that

three-dimensional metal complexes are used for the chemosensing of cations [10 - 15]. Many obstacles arise in the utilization of chemosensors. The major problem is that water is the traditional media for most of the applications, and sensors that are soluble in water are difficult to achieve [16]. Another obstacle is detecting organic molecules and anions [17]. Molecular sensors are classified according to the variety of interactions of receptor-anion, like metal ligand-interaction or hydrogen bonding [18]. In general, metal-ligand interaction is stronger than electrostatic interaction. Here, for substrate recognition, the interaction that needs to be explored, like electrostatic attraction and hydrogen bonding, are not strong enough to provide efficient binding in water [19]. Anion sensor design requires well-organized planning based on a modular or multicomponent approach [20]. For this purpose, light-emitting fragment fluorescent chemosensors are linked together, and these chemosensors have gained attraction owing to their versatile applications in various sectors [21]. Anionic substrates can be identified by interacting coordinately, which is stronger in comparison to electrostatic interaction [22]. Cations are smaller than anions; hence, an electrical charge is spread more over anions as they have a greater surface area, thereby allowing the electrostatic interaction with the receptor bearing the opposite sign of charges, which is less intense in comparison to those of cations [23]. Anions can act as ligands for metal ions, thereby forming complexes of distinctive stability that are bonded together by coordinative interaction. As a result, their nature change to covalent from electrostatic, depending upon their metallic properties. Hence, metal complexes can be applied as a wide variety of anion receptors. The metal site needs to be unsaturated. As a result, some of the coordination centers remain empty and can thus be occupied by anions for providing reversible fast analyte binding, which is a primary requirement in the recognition procedure. The detailed mechanism of a sensor to detect the analytes is shown in Fig. (1).



**Fig. (1).** Schematic presentation of a sensor to detect analytes.



## CHEMOSENSORS BASED ON METAL COMPLEXES

Generally, the charges of transition metal complexes are significantly different in comparison to their counterpart ligands due to the following chemical characteristics [10].

- Charge: The charge of metal complexes is controlled by the coordination sphere, which can be neutral, anionic or cationic.
- During bond-making with the ligands, selective and strong interaction between ligands and metals suggest distinct coordination shapes and geometries.
- Acidic properties: Lewis acid property of the metal ions causes polarization
- Half-filled d-orbitals: Transition metal orbitals contain varying numbers of d-electrons, which result in impressive electronic characteristics of transition metal complexes.
- Redox reactivity: Many metal ions can perform one-electron redox reactions. But, few of them, like Cd (II) and Zn (II), are inactive to redox reactions, which decreases the charge transfer characteristics of the complexes based on these particular metal ions.

The role of the metal complexes as fluorescent chemosensors depends on the behavior of both ligands and metal ions. Every metal site has a particular geometry depending upon the number of valence d-electrons and is associated with ligand field stabilization energy (LFSE) [24]. When metal ions in their desirable oxidation states, like  $\text{Fe}^{3+}$  and  $\text{Fe}^{2+}$ , bind with strong ligands, then distorted octahedral and octahedral geometry is preferred. Similarly,  $\text{Cu}^+(\text{d}^{10})$  has no geometrical preferences based on LFSE, whereas  $\text{Cu}^{2+}(\text{d}^9)$  prefers tetragonally elongated octahedral, square pyramidal, and square planar geometry. Depending on the metal ions and ligands, complexes are capable of further interacting with other metal ions, and hence, the resulting complexes' characteristics can be modified significantly. The design of metal complexes-based fluorescent sensors depends upon the selection of chromophores along with the location and nature of the receptor. Unlike organic probes, the phenomenon of signaling *i.e.*, turn off and turn on in metal complexes, is not simple owing to the occurrence of different charge transfer procedures like spin-orbital coupling, electron transfer process, metal-ligand charge transfer, intra-ligand charge transfer, and ligand-to-ligand charge transfer [25]. Metal complexes and coordinated water molecules or anions, along with the ligands, increase the solubility of metal complexes in water.

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