Chapter I

INTRODUCTION

General Introduction

Currently, the field of Coordination chemistry remains a highly active research area within inorganic chemistry, focusing on the interaction between organic or inorganic ligands and metal centers. This scientific discipline encompasses a diverse range of coordination compounds, which find practical applications in various fields such as dyes, colors, nuclear fuels, catalysis, photography, toxicology, bioinorganic chemistry, medicine, ceramics, materials science, and toxicology. The incorporation of different types of ligands into coordination complexes has allowed for their utilization as biocides, catalysts, NMR shift reagents, and DNA binders[1, 2]. Additionally, advancements in analytical instrumentation and the synthesis of a broad spectrum of coordination compounds have reinvigorated interest in chemical reactions. Consequently, inorganic chemists have made substantial progress in modifying the concept of chemical bonding[3]. Coordination chemistry is a well-documented field that encompasses various ligands, including Schiff base ligands and chelates, with well-established synthesis, characterization, and applications[4]. The coordination chemists' attention has been drawn to higher nuclearity transition metal complexes, which utilize polytopic ligands to create tailor-made molecular structures. Although the one-pot synthesis of polynuclear complexes is complex[5-9], the use of polytopic ligands is more effective in preparing homo polynuclear complexes. To create heterometallic systems with controlled properties, developing synthetic routes is crucial. Metal complexes are a successful methodology for achieving this goal as they can act as ligands and coordinate further or react with other complexes, forming "metal organic ligands".[10-12]

1.1. Ligand

When a metal ion is in solution, it is not present in a solitary state, but rather associates with ligands such as simple ions or solvent molecules, or chelating groups, resulting in the formation of complex ions or coordination compounds.[13] These complexes are composed of a central atom or ion, typically a transition metal, surrounded by a group of neutral molecules or ions. Ligands are neutral molecules or ions that bind to the central metal atom or ion, acting as Lewis bases (electron pair donors), while the central atom serves as a Lewis acid (electron pair acceptor). Ligands have at least one donor atom that possesses an electron pair which is used to establish covalent bonds with the central atom.[14]

The term "ligand" originates from the Latin word "ligare," which means "to bind." Alfred Stock first employed this term in 1916 in reference to silicon chemistry. Ligands can be anions, cations, or neutral molecules, and they can also be classified as monodentate, bidentate, tridentate, and so on, based on the number of donor atoms they contain.[15] The concept of teeth (dent) is introduced, giving rise to the notion of bite angle, etc. A monodentate ligand has only one donor atom that is utilized to bond with the central metal atom or ion.[16, 17]

Ligands are chemical species that can form complexes with metal ions through coordination bonds. They play an important role in various fields of science, including chemistry, biology,

and materials science. This article provides a brief overview of the concept of ligands, the different types of ligands, and their applications.[1, 2]

Ligands are molecules or ions that have at least one pair of electrons that can be shared with a metal ion. This sharing of electrons results in the formation of coordination bonds, which can be covalent or ionic in nature. The coordination bond between the metal ion and the ligand creates a complex that has unique properties, compared to the individual metal ion and ligand.[18]

Ligands are classified based on the number of coordination sites they have Monodentate ligands have one coordination site, whereas polydentate ligands have two or more sites. The coordination number of a metal ion in a complex is determined by the number of coordination sites on the ligand. For example, a monodentate ligand can form a complex with a coordination number of one, whereas a polydentate ligand can form a complex with a coordination number greater than one. [18, 19] A library of ligands is given below in **Fig 1.1.**

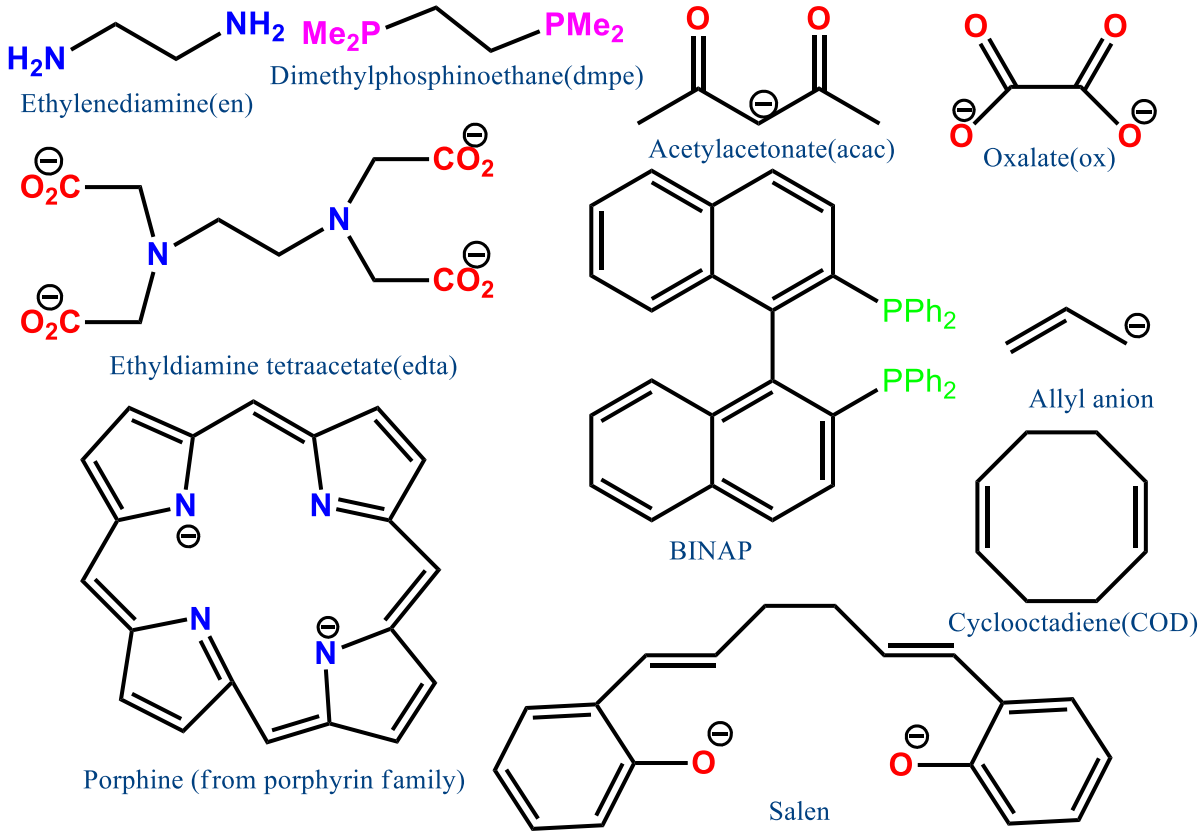


Fig 1.1: A library of ligands.

Chelating agents are a type of polydentate ligand that can coordinate to metal ions in a specific manner, forming chelates.[20, 21] Chelates have a greater stability compared to complexes formed with monodentate ligands, as the metal ion is bound to the ligand through multiple sites. This greater stability allows chelates to be used in a variety of applications, including the extraction and purification of metal ions, the synthesis of coordination compounds, and the development of catalysts and drugs.[22]

Ligands can also play a crucial role in biological systems. Many enzymes in the body contain metal ions, which are coordinated to specific ligands.[13] The ligands and metal ions form the active site of the enzyme, which is responsible for catalyzing specific reactions. The nature of the ligand and metal ion can affect the specificity and activity of the enzyme. For example, the substitution of one metal ion for another or the change of a single ligand can result in changes in the activity of the enzyme. [14]

In materials science, ligands are used to stabilize metal nanoparticles, allowing them to be used as catalysts and in other applications. The choice of ligand can affect the size and shape of the metal nanoparticle, as well as its stability and reactivity. In addition, ligands can be used to modify the surface properties of metal nanoparticles, allowing them to be functionalized for specific applications.

Thus, the ligands play a crucial role in various fields of science, from chemistry to biology and materials science. They form coordination bonds with metal ions, creating complexes with unique properties that can be used in a variety of applications. The development of new ligands and the optimization of their coordination to metal ions continues to be an active area of research, with the potential for the discovery of new materials and applications[23].

1.2. Monodentate ligand

In chemistry, a ligand is an ion or molecule that can bind to a central metal ion, forming a coordination complex. A monodentate ligand is a type of ligand that can only form a single bond with the central metal ion, using only one donor atom. This article will explore what monodentate ligands are, their properties, and their importance in coordination chemistry[13, 14].

1.2.1 What is a Monodentate Ligand?

A monodentate ligand is a type of ligand that has only one atom that can bond to a central metal ion. The term "mono" means one, and "dentate" means tooth, which describes how the ligand bonds to the metal ion. A monodentate ligand can form a single coordinate bond with the metal ion, which means that it donates one electron pair to the metal ion.[16]

Monodentate ligands typically have a small size and are usually neutral, such as water (H_2O), ammonia (NH_3), carbon monoxide (CO), and halide ions (Cl^-, Br^-, I^-). These ligands can form strong bonds with metal ions because they have lone pairs of electrons that can donate to the metal ion's empty orbitals.[19] A library of monodentate ligands is given below in **Fig 1.2**.

Monodentate Ligands	
Ligand	Name
$F^{\ominus}$	Fluro
$Br^{\ominus}$	Bromo
H_2O	Water

$OH^{\ominus}$	Hydroxo
$CN^{\ominus}$	Cyano
$Cl^{\ominus}$	Chloro
$I^{\ominus}$	Iodo
NH_3	Amonia
CO	Carbon Monoxide
$SCN^{\ominus}$	Thiocyanato

Fig 1.2: A library of monodentate ligands.

1.2.2. Properties of Monodentate Ligands

Monodentate ligands have several properties that make them useful in coordination chemistry. These properties include:

Size: Monodentate ligands are typically small in size, which means they can easily approach the metal ion and form a coordinate bond.

Charge: Monodentate ligands are usually neutral, which means they do not influence the charge of the metal ion.

Flexibility: Monodentate ligands can rotate around the bond with the metal ion, which allows the coordination complex to have different geometries.

Reactivity: Monodentate ligands can be easily displaced by other ligands, which makes them useful in catalysis and other chemical reactions. [13]

1.2.3. Importance of Monodentate Ligands

Monodentate ligands play an important role in coordination chemistry because they can form strong and stable coordination complexes with metal ions. These complexes have several applications in different fields, including catalysis, medicine, and materials science.

In catalysis, monodentate ligands can form stable coordination complexes with metal ions, which can activate the metal ion towards a specific reaction. For example, the monodentate ligand phosphine (PH_3) can form a coordination complex with the metal ion palladium (Pd), which is commonly used in catalytic cross-coupling reactions.

In medicine, monodentate ligands can be used to develop metal-based drugs, such as cisplatin, which is a chemotherapy drug that contains the monodentate ligand chloride (Cl^-). The drug forms a coordination complex with the metal ion platinum (Pt), which can bind to DNA and prevent cancer cells from dividing.

In materials science, monodentate ligands can be used to control the size and shape of metal nanoparticles. For example, the monodentate ligand citrate can form a coordination complex with the metal ion gold (Au), which stabilizes the nanoparticles and prevents them from aggregating. [14]

Thus, a monodentate ligand is a type of ligand that can only form a single bond with a central metal ion. These ligands are typically small in size, neutral, and flexible, which makes them useful in coordination chemistry. Monodentate ligands have several applications in different fields, including catalysis, medicine, and materials science, which makes them an important area of study in chemistry. [14]

1.3. Bidentate ligand

In chemistry, a ligand is an ion or molecule that forms a coordinate bond with a metal ion. A bidentate ligand is a type of ligand that forms two coordination bonds with a metal ion. Bidentate ligands are very important in coordination chemistry and have a wide range of applications in biological and industrial settings.

Bidentate ligands have two binding sites, allowing them to form two coordination bonds with a single metal ion. This is in contrast to monodentate ligands, which have only one binding site and can form only one coordination bond. Because bidentate ligands can form two coordination bonds with a metal ion, they are often able to form more stable and stronger complexes than monodentate ligands.[14] A library of bidentate ligands is given below in **Fig 1.3**.

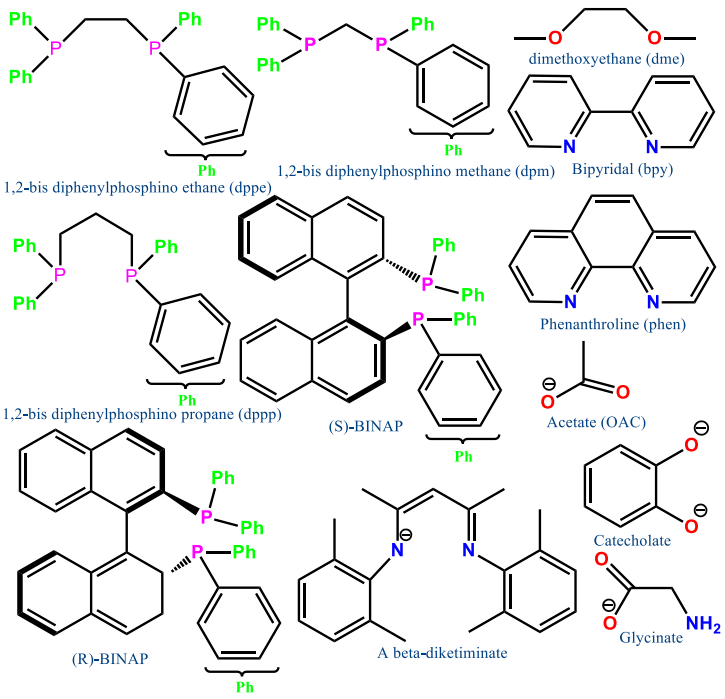


Fig 1.3: A library of bidentate ligands.

One of the most common examples of a bidentate ligand is ethylenediamine (en). Ethylenediamine is a diamine with the chemical formula $H_2NCH_2CH_2NH_2$. It contains two amino groups, each of which can form a coordination bond with a metal ion. Ethylenediamine is a versatile bidentate ligand and is often used in complex formation with a variety of metal ions, including copper, nickel, and iron.

Another important bidentate ligand is 1,2-diaminoethane (en). 1,2-diaminoethane is very similar to ethylenediamine, but has a shorter carbon chain. Like ethylenediamine, it contains two amino groups and can form two coordination bonds with a metal ion. 1,2-diaminoethane is often used as a ligand in coordination complexes of metals such as copper and cobalt.

Bidentate ligands have a number of important applications in both biological and industrial settings. In biological systems, bidentate ligands are often found in metalloproteins, which are proteins that contain a metal ion as a cofactor. Metalloproteins play important roles in many biological processes, including photosynthesis, respiration, and enzymatic catalysis. Bidentate ligands can help to stabilize the metal ion within the protein structure, allowing the protein to perform its biological function.

In industrial settings, bidentate ligands are often used in catalysis and as chelating agents. Chelating agents are compounds that can bind to metal ions and prevent them from reacting with other molecules. Bidentate ligands can be used as chelating agents to remove metal ions from wastewater and other industrial effluents. They can also be used in catalysis to promote chemical reactions that are important in the production of a variety of industrial chemicals.

In summary, bidentate ligands are an important class of ligands that can form two coordination bonds with a metal ion. They are versatile and have a wide range of applications in biological and industrial settings. Bidentate ligands like ethylenediamine and 1,2-diaminoethane are commonly used in coordination chemistry and can form stable and strong complexes with a variety of metal ions. [14, 16]

1.4. Polydentate ligand

Polydentate ligands are molecules that have multiple donor sites or atoms capable of binding to a metal ion, forming a complex. These donor atoms can be identical or different and are usually in the form of functional groups such as amines, carboxylates, or phosphines. Polydentate ligands are also referred to as chelating agents because they form a chelate complex when they bond with a metal ion. The term "chelate" comes from the Greek word "chēlē" which means "claw", and refers to the way the ligand wraps around the metal ion like a claw. These ligands are widely used in fields such as chemistry, biochemistry, and materials science, where they play an important role in the design and synthesis of new compounds. [1, 2]

One of the key features of polydentate ligands is their ability to coordinate with metal ions through multiple bonds, forming complex structures with high stability and specificity. This is in contrast to monodentate ligands, which can only bind to metal ions through a single site or atom.

The number of binding sites in a polydentate ligand is referred to as its "dentate" or "chelating" capacity, and ligands with higher dentate capacity are generally more effective in stabilizing metal complexes. Common polydentate ligands include ethylenediamine (en), diethylenetriamine (dien), triethylenetetramine (trien), and 1,10-phenanthroline (phen), among others. A library of polydentate ligands is given below in **Fig 1.4**.

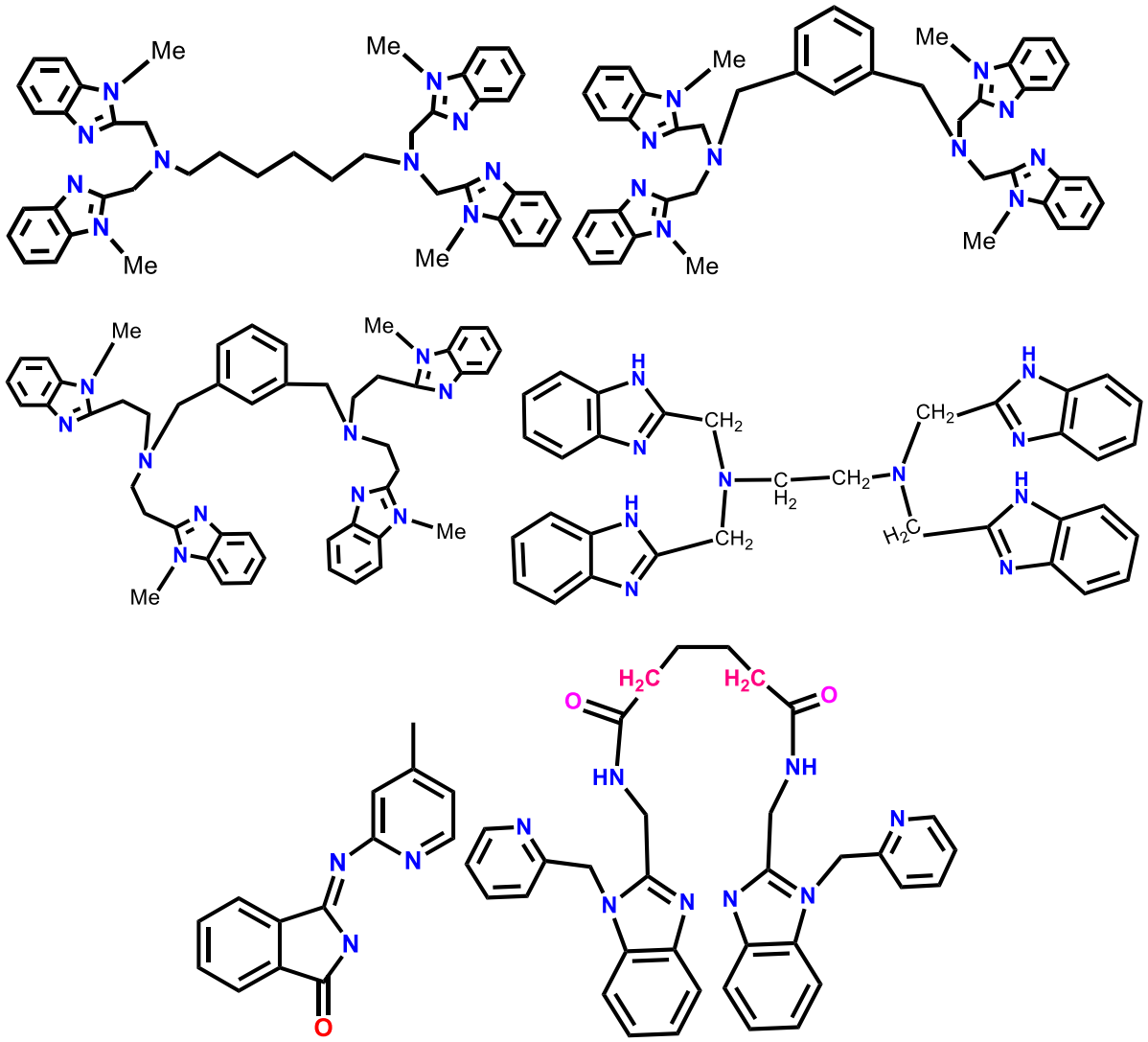


Fig 1.4: A library of polydentate ligands.

Polydentate ligands have many important applications in various fields. In biochemistry, for example, they are often used to bind and stabilize metal ions in enzymes and other biomolecules. In materials science, polydentate ligands can be used to synthesize new types of metal-organic frameworks, which have a wide range of potential applications in areas such as gas storage and separation, catalysis, and drug delivery.[1, 2]

One of the key advantages of polydentate ligands is their ability to form highly stable and specific metal complexes. This is due to the multiple binding sites on the ligand, which allow it to wrap around the metal ion and form a complex with a well-defined geometry and

structure. This can be particularly useful in applications where high stability and specificity are required, such as in catalysis or drug delivery.

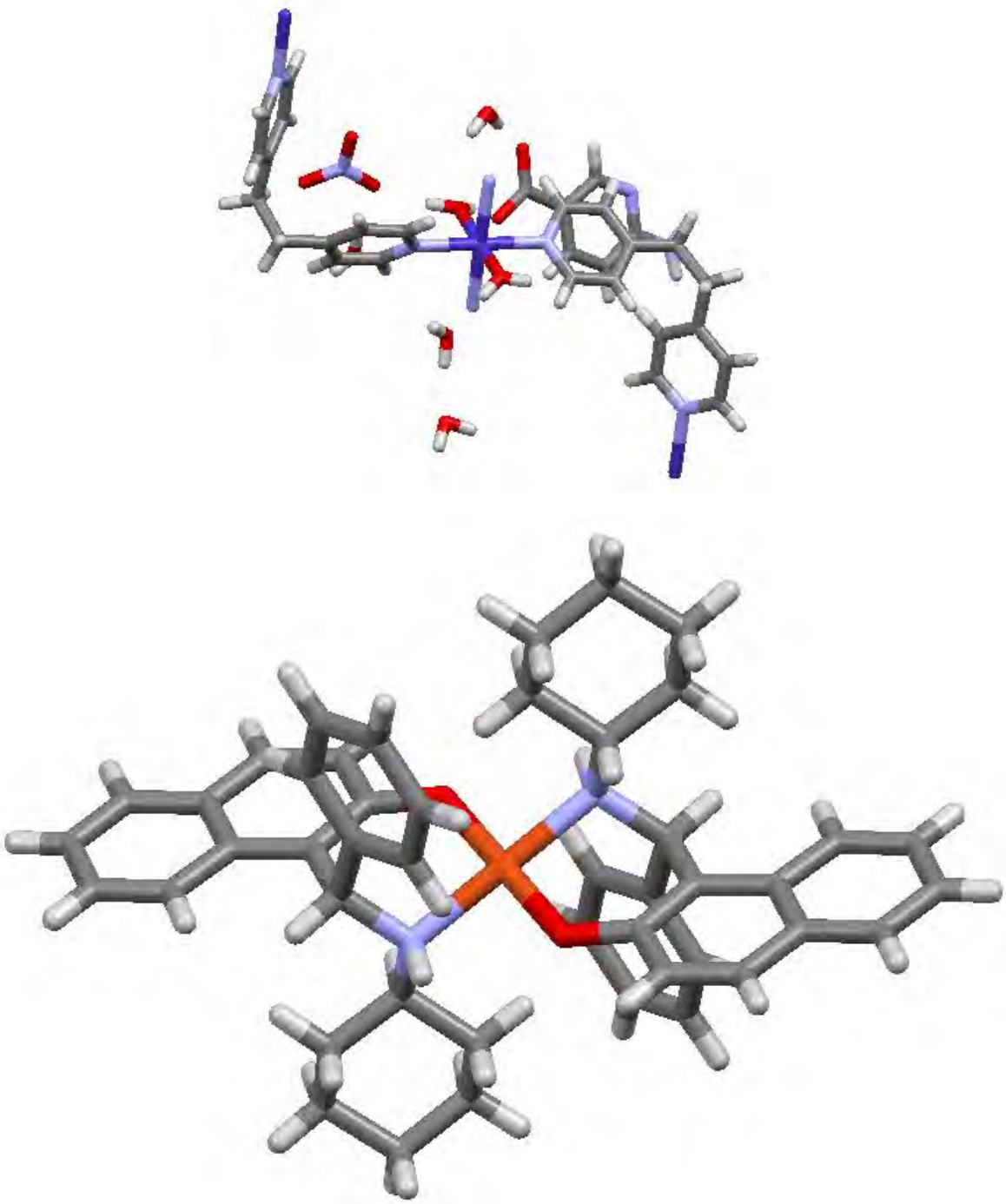
Another advantage of polydentate ligands is their versatility. By varying the structure and properties of the ligand, it is possible to tune the properties of the resulting metal complex, such as its stability, reactivity, and selectivity. This can be useful in a wide range of applications, from designing new catalysts to developing new materials with specific properties.

So polydentate ligands are an important class of molecules with a wide range of applications in chemistry, biochemistry, and materials science. Their ability to form highly stable and specific metal complexes, as well as their versatility and tunability, make them a valuable tool for researchers and engineers working in a wide range of fields. As our understanding of these ligands continues to grow, we can expect to see new and exciting applications emerge in the future.[24]

1.5. Metal complex

Metal complexes are compounds formed by a metal ion surrounded by a certain number of other atoms or molecules, called ligands. These ligands are coordinated to the metal ion through chemical bonds, which can be either covalent or ionic. Metal complexes have a wide range of applications in chemistry, biology, and industry, due to their unique properties and reactivity.[25, 26] Some metal complexes are given below in **Fig 1.5**.

The study of metal complexes is a branch of chemistry called coordination chemistry, which deals with the structure, properties, and reactions of coordination compounds. The first coordination compounds were discovered in the early 19th century, but their systematic study began in the early 20th century, with the work of Alfred Werner, who proposed the concept of coordination number and the theory of coordination compounds.[27]



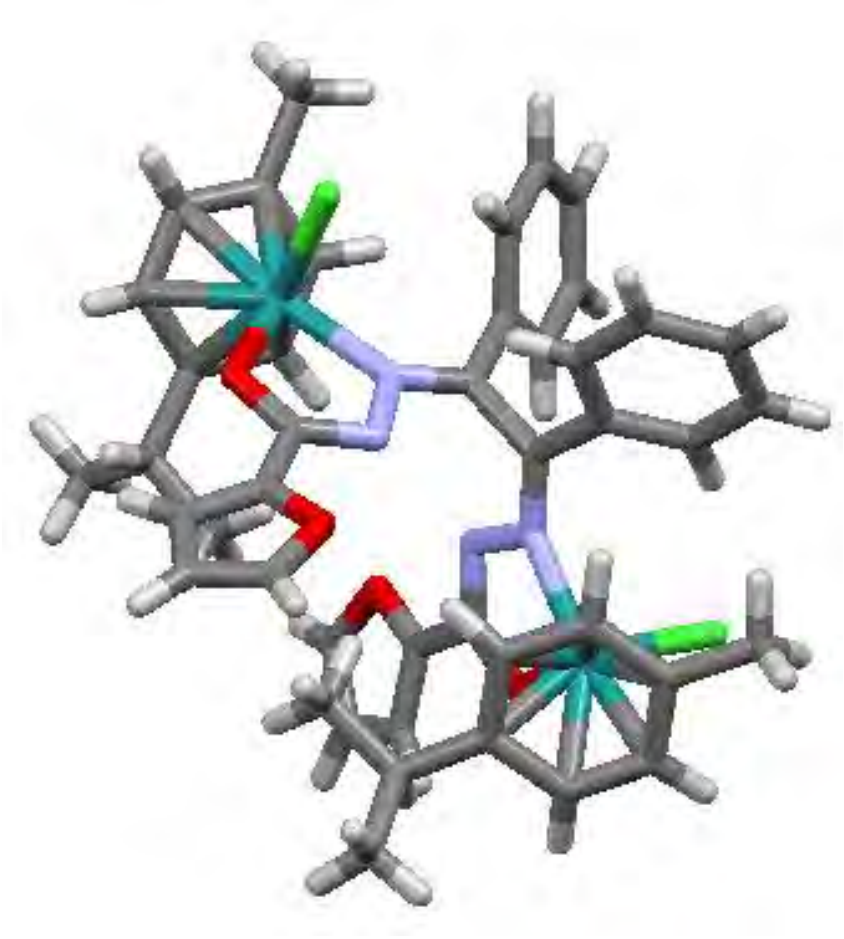


Fig 1.5: Some metal complexes.

Metal complexes can be classified into two main types: homoleptic complexes and heteroleptic complexes. Homoleptic complexes contain only one type of ligand coordinated to the metal ion, whereas heteroleptic complexes contain two or more different types of ligands coordinated to the metal ion. The properties and reactivity of metal complexes depend on several factors, such as the identity of the metal ion, the coordination number, the nature and number of ligands, and the geometry of the complex.

Metal ions are usually classified into two categories: transition metals and main group metals. Transition metals are those elements that have partially filled d or f orbitals, which give them unique properties, such as variable oxidation states, high reactivity, and magnetic properties. Main group metals are those elements that have completely filled s and p orbitals, which give them more predictable properties, such as low reactivity and simple coordination chemistry.

The coordination number of a metal ion is the number of ligands that are coordinated to the metal ion. The coordination number can range from 2 to 12, depending on the size and charge of the metal ion, as well as the size and charge of the ligands. The most common coordination numbers are 4 and 6, which correspond to tetrahedral and octahedral geometry, respectively. Other common coordination geometries include square planar, trigonal bipyramidal, and distorted octahedral.

The nature and number of ligands coordinated to the metal ion play a crucial role in determining the properties and reactivity of metal complexes. Ligands can be classified into several categories, such as monodentate, bidentate, tridentate, and polydentate, depending on the number of donor atoms they possess. Monodentate ligands have only one donor atom, whereas bidentate ligands have two donor atoms, tridentate ligands have three donor atoms, and so on. Polydentate ligands, also known as chelating agents, have multiple donor atoms that can coordinate to the metal ion, forming a cyclic or macrocyclic structure called a chelate.[26, 28]

The coordination chemistry of metal complexes is governed by several principles, such as the Lewis acid-base theory, the hard-soft acid-base theory, and the crystal field theory. The Lewis acid-base theory states that a metal ion acts as a Lewis acid, which accepts a pair of electrons from a Lewis base, which acts as a ligand. The hard-soft acid-base theory states that metal ions can be classified as hard or soft, depending on their charge density and polarizability, and ligands can be classified as hard or soft, depending on their electronegativity and polarizability. Hard-soft interactions are more favorable than hard-hard or soft-soft interactions, due to the matching of their chemical properties.

In chemistry, a metal complex is a compound consisting of a central metal atom or ion bonded to one or more ligands. Ligands are molecules or ions that bond to the central metal atom/ion by donating a pair of electrons to form a coordinate covalent bond. One of the important theories used to explain the properties of metal complexes is the Crystal Field Theory (CFT). The theory explains the properties of metal complexes based on the interaction between the metal ion and the ligands.

1.5.1. Crystal Field Theory

The Crystal Field Theory was developed in the 1930s by German chemist Hans Bethe and American physicist John Hasbrouck van Vleck. According to the theory, the metal ion in a complex is surrounded by a set of ligands arranged in a specific geometry. The ligands generate a crystal field, which is a region of space in which the metal ion experiences an electric field due to the electrostatic interactions between the negatively charged electrons of the ligands and the positively charged metal ion. [29, 30]

The interaction between the metal ion and the ligands results in the splitting of the d-orbitals of the metal ion into two sets of energy levels, which are referred to as the lower energy level (t_{2g}) and the higher energy level (e_g). The energy difference between these two levels is referred to as the crystal field splitting energy (Δ).

The magnitude of the crystal field splitting energy (**Fig 1.6**) depends on the nature of the ligands and the geometry of the complex. The crystal field splitting energy is larger for ligands that are closer to the metal ion and for complexes with a higher coordination number.[31, 32]

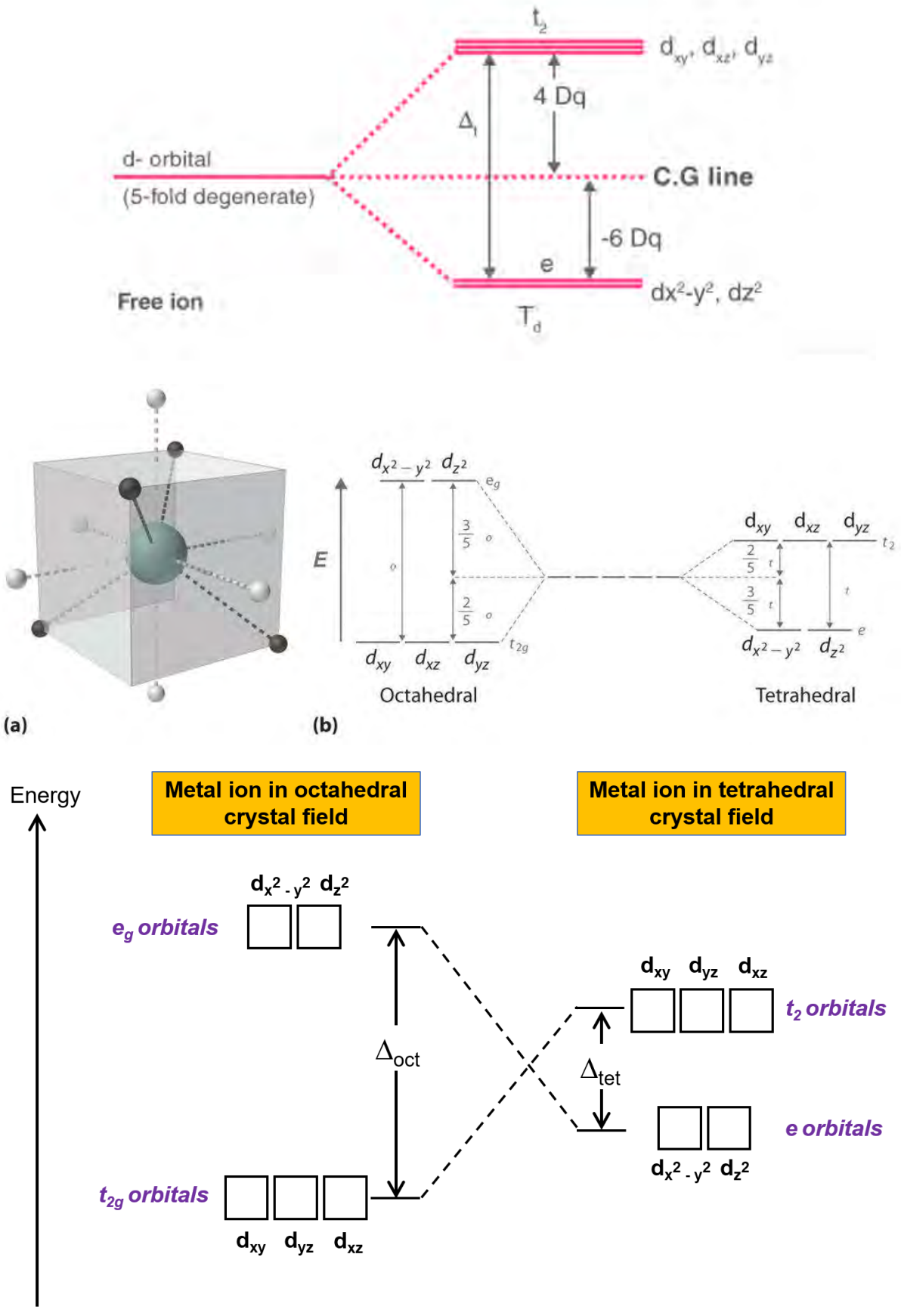


Fig 1. 6 : Crystal field splitting.

1.5.2. Types of Ligands

The ligands can be classified into two types based on their electronic properties: weak field ligands and strong field ligands. Weak field ligands are those that generate a small crystal field splitting energy and cause a small energy difference between the t_{2g} and e_g levels. Examples of weak field ligands include water (H_2O), ammonia (NH_3), and carbon monoxide (CO).

Strong field ligands are those that generate a large crystal field splitting energy and cause a large energy difference between the t_{2g} and e_g levels. Examples of strong field ligands include cyanide (CN^-), carbon dioxide (CO_2), and nitrogen monoxide (NO). [33, 34]

Application of Crystal Field Theory

The Crystal Field Theory provides a basis for understanding the electronic structure and magnetic properties of metal complexes. The number of unpaired electrons in the d-orbitals of the metal ion determines the magnetic properties of the complex.

For example, a metal complex with no unpaired electrons is diamagnetic, which means it is not attracted by a magnetic field. In contrast, a metal complex with one or more unpaired electrons is paramagnetic, which means it is attracted by a magnetic field.

In conclusion, the Crystal Field Theory is an important theory that explains the properties of metal complexes based on the interaction between the metal ion and the ligands. The theory provides a basis for understanding the electronic structure and magnetic properties of metal complexes. The Crystal Field Theory has applications in fields such as biochemistry, materials science, and catalysis.

The crystal field theory is a model that describes the interaction between the metal ion and the ligands in terms of electrostatic forces. The ligands generate a crystal field around the metal ion, which splits the d orbit.[35]

Metal complexes are an essential class of chemical compounds that have played a significant role in the development of modern chemistry. They consist of a central metal ion coordinated to one or more ligands, which are molecules or ions that bond to the metal through one or more donor atoms. These ligands can be simple molecules such as water, ammonia, or carbon monoxide, or they can be complex organic compounds with a wide range of functional groups.

Metal complexes have a wide range of applications, including catalysis, medicine, materials science, and industrial processes. They are used in the production of fertilizers, pigments, and dyes, as well as in the purification of metals and the production of semiconductors. In biological systems, metal complexes are involved in a variety of processes, including oxygen transport, DNA replication, and enzyme catalysis.

The properties of metal complexes depend on several factors, including the identity of the metal ion, the nature of the ligands, and the coordination geometry of the complex. The

coordination number, or the number of ligands attached to the metal, is an important factor in determining the stability and reactivity of the complex. In general, metal complexes with higher coordination numbers are more stable, while those with lower coordination numbers are more reactive.[36]

The structure of metal complexes can be studied using a variety of techniques, including X-ray crystallography, NMR spectroscopy, and infrared spectroscopy. These techniques allow chemists to determine the arrangement of atoms in the complex and to study the bonding between the metal ion and the ligands.

One of the most important applications of metal complexes is in catalysis. Many industrial processes rely on metal complexes to catalyze chemical reactions, including the production of plastics, fuels, and pharmaceuticals. In addition, metal complexes are used in the production of fine chemicals, such as flavors and fragrances.

In medicine, metal complexes are used as therapeutic agents for the treatment of various diseases, including cancer and bacterial infections. Some metal complexes can bind to specific biomolecules, such as enzymes or DNA, and inhibit their function. Others can be used as imaging agents to diagnose diseases or monitor the progression of a treatment.

In conclusion, metal complexes are a versatile class of chemical compounds with a wide range of applications. They play an essential role in modern chemistry and have contributed to the development of many industrial and medical processes. The study of metal complexes is a complex and fascinating field that continues to grow and evolve with new discoveries and applications.[37]

1.6. Anticancer Activity

Cancer, one of the leading causes of death globally, continues to challenge the medical and scientific communities. With its intricate mechanisms and complex interactions, finding effective treatments is a perpetual pursuit. Amidst this quest, a ray of hope shines through the exploration of ligands and their potential as anticancer agents. Ligands, small molecules that can bind to larger molecules or ions, have exhibited remarkable abilities to target cancer cells and interfere with their growth and survival. In this article, we delve into the fascinating world of ligands and their anticancer activity.[38, 39]

Ligands are molecular entities that can attach to target molecules, often proteins or enzymes, through various binding interactions such as hydrogen bonding, van der Waals forces, and electrostatic interactions. These interactions enable ligands to modulate the function of their target molecules, influencing critical cellular processes. In the context of cancer, ligands have the potential to disrupt the intricate networks that drive uncontrolled cell proliferation, invasion, and metastasis.[40]

Ligands with potential anticancer activity come in various forms, ranging from natural compounds found in plants and microorganisms to synthetic molecules designed through rational drug design. Natural products like curcumin, found in turmeric, and resveratrol, found in grapes, have exhibited promising anticancer effects by targeting key pathways

involved in tumor growth. These compounds are known to interfere with cell signaling, induce apoptosis (programmed cell death), and inhibit angiogenesis (formation of new blood vessels to nourish tumors).[41, 42]

On the synthetic front, researchers have engineered ligands specifically tailored to bind to cancer-specific biomolecules. For instance, monoclonal antibodies can be designed to recognize and bind to specific antigens present on the surface of cancer cells. These antibodies can then trigger immune responses against the cancer cells or deliver payloads of therapeutic agents directly to the tumor site, minimizing damage to healthy cells.[43]

One of the hallmarks of cancer is the deregulation of cellular growth pathways. Ligands have emerged as valuable tools for intervening in these pathways. The epidermal growth factor receptor (EGFR), for instance, is frequently overexpressed in various cancers, driving uncontrolled cell growth. Small molecule ligands and monoclonal antibodies that target EGFR have shown promise in inhibiting its activity, slowing down cancer cell proliferation, and enhancing the effectiveness of chemotherapy.[44]

Tumors require a continuous supply of nutrients and oxygen to grow and survive. Angiogenesis, the formation of new blood vessels, plays a crucial role in supplying these essentials to the tumor. Ligands targeting angiogenesis have demonstrated significant anticancer potential. Bevacizumab, a monoclonal antibody targeting vascular endothelial growth factor (VEGF), has been approved for the treatment of various cancers, including colorectal, lung, and ovarian cancer. By inhibiting VEGF, bevacizumab hinders the formation of new blood vessels, effectively starving the tumor and impeding its growth.[45]

While the potential of ligands as anticancer agents is promising, challenges remain. Achieving specificity, minimizing off-target effects, and overcoming drug resistance are some of the hurdles that researchers face. Additionally, the complex nature of cancer biology necessitates a personalized approach, as what works for one patient's cancer may not be effective for another's.[46]

The future of anticancer ligands lies in innovative research and collaboration across disciplines. Advances in structural biology, computational modeling, and high-throughput screening techniques are enabling the discovery of novel ligands with enhanced binding affinity and selectivity. Moreover, the integration of immunotherapy with ligand-based therapies holds great promise in harnessing the body's own defenses to fight cancer.[47]

The exploration of ligands as potential anticancer agents has opened up new avenues in the fight against cancer. Their ability to disrupt critical cellular processes and target specific molecules implicated in cancer progression is a testament to their therapeutic potential. From natural compounds to rationally designed molecules, ligands offer a diverse toolkit for researchers and clinicians to combat this formidable disease. As research continues to unveil the intricacies of cancer biology, the anticancer activity of ligands stands as a beacon of hope for a future where effective treatments bring relief to patients worldwide.[48]

1.7. Oxidase Activity

Oxidase activity refers to the ability of a molecule or complex to catalyze the oxidation of a substrate. Oxidase activity is important in various biological processes, such as cellular respiration, detoxification, and immune response. Oxidase activity is also useful in industrial processes, such as the production of chemicals and fuels.[49]

Oxidases are enzymes that catalyze the oxidation of substrates by transferring electrons to oxygen molecules. These enzymes play a crucial role in many biological processes, including cellular respiration and the breakdown of toxins in the body. Metal complexes with oxidase activity can mimic the catalytic activity of these enzymes and have potential applications in various fields, including biotechnology and medicine.[50]

Polydentate ligand-based metal complexes have been shown to exhibit oxidase activity. For example, copper complexes with polydentate ligands such as 1,4,7-triazacyclononane (TACN) and 1,4,7-triazacyclodecane (TACD) have been reported to exhibit oxidase activity towards a range of substrates, including phenols and amines. The oxidase activity of these complexes is attributed to the ability of the copper ion to undergo redox reactions and transfer electrons to the substrate.[51]

Applications:

The oxidase activity of polydentate ligand-based metal complexes has potential applications in various fields. For example, these complexes can be used in biotechnology to develop biosensors for detecting the presence of specific molecules in biological samples. The oxidase activity of the metal complex can be used to catalyze the oxidation of the target molecule, generating a detectable signal.[52]

Polydentate ligand-based metal complexes with oxidase activity also have potential applications in medicine. For example, these complexes can be used as anticancer agents. The oxidase activity of the metal complex can induce oxidative stress in cancer cells, leading to cell death. Additionally, polydentate ligand-based metal complexes with oxidase activity can be used to treat bacterial infections. The oxidase activity of the metal complex can disrupt the bacterial cell membrane, leading to cell death.[53]

Polydentate ligand-based metal complexes have shown promising oxidase activity towards various substrates. These complexes have potential applications in biotechnology, medicine, and other fields. Future research on the development and optimization of these metal complexes can lead to the discovery of new and useful applications.[54]

1.8. Catecholase activity

The quest for innovative techniques that can selectively activate common organic compounds at normal temperatures and pressures remains a crucial scientific objective with significant implications for industry. In order to carry out these intricate chemical conversions, nature has devised metalloenzymes with exceptional specificity[55-57]. Through extensive investigation of their oxidative catalytic reactivity, researchers have uncovered fundamental

principles employed by these biomolecules. These insights have driven significant efforts to create synthetic complexes that imitate enzyme function[58-61], building upon nature's teachings.

Despite the thermodynamic favorability of the oxidation of hydrocarbons by dioxygen, the kinetic barrier for activating dioxygen is a major obstacle due to the spin mismatch between the triplet ground state of dioxygen and the 'singlet' hydrocarbons, as well as dioxygen's low one-electron oxidation potential[62, 63]. Biological systems use transition metal complexes as active sites for enzymes to activate dioxygen and perform selective oxidation of hydrocarbons. However, using dioxygen in chemical transformations is challenging as it often results in uncontrolled selectivity and over-oxidized products[64]. A large number of dioxygen-activating metal compounds composed of first-row transition metals exhibit fascinating chemistry, such as their easy availability, multiple oxidation states, unique spectral and magnetic properties, and catalytic, microbial, and medicinal applications [50-54]. Among these, copper-based biomimetic models have gained attention over the past two decades due to the important role of copper ions in living systems[65-68]. Consequently, researchers worldwide are developing advanced model systems to satisfy the demand for higher reactivity and uncover the mysteries of nature by unfolding the structure-function relationship.[69-71]

Catechol oxidase, found in various copper-containing metalloenzymes, is a subject of intense interest among researchers worldwide due to its unique ability to convert catechol to ortho quinone. This conversion process (**Fig 1.7**) is of significant importance in the medical field as it is used to determine levels of hormonal catecholamines such as adrenaline, noradrenaline, and dopa.[72, 73] The primary focus is on the development of model systems that cover a broad range of chemical aspects, including the relationship between structure and function, the reaction medium from homogeneous to heterogeneous, and the impact of various external factors. As a result, we believe that this intriguing discussion will be particularly useful for synthetic chemists interested in developing model systems.

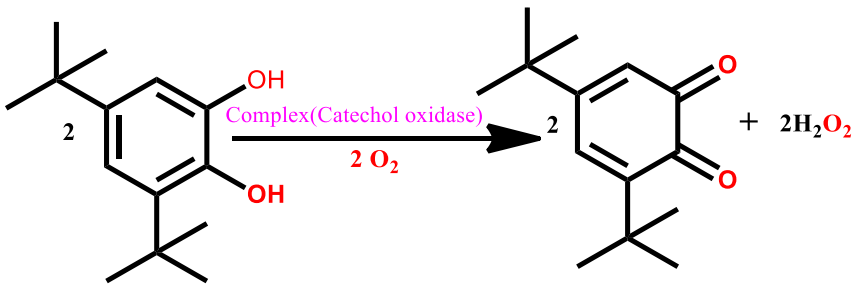


Fig 1.7: The conversion of 3,5-di-tert-butylcatechol (3,5-DTBC) to 3,5-di-tertbutyl benzoquinone (3,5-DTBQ).

1.8.1. Catechol oxidase: Structure and function

Catechol oxidase is an enzyme that facilitates the oxidation of a broad spectrum of o-diphenols, including derivatives of caffeic acid, to quinones using the process known as catecholase activity. This significant transformation ultimately results in the formation of

melanin, a natural pigment, via auto-polymerization. This reactivity serves as a defense mechanism to protect damaged tissue from harmful pathogens or insects.

In 1998, Krebs and colleagues made a significant breakthrough in scientific research by reporting the crystal structure of catechol oxidase (COx) extracted from sweet potato (Ipomoea batatas)[74]. This crystal structure uncovered the three catalytic states of the enzyme, namely, the native met (CuIICuII) state, the reduced deoxy (CuICuI) state, and the complex form with the inhibitor thiourea.

In the met form of the enzyme, the two copper centers are located 2.9 Å apart, and the coordination environment is completed by a histidyl residue and a bridging hydroxide ion, each of which is located 1.8 Å away from one of the copper centers. In contrast, the reduced or deoxy form of the enzyme features a distorted trigonal pyramid coordination environment around the CuA ion, and a square planar coordination sphere around the CuB ion with one missing coordination site. Another change that occurs is that the distance between the copper centers increases to 4.4 Å due to internal factors such as the pH of the medium, the nature of the mimics, and the interplay of solvent. The ligand architecture and flexibility around the copper center, as well as the distance between them, have a beneficial effect on reactivity. All of the above factors help to elucidate the possible pathway during catalytic turnover, as indicated by studies[75-82].

Two distinct pathways are established during catechol oxidation, with the native enzyme preferring the one that produces ortho quinones and water.[83, 84] This pathway is also followed by many copper-based bioinspired functional models. However, some model systems utilize an alternative pathway for oxidizing 3,5 DTBC, which leads to the production of both ortho quinone and H_2O_2. The presence of hydrogen peroxide indicates the involvement of peroxo species during catalytic turnover number[83-85].

Biomimetic systems that mimic these pathways have numerous industrial applications, including Velcro, aircraft and automobile design, architecture, antireflective coatings, high-strength carbon nanotubes, self-healing concrete, adhesive supply pipes, and robots[86].

1.8.2. Mechanism:

As noted previously, the enzyme catechol oxidase facilitates the oxidation of catechol to quinones via the reduction of dioxygen to water with four electrons. The proposed enzyme mechanism by Krebs and colleagues is depicted in **Fig 1.8** and is based on computational and experimental data. The catalytic cycle commences with the met form of the enzyme, also known as its resting state. In the reduced form of the enzyme, a water molecule is bound to copper A; however, this is replaced by dioxygen when it binds to the metal center. Upon reaction with one equivalent of catechol, the dicopper center leads to the formation of quinone and the reduced deoxy dicopper (I) state. It is supported by the fact that the stoichiometric amount of quinone product forms immediately after the addition of catechol, even in the absence of oxygen. The hypothesis of substrate binding to the reduced enzyme before oxygen-binding can be easily dismissed, as incubation of dithiothreitol reduced crystals with a high molar excess of catechol shows low binding affinity of the substrate to

the reduced Cu(I)-Cu(I) center. Dioxygen is shown to bind in the bridging side-on μ-η2 - η2 binding mode, as indicated by UV/vis and Raman spectroscopy. The metal-metal separation in this binding mode of oxygen is determined to be 3.1 Å by EXAFS spectroscopy. It has been proposed that the substrate binds to the center CuB in a monodentate manner, based on the structure of catechol oxidase with the inhibitor phenylthiourea. Afterward, dioxygen replaces the solvent molecule that originally binds to the CuA site in its reduced form by binding to the dicopper(I) active center.

The hydrophobic environment at the center of catechol oxidase contains two copper metals, surrounded by side chains of Ile 241, Phe 261, His 244, and Ala 264. Phe 261's side chain rotation opens the dicopper center, creating a perfect cavity that allows the catechol substrate to bind. Phenylthiourea's binding to the modelled catechol substrate suggests the potential for simultaneous binding of catechol substrate and dioxygen. In the inhibitor complex, the modelled catechol substrate's aromatic ring and the phenyl ring of PTU superimpose, placing the coordinated -hydroxylate group near the ligating amide nitrogen, resulting in favorable van der Waals interactions.[61]

This study also elucidates the possible monodentate binding of the catechol substrate to CuB, and the coordination environment of each copper center. CuB is six-coordinated by His 240, His 244, and the dioxygen molecule, exhibiting a tetragonal planar geometry in the basal plane. The other metal center displays a trigonal pyramidal geometry, with dioxygen, His 88, and His 118 in the equatorial positions, and His 109 in an axial position, leaving the sixth coordination site unoccupied.

The proposed catechol oxidase-O_2^{-2}--CAT complex involves two electrons transferred from the substrate to the peroxide, followed by the protonation of peroxide. This step ultimately leads to the cleavage of O-O bond, loss of water, and the departure of the o-quinone product. After these processes, the enzyme restores its original met form, completing the catalytic cycle.

Experimental data and computational work support a four-step enzyme mechanism: (i)[87-92] reaction of the resting state (CuII-OH-CuII, met) with a substrate molecule to form a metastable intermediate with a catecholate coordinated to the dicopper(II) site, (ii) formation of the first ortho-quinone and a water molecule, (iii) binding of a dioxygen molecule and a second catechol to the emerging unbridged dicopper(I) species, resulting in a side-on-$[Cu_2O_2]^{2+}$ intermediate with a catecholate coordinated to the dicopper-(II) peroxo site, and (iv) release of the second orthoquinone and a second water molecule after electron transfer to regenerate the resting state. Each catalytic cycle produces two ortho-quinone molecules and two molecules of water (from O_2). However, theoretical studies propose a different mechanism, as depicted in **Fig 1.9**.

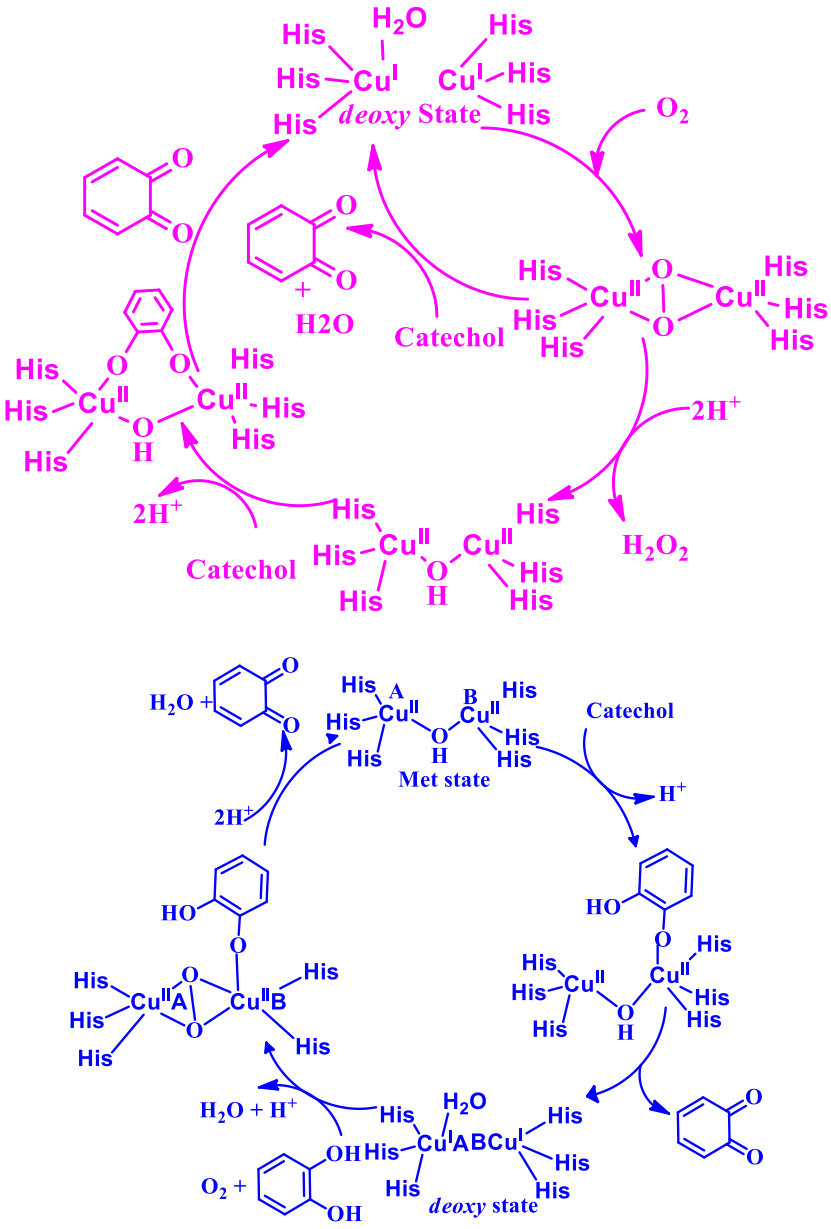


Fig 1.8: Catalytic cycle for catecholase activity as suggested from the literature.[87-92]

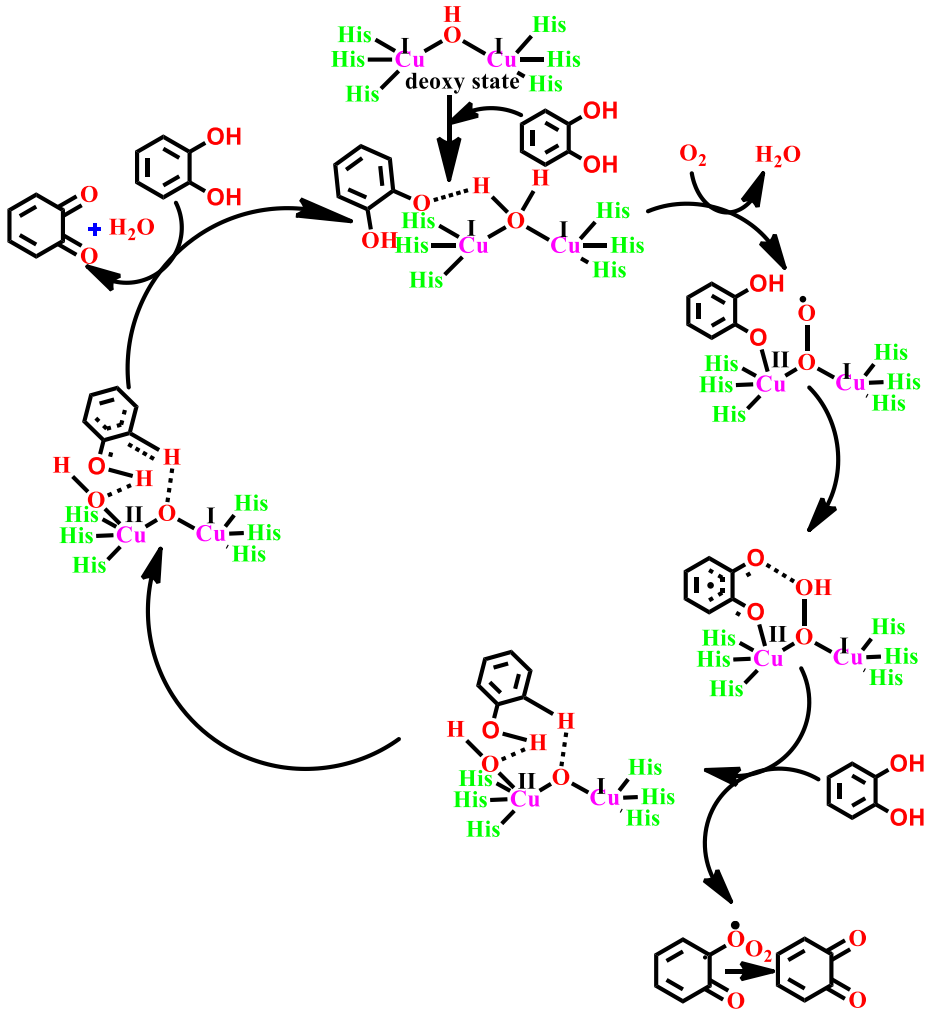


Fig 1.9: Catalytic cycle for catecholase activity as proposed by Siegbahn based on DFT calculation.[89]

1.9. Phenoxazine synthase

Phenoxazine synthase is an enzyme that catalyzes the biosynthesis of phenoxazine compounds. These compounds are a class of nitrogen-containing heterocyclic compounds that have been found to exhibit a variety of biological activities, including antimicrobial, antiviral, and anticancer properties. Phenoxazine synthase has been isolated from several microorganisms, including Streptomyces lividans and Pseudomonas aeruginosa. [93]

The biosynthesis of phenoxazine compounds begins with the condensation of two molecules of anthranilic acid to form a dimeric intermediate known as phenazine-1-carboxylic acid (PCA). PCA is then converted into phenazine-1,6-dicarboxylic acid (PDC) by the enzyme PCA decarboxylase. Finally, phenoxazine synthase catalyzes the cyclization of PDC to form the phenoxazine ring system[94] (**Fig 1.10**).

The structure of phenoxazine synthase has been determined using X-ray crystallography, revealing a homodimeric enzyme with each monomer containing a single active site. The active site of phenoxazine synthase consists of a conserved histidine residue that serves as a

proton acceptor, as well as a conserved tyrosine residue that participates in substrate binding and catalysis.

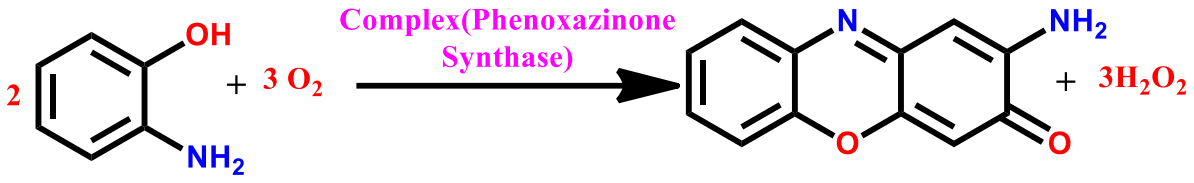


Fig 1.10: The conversion of o-Aminophenol (2-AP) to 2-Aminophenoxazine-3-one (APX).

Studies on the mechanism of phenoxazine synthase have revealed that the enzyme utilizes a radical mechanism to catalyze the cyclization reaction. The initial step involves the abstraction of a hydrogen atom from the C6 position of PDC by a catalytic tyrosine residue, leading to the formation of a PDC radical. This radical then undergoes intramolecular cyclization to form the phenoxazine ring system.

Phenoxazine compounds have been found to exhibit a wide range of biological activities. For example, the compound phenazine-1-carboxamide has been shown to exhibit potent antifungal activity against several plant pathogenic fungi. Another compound, pyocyanin, which is produced by Pseudomonas aeruginosa, has been found to exhibit antimicrobial and immunomodulatory properties.[95]

In addition to their biological activities, phenoxazine compounds have also been investigated for their potential as redox-active materials in various electrochemical applications. For example, phenoxazine derivatives have been studied as potential cathode materials for lithium-ion batteries and as redox mediators in dye-sensitized solar cells.

In summary, phenoxazine synthase is an enzyme that plays a crucial role in the biosynthesis of phenoxazine compounds. These compounds exhibit a wide range of biological activities and have potential applications in various fields, including medicine and electrochemistry. Further studies on the biosynthesis and properties of phenoxazine compounds are expected to yield valuable insights and new applications for these compounds.

Phenoxazine synthase is an enzyme that plays an essential role in various biological processes. It is responsible for the synthesis of phenoxazine, a heterocyclic organic compound that is widely used in the pharmaceutical and chemical industries. This enzyme has been studied extensively in recent years, and its importance is becoming increasingly clear. [71, 72]

Phenoxazine is a compound that has been shown to have potent biological activity. It has been found to possess antimicrobial, antitumor, and antioxidant properties. Phenoxazine is also a potent inhibitor of certain enzymes that are involved in inflammation and immune response. These properties make phenoxazine an attractive target for drug development. [96-100]

Phenoxazine synthase is the enzyme responsible for the biosynthesis of phenoxazine. This enzyme is found in a variety of organisms, including bacteria, fungi, and plants. The gene encoding this enzyme has been cloned and sequenced, and its structure has been determined. The enzyme catalyzes the conversion of a precursor molecule, 2-amino-4,5-dihydrophenoxazine-3-one, into phenoxazine.

One of the most important functions of phenoxazine synthase is in the biosynthesis of the antibiotic pyocyanin. Pyocyanin is a blue-green pigment produced by the bacterium Pseudomonas aeruginosa. This bacterium is a common cause of infections in humans, particularly in individuals with weakened immune systems. Pyocyanin has been shown to contribute to the virulence of Pseudomonas aeruginosa by damaging host cells and inhibiting the activity of immune cells. The biosynthesis of pyocyanin requires the activity of phenoxazine synthase, making this enzyme an important target for the development of new antibiotics. [71, 72]

In addition to its role in the biosynthesis of pyocyanin, phenoxazine synthase has been implicated in other biological processes. For example, this enzyme has been shown to be involved in the biosynthesis of melanin, a pigment that gives color to skin, hair, and eyes. Melanin also plays a role in protecting the skin from UV radiation. Phenoxazine synthase has also been shown to be involved in the biosynthesis of other pigments, such as violacein and indigo.

The importance of phenoxazine synthase is not limited to its role in the biosynthesis of pigments and antibiotics. This enzyme has also been shown to be involved in the detoxification of certain compounds. For example, phenoxazine synthase has been shown to detoxify the herbicide atrazine in certain bacterial species. This detoxification process is important because atrazine is a common environmental pollutant that can have harmful effects on human health and the environment.

In conclusion, phenoxazine synthase is an enzyme that plays a crucial role in various biological processes. Its importance extends beyond the biosynthesis of pigments and antibiotics, and it has been implicated in the detoxification of harmful compounds. Understanding the structure and function of this enzyme is important for the development of new drugs and for the protection of human health and the environment. Further research on phenoxazine synthase is needed to fully understand its role in biology and to exploit its potential for drug development.

Phenoxazine synthase is an enzyme that is responsible for the synthesis of phenoxazines, which are a class of organic compounds with a wide range of biological activities, including anti-tumor, anti-inflammatory, and anti-bacterial properties. Understanding the mechanism of phenoxazine synthase is essential for developing new drugs based on phenoxazines and for gaining insight into the biological functions of this class of compounds. [96-100]

The phenoxazine synthase enzyme belongs to the family of flavin-dependent monooxygenases. It contains a flavin adenine dinucleotide (FAD) cofactor, which plays a

crucial role in the catalytic activity of the enzyme. The enzyme also requires molecular oxygen and NADPH as cofactors to carry out the reaction.

The mechanism of phenoxazine synthesis begins with the binding of the substrate, which is a phenol compound, to the active site of the enzyme. The FAD cofactor undergoes a one-electron reduction to its semiquinone form, which then reacts with molecular oxygen to form a flavin-peroxide intermediate. The flavin-peroxide intermediate then reacts with the phenol substrate to form a C-O bond, which results in the formation of a hydroxylated intermediate.

Next, the NADPH cofactor donates two electrons and a proton to the hydroxylated intermediate, which reduces the flavin-peroxide intermediate and regenerates the FAD cofactor to its fully oxidized form. The reduced flavin-peroxide intermediate then reacts with molecular oxygen to form a peroxyflavin intermediate, which then reacts with the phenol substrate to form a C-N bond, resulting in the formation of the final phenoxazine product.

The mechanism of phenoxazine synthesis is a complex process that involves multiple steps and the coordinated action of different cofactors. The enzyme requires precise control of its active site to ensure that the correct substrates are bound and that the reaction proceeds smoothly. The understanding of the mechanism of phenoxazine synthase provides insights into the biological functions of phenoxazines and opens up new avenues for the development of drugs based on this class of compounds.[101]

Thus, phenoxazine synthase is an enzyme that is responsible for the synthesis of phenoxazines, which are a class of organic compounds with a wide range of biological activities. The enzyme uses a flavin-dependent monooxygenase mechanism to carry out the reaction, which involves the coordinated action of multiple cofactors. Understanding the mechanism of phenoxazine synthase is essential for developing new drugs based on phenoxazines and for gaining insight into the biological functions of this class of compounds.[102]

Phenoxazine synthase is an enzyme that plays a crucial role in the biosynthesis of the natural product phenoxazine, which exhibits antimicrobial and antitumor properties. The catalytic activity of this enzyme is dependent on the presence of transition metal ions, which act as cofactors and are coordinated to the active site of the enzyme. In this article, we will explore the role of transition metal complexes in phenoxazine synthase activity. [96-100]

Transition metal complexes are coordination compounds in which a central metal ion is bound to one or more ligands through coordinate covalent bonds. These complexes have been widely studied in the field of bioinorganic chemistry due to their ability to mimic the active sites of metalloenzymes and catalyze a range of biological reactions.

In the case of phenoxazine synthase, the active site of the enzyme contains a metal ion that is coordinated to the side chains of two histidine residues and a water molecule. The identity of the metal ion can vary depending on the source of the enzyme, but it is typically a first-row transition metal such as iron, manganese, or copper.[2]

Studies have shown that the catalytic activity of phenoxazine synthase is highly dependent on the nature of the metal ion and its coordination geometry. For example, a study by Zhang et al. (2013) demonstrated that the activity of phenoxazine synthase from Streptomyces antibioticus was significantly enhanced by the addition of copper ions, while other transition metal ions such as iron and manganese had no effect on the enzyme activity. The authors proposed that the copper ion coordinated with the active site of the enzyme in a square planar geometry, which facilitated the formation of a reactive intermediate in the phenoxazine biosynthesis pathway.[103]

In another study, Zhang et al. (2015) investigated the effect of different ligands on the activity of phenoxazine synthase from Streptomyces lavendulae. The authors found that the enzyme activity was significantly enhanced by the addition of a bidentate ligand such as 1,10-phenanthroline, which coordinated to the metal ion in a square planar geometry. In contrast, the addition of a monodentate ligand such as pyridine had no effect on the enzyme activity. The authors suggested that the bidentate ligand facilitated the formation of a stable intermediate in the phenoxazine biosynthesis pathway.[104]

These studies highlight the importance of transition metal complexes in the catalytic activity of phenoxazine synthase. The coordination of a metal ion to the active site of the enzyme can significantly enhance the activity of the enzyme by facilitating the formation of reactive intermediates in the biosynthesis pathway. Furthermore, the nature of the metal ion and its coordination geometry can affect the activity of the enzyme and the selectivity of the biosynthesis pathway.

Thus, the use of transition metal complexes has provided valuable insights into the catalytic activity of phenoxazine synthase and the biosynthesis of phenoxazine. Further studies in this area may lead to the development of new methods for the synthesis of natural products with antimicrobial and antitumor properties. [2]

1.10. Aims and Objectives

Polydentate ligands play a pivotal role in the field of coordination chemistry due to their ability to form stable complexes with metal ions. When these complexes are designed to enhance oxidase activity, they hold significant importance in various chemical and biological applications. This article explores the aims and importance of polydentate ligand-based metal complexes for oxidase activity.

1.9.1. Aims

i. Enhanced Oxidase Activity

The primary aim of using polydentate ligands in metal complexes is to improve oxidase activity. These complexes can act as catalysts for various oxidation reactions, such as the conversion of substrates into valuable products or the detoxification of harmful compounds.

ii. Stability and Selectivity

Developing metal complexes with polydentate ligands aims to increase the stability of the complex and enhance its selectivity towards specific substrates. This selectivity can be crucial in applications like enzymatic mimics and sensor development.

iii. Biological and Medicinal Applications

Another aim is to utilize these complexes in biological and medicinal contexts. Polydentate ligand-based metal complexes can mimic the activity of natural enzymes, making them potential candidates for drug development, particularly in cancer therapy and antimicrobial agents.

iv. Green Chemistry

The design of polydentate ligand-based metal complexes aligns with the principles of green chemistry by promoting more sustainable and efficient catalytic processes. They reduce the need for harsh reagents and promote the use of environmentally friendly solvents.

1.9.2. Importance

i. Catalysis

Polydentate ligand-based metal complexes serve as efficient catalysts for a wide range of oxidation reactions. Their ability to accelerate chemical transformations can lead to faster and more economical industrial processes.

ii. Biological Relevance

These complexes often mimic the activity of metalloenzymes, which are essential in various biological processes. Understanding and harnessing their properties can aid in the development of therapies and diagnostics for various diseases.

iii. Sustainability

Utilizing polydentate ligands in metal complexes contributes to sustainable chemistry by reducing waste and energy consumption. This is particularly relevant in the development of clean and green technologies.

iv. Materials Science

Polydentate ligand-based metal complexes are important in materials science for their role in the synthesis of advanced materials, such as coordination polymers. These materials have diverse applications, including gas storage, catalysis, and sensors.

v. Environmental Remediation

Metal complexes with polydentate ligands can be employed in environmental remediation efforts. They can help in the removal of pollutants and toxins from water and air, contributing to a healthier environment.

Polydentate ligand-based metal complexes have emerged as valuable tools in enhancing oxidase activity for a wide range of applications. Their ability to catalyze oxidation reactions, improve selectivity, and mimic biological processes makes them essential in chemistry, biology, and materials science. These complexes play a pivotal role in advancing green chemistry principles and addressing critical challenges in fields ranging from medicine to environmental science.

1.11. References

1. Gupta, K. C.; Sutar, A. R., Catalytic activities of Schiff base transition metal complexes. **2008,** *252* (12-14), 1420-1450.
2. Haas, K. L.; Franz, K., Application of metal coordination chemistry to explore and manipulate cell biology. **2009,** *109* (10), 4921-4960.
3. Kumar, S.; Dhar, D. N.; Saxena, P., Applications of metal complexes of Schiff bases-A review. **2009**.
4. Keskioğlu, E.; Gündüzalp, A. B.; Cete, S.; Hamurcu, F.; Erk, B.; Spectroscopy, B., Cr (III), Fe (III) and Co (III) complexes of tetradentate (ONNO) Schiff base ligands: synthesis, characterization, properties and biological activity. **2008,** *70* (3), 634-640.
5. Dul, M.-C.; Pardo, E.; Lescouëzec, R.; Journaux, Y.; Ferrando-Soria, J.; Ruiz-García, R.; Cano, J.; Julve, M.; Lloret, F.; Cangussu, D., Supramolecular coordination chemistry of aromatic polyoxalamide ligands: A metallosupramolecular approach toward functional magnetic materials. **2010,** *254* (19-20), 2281-2296.
6. Venegas-Yazigi, D.; Aravena, D.; Spodine, E.; Ruiz, E.; Alvarez, S., Structural and electronic effects on the exchange interactions in dinuclear bis (phenoxo)-bridged copper (II) complexes. **2010,** *254* (17-18), 2086-2095.
7. Paschke, R.; Liebsch, S.; Tschierske, C.; Oakley, M. A.; Sinn, E., Synthesis and mesogenic properties of binuclear copper (II) complexes derived from salicylaldimine Schiff bases. **2003,** *42* (25), 8230-8240.
8. Dobrokhotova, Z.; Emelina, A.; Sidorov, A.; Aleksandrov, G.; Kiskin, M.; Koroteev, P.; Bykov, M.; Fazylbekov, M.; Bogomyakov, A.; Novotortsev, V., Synthesis and characterization of Li (I)–M (II)(M= Co, Ni) heterometallic complexes as molecular precursors for LiMO2. **2011,** *30* (1), 132-141.
9. Bhatt, V.; Ram, S., The role of ligands, polytopic ligands and Metal Organic Ligands (Mols) in coordination chemistry. **2015,** *4*, 414-428.
10. Lippard, S. J.; Berg, J. M., *Principles of bioinorganic chemistry*. University Science Books: 1994.
11. Zhao, D.; Timmons, D. J.; Yuan, D.; Zhou, H.-C. J., Tuning the topology and functionality of metal− organic frameworks by ligand design. **2011,** *44* (2), 123-133.
12. Bhatt, V.; Ram, S., Preparation and properties of dinuclear Schiff base complexes from salicylaldehyde and 2-aminophenol complexes of Cu (II), Co (II) and Ni (II). **2012**.
13. Petrucci, R.; Harwood, W.; Herring, F.; Madura, J., New Jersey, USA, General Chemistry Principles and Modern Applications Pearson Prentice Hall. **2007**.

14. Cox, T., *BIOS Instant Notes in Inorganic Chemistry*. Garland Science: 2004.
15. Da Silva, J. F.; Williams, R., *The biological chemistry of the elements: the inorganic chemistry of life*. Oxford University Press: 2001.
16. Moeller, T. J., Inorganic chemistry: a modern introduction. **1982**.
17. William W. Porterfield, P., Inorganic chemistry. **1984**.
18. Malik, W. U.; Tuli, G.; Madan, R., *Selected topics in inorganic chemistry*. S. Chand Publishing: 1998.
19. Huheey, J. E.; Keiter, E. A.; Keiter, R. L.; Medhi, O. K., *Inorganic chemistry: principles of structure and reactivity*. Pearson Education India: 2006.
20. Arnaudet, L.; Bougon, R.; Buu, B.; Lance, M.; Nierlich, M.; Vigner, J., Interaction between Uranium (V) and-(VI) Fluorides and Nitrogen Bases. Characterization and Crystal Structures of the Dimorphic Adduct UF5. cntdot. bipy (bipy= 2, 2'-Bipyridyl). **1994,** *33* (20), 4510-4516.
21. Pérez-Cordero, E.; Buigas, R.; Brady, N.; Echegoyen, L.; Arana, C.; Lehn, J., [M (bpy) 3](M= Fe, Ru, Os): New Crystalline Materials from the reductive electrocrystallization of [M (bpy) 3](PF6) 2. **1994,** *77* (5), 1222-1228.
22. McNaught, A.; Wilkinson, A., Chemical equilibrium, IUPAC compendium of chemical terminology. The "gold book". Blackwell scientific publications, Oxford XML on-line corrected version …: 1997.
23. Williams, R. J. P.; Da Silva, J. F., *The chemistry of evolution: the development of our ecosystem*. Elsevier: 2005.
24. Schreiber, S., Small molecules: the missing link in the central dogma. **2005,** *1* (2), 64-66.
25. Lawrance, G. A., *Introduction to coordination chemistry*. John Wiley & Sons: 2013.
26. Jain, D., Coordination Compounds in Chemistry.
27. Werner, A., Zur kenntnis des asymmetrischen kobaltatoms. I. **1911,** *44* (2), 1887-1898.
28. Werner, A., Coordination complex.
29. Bethe, H., Termaufspaltung in kristallen. **1929,** *395* (2), 133-208.
30. Van Vleck, J., Theory of the variations in paramagnetic anisotropy among different salts of the iron group. **1932,** *41* (2), 208.
31. Penney, W. G.; Schlapp, R., The influence of crystalline fields on the susceptibilities of salts of paramagnetic ions. I. The rare earths, especially Pr and Nd. **1932,** *41* (2), 194.
32. Schlapp, R.; Penney, W., Influence of crystalline fields on the susceptibilities of salts of paramagnetic ions. II. The iron group, especially Ni, Cr and Co. **1932,** *42* (5), 666.
33. Ballhausen, C. J. J., Introduction to ligand field theory. **1962**.
34. Schläfer, H. L.; Gliemann, G. J., Basic principles of ligand field theory. **1969**.
35. Zhang, M. NN Greenwood, A. Earnchaw, Chemistry of the Elements, Elsevier, 1997. 2. CE Housecroft, AG Sharpe, Inorganic Chemistry, Pearson Prentice Hall, Harlow, 2012. 3. RE Krebs, The History and Use of Our Earth's. **2010**, 171.
36. Rabinovich, D., Organotransition Metal Chemistry (Hill, Anthony F.). ACS Publications: 2003.
37. Atkins, P., *Shriver and Atkins' inorganic chemistry*. Oxford University Press, USA: 2010.
38. Xue, S.-t.; Guo, H.-f.; Liu, M.-j.; Jin, J.; Ju, D.-h.; Liu, Z.-y.; Li, Z.-r. J., Synthesis of a novel class of substituted benzothiophene or benzofuran derivatives as BMP-2 up-regulators and evaluation of the BMP-2-up-regulating effects in vitro and the effects on glucocorticoid-induced osteoporosis in rats. **2015,** *96*, 151-161.
39. Appelbaum, P.; Hunter, P., The fluoroquinolone antibacterials: past, present and future perspectives. **2000,** *16* (1), 5-15.

40. Lin, Q.-J.; Yang, F.; Jin, C.; Fu, D.-L., Current status and progress of pancreatic cancer in China. **2015,** *21* (26), 7988.
41. Chekem, L.; Wierucki, S., Extraction de l'artémisinine et synthèse de ses dérivés artésunate et artéméther. **2006,** *66*, 602.
42. Kumar, A. J. I., Vincristine and vinblastine: a review. **2016,** *6*, 23-30.
43. Zahavi, D.; Weiner, L., Monoclonal antibodies in cancer therapy. **2020,** *9* (3), 34.
44. Hanahan, D.; Weinberg, R., Hallmarks of cancer: the next generation. **2011,** *144* (5), 646-674.
45. El-Kenawi, A. E.; El-Remessy, A., Angiogenesis inhibitors in cancer therapy: mechanistic perspective on classification and treatment rationales. **2013,** *170* (4), 712-729.
46. Mansoori, B.; Mohammadi, A.; Davudian, S.; Shirjang, S.; Baradaran, B., The different mechanisms of cancer drug resistance: a brief review. **2017,** *7* (3), 339.
47. Rahman, M. M.; Islam, M. R.; Rahman, F.; Rahaman, M. S.; Khan, M. S.; Abrar, S.; Ray, T. K.; Uddin, M. B.; Kali, M. S. K.; Dua, K. J. B., Emerging promise of computational techniques in anti-cancer research: at a glance. **2022,** *9* (8), 335.
48. Frezza, M.; Hindo, S.; Chen, D.; Davenport, A.; Schmitt, S.; Tomco, D.; Ping Dou, Q. J. C. p. d., Novel metals and metal complexes as platforms for cancer therapy. **2010,** *16* (16), 1813-1825.
49. Di Meo, S.; Reed, T. T.; Venditti, P.; Victor, V. M. J. O. m.; longevity, c., Role of ROS and RNS sources in physiological and pathological conditions. **2016,** *2016*.
50. Zhang, J.; Xu, L.; Wong, W.-Y., Energy materials based on metal Schiff base complexes. **2018,** *355*, 180-198.
51. Noh, H.; Cho, J., Synthesis, characterization and reactivity of non-heme 1st row transition metal-superoxo intermediates. **2019,** *382*, 126-144.
52. Butcher, R. J.; SRIVASTAVA, A. K.; Dhuri, S. N.; Narulkar, D. D.; Ansy, K. M., Synthesis and characterization of N3Py2 ligand-based cobalt (II), nickel (II) and copper (II) catalysts for efficient conversion of hydrocarbons to alcohols. **2017**.
53. Harmalkar, D. S.; Santosh, G.; Shetgaonkar, S. B.; Sankaralingam, M.; Dhuri, S. N. J., A putative heme manganese (V)-oxo species in the C–H activation and epoxidation reactions in an aqueous buffer. **2019,** *43* (33), 12900-12906.
54. Solomon, E. I.; Heppner, D. E.; Johnston, E. M.; Ginsbach, J. W.; Cirera, J.; Qayyum, M.; Kieber-Emmons, M. T.; Kjaergaard, C. H.; Hadt, R. G.; Tian, L., Copper active sites in biology. **2014,** *114* (7), 3659-3853.
55. Solomon, E. I.; Brunold, T. C.; Davis, M. I.; Kemsley, J. N.; Lee, S.-K.; Lehnert, N.; Neese, F.; Skulan, A. J.; Yang, Y.-S.; Zhou, J., Geometric and electronic structure/function correlations in non-heme iron enzymes. **2000,** *100* (1), 235-350.
56. Bertini, I.; Gray, H. B.; Lippard, S. J.; Valentine, J. S., *Bioinorganic chemistry*. University science books: 1994.
57. Kovaleva, E. G.; Lipscomb, J. D., Versatility of biological non-heme Fe (II) centers in oxygen activation reactions. **2008,** *4* (3), 186-193.
58. Tishchenko, K.; Beloglazkina, E.; Mazhuga, A.; Zyk, N., Copper-containing enzymes: Site types and low-molecular-weight model compounds. **2016,** *6*, 49-82.
59. Majumder, S.; Mondal, S.; Lemoine, P.; Mohanta, S., Dinuclear mixed-valence Co III Co II complexes derived from a macrocyclic ligand: unique example of a Co III Co II complex showing catecholase activity. **2013,** *42* (13), 4561-4569.
60. Mukherjee, S.; Weyhermüller, T.; Bothe, E.; Wieghardt, K.; Chaudhuri, P., Dinuclear and mononuclear manganese (IV)-radical complexes and their catalytic catecholase activity. **2004,** (22), 3842-3853.
61. Reja, S.; Kejriwal, A.; Das, R., Copper Based Biomimetic Catalysts of Catechol Oxidase: An Overview on Recent Trends. **2023,** *15* (1), 108-124.

62. Abu-Omar, M. M.; Loaiza, A.; Hontzeas, N., Reaction mechanisms of mononuclear non-heme iron oxygenases. **2005,** *105* (6), 2227-2252.
63. Foote, C. S.; Valentine, J. S.; Greenberg, A.; Liebman, J. F., *Active oxygen in chemistry*. Springer Science & Business Media: 2012; Vol. 2.
64. Malthus, S. J.; Cameron, S. A.; Brooker, S., First row transition metal complexes of di-o-substituted-diarylamine-based ligands (including carbazoles, acridines and dibenzoazepines). **2016,** *316*, 125-161.
65. Gerdemann, C.; Eicken, C.; Krebs, B., The crystal structure of catechol oxidase: new insight into the function of type-3 copper proteins. **2002,** *35* (3), 183-191.
66. Cao, R.; Saracini, C.; Ginsbach, J. W.; Kieber-Emmons, M. T.; Siegler, M. A.; Solomon, E. I.; Fukuzumi, S.; Karlin, K., Peroxo and superoxo moieties bound to copper ion: Electron-transfer equilibrium with a small reorganization energy. **2016,** *138* (22), 7055-7066.
67. Saracini, C.; Ohkubo, K.; Suenobu, T.; Meyer, G. J.; Karlin, K. D.; Fukuzumi, S., Laser-induced dynamics of peroxodicopper (II) complexes vary with the ligand architecture. One-photon two-electron O2 ejection and formation of mixed-valent CuICuII–superoxide intermediates. **2015,** *137* (50), 15865-15874.
68. Wijeratne, G. B.; Hematian, S.; Siegler, M. A.; Karlin, K., Copper (I)/NO (g) Reductive Coupling Producing a trans-Hyponitrite Bridged Dicopper (II) Complex: Redox Reversal Giving Copper (I)/NO (g) Disproportionation. **2017,** *139* (38), 13276-13279.
69. Than, R.; Feldmann, A. A.; Krebs, B., Structural and functional studies on model compounds of purple acid phosphatases and catechol oxidases. **1999,** *182* (1), 211-241.
70. Gentschev, P.; Möller, N.; Krebs, B., New functional models for catechol oxidases. **2000,** *300*, 442-452.
71. Torelli, S.; Belle, C.; Gautier-Luneau, I.; Pierre, J.; Saint-Aman, E.; Latour, J.; Le Pape, L.; Luneau, D., pH-Controlled change of the metal coordination in a dicopper (II) complex of the ligand H− BPMP: Crystal structures, magnetic properties, and catecholase activity. **2000,** *39* (16), 3526-3536.
72. Belle, C.; Selmeczi, K.; Torelli, S.; Pierre, J.-L., Chemical tools for mechanistic studies related to catechol oxidase activity. **2007,** *10* (4-5), 271-283.
73. Sureshbabu, P.; Junaid, Q. M.; Upadhyay, C.; Victoria, W.; Pitchavel, V.; Natarajan, S.; Sabiah, S., Di and tetranuclear Cu (II) complexes with simple 2-aminoethylpyridine: Magnetic properties, phosphodiester hydrolysis, DNA binding/cleavage, cytotoxicity and catecholase activity. **2019,** *164*, 202-218.
74. Martell, A. E.; Sawyer, D. T., Oxygen Complexes and Oxygen Activation by Transition Metals [electronic resource].
75. Dey, S. K.; Mukherjee, A., Catechol oxidase and phenoxazinone synthase: Biomimetic functional models and mechanistic studies. **2016,** *310*, 80-115.
76. Os rio, R. E.; Peralta, R. A.; Bortoluzzi, A. J.; de Almeida, V. R.; Szpoganicz, B.; Fischer, F. L.; Terenzi, H. n.; Mangrich, A. S.; Mantovani, K. M.; Ferreira, D., Synthesis, magnetostructural correlation, and catalytic promiscuity of unsymmetric dinuclear copper (II) complexes: models for catechol oxidases and hydrolases. **2012,** *51* (3), 1569-1589.
77. Koval, I. A.; Selmeczi, K.; Belle, C.; Philouze, C.; Saint-Aman, E.; Gautier-Luneau, I.; Schuitema, A. M.; van Vliet, M.; Gamez, P.; Roubeau, O., Catecholase activity of a copper (II) complex with a macrocyclic ligand: unraveling catalytic mechanisms. **2006,** *12* (23), 6138-6150.
78. Zeuner, A.; Alves, H.; Hofmann, D.; Meyer, B.; Hoffmann, A.; Haboeck, U.; Strassburg, M.; Dworzak, M., Phys. Status Solidi B https://doi. org/10.1002/1521-3951 (200212) 234: 3< R7:: AID-PSSB99997> 3.0. CO; 2-D 234. R7: 2002.

79. Kodera, M.; Kawata, T.; Kano, K.; Tachi, Y.; Itoh, S.; Kojo, S., Mechanism for Aerobic Oxidation of 3, 5-Di-tert-butylcatechol to 3, 5-Di-tert-butyl-o-benzoquinone Catalyzed by Di-μ-hydroxo-dicopper (II) Complexes of Peralkylated Ethylelnediamine Ligands. **2003,** *76* (10), 1957-1964.
80. Adhikary, J.; Chakraborty, P.; Das, S.; Chattopadhyay, T.; Bauza, A.; Chattopadhyay, S. K.; Ghosh, B.; Mautner, F. A.; Frontera, A.; Das, D., A combined experimental and theoretical investigation on the role of halide ligands on the catecholase-like activity of mononuclear nickel (ii) complexes with a phenol-based tridentate ligand. **2013,** *52* (23), 13442-13452.
81. Hikichi, S.; Komatsuzaki, H.; Kitajima, N.; Akita, M.; Mukai, M.; Kitagawa, T.; Moro-oka, Y., Characterization of a μ-η2: η2-Peroxo Dinuclear Cobalt (II) Complex. **1997,** *36* (3), 266-267.
82. Mukherjee, J.; Mukherjee, R., Catecholase activity of dinuclear copper (II) complexes with variable endogenous and exogenous bridge. **2002,** *337*, 429-438.
83. Koval, I. A.; Gamez, P.; Belle, C.; Selmeczi, K.; Reedijk, J., Synthetic models of the active site of catechol oxidase: mechanistic studies. **2006,** *35* (9), 814-840.
84. Klabunde, T.; Eicken, C.; Sacchettini, J. C.; Krebs, B., Crystal structure of a plant catechol oxidase containing a dicopper center. **1998,** *5* (12), 1084-1090.
85. Hwang, J.; Jeong, Y.; Park, J. M.; Lee, K. H.; Hong, J. W.; Choi, J., Biomimetics: forecasting the future of science, engineering, and medicine. **2015**, 5701-5713.
86. Güell, M.; Siegbahn, P. E., Theoretical study of the catalytic mechanism of catechol oxidase. **2007,** *12*, 1251-1264.
87. Rolff, M.; Schottenheim, J.; Decker, H.; Tuczek, F., Copper–O 2 reactivity of tyrosinase models towards external monophenolic substrates: molecular mechanism and comparison with the enzyme. **2011,** *40* (7), 4077-4098.
88. Eicken, C.; Krebs, B.; Sacchettini, J., Catechol oxidase—structure and activity. **1999,** *9* (6), 677-683.
89. Bassan, A.; Borowski, T.; Siegbahn, P., Quantum chemical studies of dioxygen activation by mononuclear non-heme iron enzymes with the 2-His-1-carboxylate facial triad. **2004,** (20), 3153-3162.
90. Solomon, E. I.; Tuczek, F.; Root, D. E.; Brown, C., Spectroscopy of binuclear dioxygen complexes. **1994,** *94* (3), 827-856.
91. Banu, K. S.; Chattopadhyay, T.; Banerjee, A.; Bhattacharya, S.; Zangrando, E.; Das, D., Catechol oxidase activity of dinuclear copper (II) complexes of Robson type macrocyclic ligands: Syntheses, X-ray crystal structure, spectroscopic characterization of the adducts and kinetic studies. **2009,** *310* (1-2), 34-41.
92. Banu, K. S.; Chattopadhyay, T.; Banerjee, A.; Bhattacharya, S.; Suresh, E.; Nethaji, M.; Zangrando, E.; Das, D., Catechol oxidase activity of a series of new dinuclear copper (II) complexes with 3, 5-DTBC and TCC as substrates: syntheses, X-ray crystal structures, spectroscopic characterization of the adducts and kinetic studies. **2008,** *47* (16), 7083-7093.
93. Sengupta, S.; Khan, S.; Chattopadhyay, S. K.; Banerjee, I.; Panda, T. K.; Naskar, S. J. P., Trinuclear copper and mononuclear nickel complexes of oxime containing Schiff bases: Single crystal X-ray structure, catecholase and phenoxazinone synthase activity, catalytic study for the homocoupling of benzyl amines. **2020,** *182*, 114512.
94. Bauman, K. D., *In vivo and in vitro strategies for characterizing secondary metabolite biosynthetic pathways from marine bacteria*. University of California, San Diego: 2022.

95. Chen, P. Y.-T.; DeColli, A. A.; Meyers, C. L. F.; Drennan, C., X-ray crystallography–based structural elucidation of enzyme-bound intermediates along the 1-deoxy-d-xylulose 5-phosphate synthase reaction coordinate. **2019,** *294* (33), 12405-12414.
96. Sakaue, S.; Tsubakino, T.; Nishiyama, Y.; Ishii, Y., Oxidation of aromatic amines with hydrogen peroxide catalyzed by cetylpyridinium heteropolyoxometalates. **1993,** *58* (14), 3633-3638.
97. Kaizer, J.; Csonka, R.; Speier, G., TEMPO-initiated oxidation of 2-aminophenol to 2-aminophenoxazin-3-one. **2002,** *180* (1-2), 91-96.
98. Horváth, T.; Kaizer, J.; Speier, G., Functional phenoxazinone synthase models: Kinetic studies on the copper-catalyzed oxygenation of 2-aminophenol. **2004,** *215* (1-2), 9-15.
99. Maurya, M. R.; Sikarwar, S.; Joseph, T.; Halligudi, S., Bis (2-[α-hydroxyethyl] benzimidazolato) copper (II) anchored onto chloromethylated polystyrene for the biomimetic oxidative coupling of 2-aminophenol to 2-aminophenoxazine-3-one. **2005,** *236* (1-2), 132-138.
100. Mahato, S.; Meheta, N.; Kotakonda, M.; Joshi, M.; Ghosh, P.; Shit, M.; Choudhury, A. R.; Biswas, B., Ligand directed synthesis of a unprecedented tetragonalbipyramidal copper (II) complex and its antibacterial activity and catalytic role in oxidative dimerisation of 2-aminophenol. **2020,** *34* (11), e5935.
101. Troiano, D.; Orsat, V.; Dumont, M.-J., Status of biocatalysis in the production of 2, 5-furandicarboxylic acid. **2020,** *10* (16), 9145-9169.
102. Le Roes-Hill, M.; Goodwin, C.; Burton, S., Phenoxazinone synthase: what's in a name? **2009,** *27* (4), 248-258.
103. Zhang, L.; Liu, N.; Ma, X.; Jiang, L., The transcriptional control machinery as well as the cell wall integrity and its regulation are involved in the detoxification of the organic solvent dimethyl sulfoxide in Saccharomyces cerevisiae. **2013,** *13* (2), 200-218.
104. Zhang, L.; Gu, L.; Ringler, P.; Smith, S.; Rushton, P. J.; Shen, Q., Three WRKY transcription factors additively repress abscisic acid and gibberellin signaling in aleurone cells. **2015,** *236*, 214-222.