CHAPTER 1

Introduction

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References
1.1 GENERAL IDEA ABOUT COORDINATION CHEMISTRY

The coordination chemistry has been of great significance in our understanding of chemical structure and bonding. Relatively few complex compounds have been found useful in industry and other fields\(^1\)-\(^{10}\). A wide range of interatomic, interionic and intermolecular reaction in solution\(^{11,12}\) as well in solid phase embraced under the coordination chemistry. The electronic structure and configuration of the complexes are related to their physical and chemical properties by the progressive development of the valence bond theory\(^{14-18}\). The crystal field theory\(^{19-27}\), ligand field theory and molecular orbital theory\(^{28-37}\).

In addition, complex compounds are of great importance in processes used for separating the rare earth elements, in the chemical technology of gold, nickel, cobalt and copper, separating the alkali metals, in electroplating and in many other fields. The compounds with nitrogen-containing ligands are of particular importance because they represent the most thoroughly investigated group of complexes. The basic principles of the coordination theory were established by investigations of these compounds.

Coordination chemistry has been a fascinating branch of chemistry. It has attracted the attention of several chemists during the last many years. Extensive investigations have been made in this branch of chemistry. The chemistry of coordination has encompassed a number of domains of chemistry and is the melting place of inorganic, organic, physical, analytical and theoretical chemistry.

The well-known Zeigler-Natta catalyst used for the low-pressure polymerization of ethylene is a complex of aluminium and titanium. Complex formation is used extensively in analytical chemistry for detection, estimation and separation of metal ions.
In living creatures, two important coordination compounds are chlorophyll in green plants and haemoglobin in the blood of vertebrate animals. Chlorophyll which is vital to photosynthesis in plants, is a magnesium complex and haemoglobin which carries oxygen to animals cells, is an iron complex. There is no doubt that complex compounds are of great importance in the life processes of organisms. Such substances haemoglobin and chlorophyll which are very important from the biological point of view belong to the category of inner complexes. In many cases such coordinated metal ions are important component parts of certain enzymes specifically, the oxidizing enzymes. Complex compounds have practical values as well as theoretical values. For example, they are important in the development of methods of qualitative and quantitative analysis.

The values of complex compounds in analysis is due to the fact that singularity of individual elements appears more clearly among coordination compounds than among the simple ones. Therefore; it is often possible to differentiate and sometimes to separate, elements which behave similarly in the usual ionic reactions. Moreover, complex formation leads to a broader variation in the properties of each individual metal ion.

This terse summary clearly indicates the important theoretical and practical uses of complex formation and explains the ever increasing interest which has been devoted to this field of chemistry in recent years. Having considered the many facts of coordination compounds from earliest times to the present, we might well inquire as to what we can except of the future.

The studies in the field of coordination chemistry originated when Disbach in 1704 prepared a new type of compound named Prussian blue. The rapid activity in this era began in 1798 when Tasert obtained orange crystalline hexamine cobalt (III) chloride at the end of nineteenth century.
numerous compounds of this type containing metals such as Co, Pt, Fe etc. with amines were prepared.

The area of chemistry concerned in this case is that of coordination or complex compounds. Such compounds contain a central atom or ion usually a metal and a cluster of ions or molecules surrounding it. It is characteristics of the complex that it retains its identity, more or less, even in solution though partial dissociation may occur. The complex may be nonionic or a cation or anion depending the charges carried by the central atom and the coordinated group.

Werner's coordination theory has been a guiding principle in inorganic chemistry and in the theory of valence since its publication sixty year ago. Indeed it might be said to underlie our modern concepts of molecular structure. The current theories of acidity, basicity, amphoterism and hydrolysis grew directly from it, and the assumption of the complete ionization of solid salts is implicit in it. In recent years, the coordination theory has found increasing application in many types of chemical work.

The progressive development of the valence bond theory viz. the crystal field, ligand field and molecular orbital theories developed on the basis of quantum chemistry allows chemists to relate the electronic structures and configurations of complex compounds to their physical and chemical properties.

1.2 ANTIBIOTICS AND THEIR COORDINATION BEHAVIOUR

Antibiotics are natural compounds produced mostly by plant micro-organisms, having marked and selective biological activity against micro-organisms. They have low toxicity, and are used to destroy microbes in vivo. These properties make antibiotics powerful drugs
applicable in combating infections diseases. Such as tuberculosis, syphilis, gastrointestinal infection, communicable, diseases of childhood\textsuperscript{41, 42} and many others\textsuperscript{43-54}.

It has been reported that complexes of antibiotics with metals are most potent and less toxic in many cases then original drug therefore; complexes of antibiotics with metal ion have great significance.

It has been mentioned that during complex formation the metal cation combines with a ligand containing donor atom, the metal, if the ligand contains two or more donor groups so that one or more rings are formed and the resulting structure is known as chelate compound or metal chelate. The ligand in this case is known as chelating agent. The term chelation was originally used for rings formed through hydrogen bonding. It was used by Morgan and Drew in a broader sense to cover the above mentioned cases of ring formation through coordination. The bond formation between the central metal ion and the chelating agent may be "essentially covalent or ionic in nature" depending on the metal atoms and the donor atom involved in the process. The number of chelating agents is quite large, with a potential capacity to be much larger, but the donor atoms undergoing coordination with metal ion are few in number from groups V and VI the most common being N, O and S.

Antibiotics also form complexes with Zn and Mn. The coordination behaviors of antibiotics with metal were studied by many workers\textsuperscript{55-60}. Tetracyclines\textsuperscript{61} possess many sites where metal binding can occur. It is natural therefore; that this group of antibiotics would attract the attention of coordination chemists. In fact it has happened and quite a number of workers have reported various TC complexes giving their possible structures.
Manganese\textsuperscript{62, 63} is an essential competent for the reduction of DPN\textsuperscript{+} by malate in certain Escherichia Cali extracts and it has been observed in such reactions that the inhibition of nitroductase by chlortetracycline is due to the complexation with manganese and preventing the formation of DPNH is essential for reduction. Pencreaticlipase in inhibited by chlortetracycline only in the presence of divalent ions.

Hunter and Iowry\textsuperscript{64} have reported that tetracycline shows uncoupled aerobic phosphorylation by interaction with magnesium bound to an enzyme without actually removing it.

Goldman\textsuperscript{65} reported that oxytetracycline is used for the inhibition of alanine dehydrogenase. He suggested that oxytetracycline inhibits crude preparation but not more purified preparation, by adding certain metal ions, concluded that a metal chelate at oxytetracycline is prepared and acts as a actual inhibitor.

Schmid\textsuperscript{66} has been reported that selective denaturation of the enzyme in some way, leading to inhibition of the parasite by coordination of antibiotics with enzyme bound metal ions.

Linden Baum and White\textsuperscript{67} reported that certain enzyme systems inhibited by metain may be reactivated by tetracycline, such as the beryllium induced inhibition of rat plasma; alkaline phosphatase is suppressed by the addition of chlortetracycline or other metain complexing agents.

Mullons\textsuperscript{68} suggested that textiles can be protected from bacteria and fungi by using the complexes of neomycin with Zn. Antibiotics form complexes with Mn and Zn. The coordination behaviour of antibiotics with metals was reported by many workers\textsuperscript{69-74}.

Conover\textsuperscript{75} concluded on the basis of absorption spectra of metal-oxytetracycline complexes that the binding group is the enolized $\beta$-
diketone group at C₁₁ and C₁₂. The same observation was made by Benet and Goyan on the basis of thermodynamic data. Doluisio and Martin⁷⁶ concluded on the basis of potentiometric data and examination of Stuart and Briegeleb models, it is postulated that tetracycline chelation with these metal ions occurs through coordination with the C₄ dimethylamino group and either C₃ or C₁₂α hydroxyl group.

According to the Baker and Brown⁷⁷, The electronic spectra indicated the coordination of tetracycline molecule through oxygen of the 1, 2, 3-tricarbonylmethane system, the amide oxygen at C₂ and hydroxyl at C₁ or C₃.

In our case, where, antibiotics are chlortetracycline, oxytetracycline and tetracycline, the oxygen of carbon atom and oxygen of amide group take part in bond formation with the metal ion making six membered ring⁷⁸,⁷⁹.

In the case of penicillin-V and penicillin-G, where the ring nitrogen and oxygen of the carboxylic group take part in coordination making five membered ring⁸⁰,⁸¹.

It is clear from the bonding of the, antibiotics, that different antibiotics make bond with the metal ions with different sites, and the resulting complexes formed have many important applications.

Keeping the importance of metal-drug complexation in mind the author has undertaken bivalent viz. neomycin, Chlortetracycline, oxytetracycline, tetracycline, penicillin-V penicillin-G, vitamin-B₂, vitamin-Bₓ and vitamin-B₅ respectively.

1.3 GENERAL IDEA ABOUT ANTIPYRETICS AND ANALGESICS

The analgesic and antipyretic group of drugs includes a small, heterogeneous group of compound which are used widely for minor aches and pains, headaches and the general feeling of malaria that fever, arthritis,
gout and other musculoskeletal disturbances\textsuperscript{82}. The salicylate group of analgesics and antipyretics are by far the most commonly employed\textsuperscript{83}. In general, salicylates are contraindicated in hypersensitive individuals and in those with gastrointestinal disturbances, particularly hemorrhaging ulcers\textsuperscript{82}. They should also be used with caution in patients on anticoagulant therapy and avoided in patients on uricosurics.

The salicylate interacts with a wide variety of agent, some of which are clinically while other are largely of theoretical interest\textsuperscript{84-87}. In the present investigation the authors have taken the most common antipyretic and analgesic drugs viz. vitamin-B\textsubscript{2}, vitamin-B\textsubscript{x} and vitamin-B\textsubscript{5} as secondary ligands and the complex study of these drugs with manganese and zinc with some antibiotics viz. neomycin, chlortetracycline, oxytetracycline, tetracycline, penicillin-V and penicillin-G have been studied at 25\textdegree{}C and 35\textdegree{}C.

It is therefore; we can say that different antibiotics make bond with metal ions from different sites and the complexes formed may have a number of applications.

1.4 \textbf{BIOLOGICAL IMPORTANCE OF MIXED LIGAND COMPLEXES OF ANTIBIOTICS}

Now a day, human beings suffer from several serious diseases owing to the polluted environment. Many bacteria cause number of diseases. Before the discovery of antibiotics in the mid of nineteenth century, the drugs that we had are not much effective in combating the diseases. A small dose of antibiotics is safe can be used for most of the diseases.

These antibiotics viz. neomycin, Chlortetracycline, oxytetracycline, tetracycline, penicillin-V and penicillin-G formed not only binary complexes but also ternary complexes as evidenced from the study done. In some biological study, ternary complexes are more the study done.
In some biological study, ternary complexes are more effective than the binary complexes. For example in the case of amino acids, the ternary system [Cu(II)-histidine-albumin] is involved in the transport phenomenon across biological membranes\(^88\). The [Cu(II)-histine-threonine] is another ternary system which plays an important role in metal ion transfer in biological systems\(^89\). Not much work has been reported regarding the mixed ligand complexes of antibiotics.

Mukherjee and Ghosh\(^{90}\) have reported mixed ligand complexes of Co, Ni, Cu, and Zn with ampicillin is an antibiotics drug of the penicillin family has growth inhibiting action on the micro organisms by causing misreading of the genetic code at the stage of protein synthesis. The genetic codes constitute sequences of three nucleic bases out of adenine. Similarly, the present ternary complexes of antibiotics with Mn(II) and Zn(II) will definitely have many biological and biochemical importance.

1.5 BIOLOGICAL ASPECTS OF TRANSITION METALS

Among the transition metal ion cupper, manganese, cobalt, molybdenum and Zinc play important roles in the biochemistry of the human body\(^91\). Organomercury compounds have been used for centuries as pharmaceuticals. Excess of these ions are, however toxic.

Most of these ions possess three chemical properties that are extremely important in carrying out biochemical processes. First they form stable complexes with proteins and other biologically active substances; they are very good catalysts and finally they exhibit various oxidation states which are readily formed and interconverted in the environment of the cell. The interconversion of oxidation states is uniquely suited to biochemical functions.

One important function of these metal ions in their role as cofactor is reaction involving enzymes. Cofactors are nonprotein constituents of enzymes
which must be bound to the enzyme in order for it to be catalytically active. Some enzymes require cofactors such as metal ions or coenzymes.

The metal ions acting as cofactors in such enzymes may act either by coordinating to the reactant species and binding it to the enzyme or they must act as the catalyst for the reaction itself. Biologically zinc is one of the most important metals and apparently necessary to all forms of life. Zinc appears to be necessary for the building of proteins which make up most of the solid matter of the cells. It is the constituent of the enzyme which release the carbon dioxide from bicarbonate in the blood. Human and animal sperms contain large amount of zinc\textsuperscript{92,93}.

\textit{Mn(II)}, is an essential element, presents in all living organisms is used as antiseptics and germicides. It is also a cofactor (these are non protein constants of enzymes which must be bound to the enzyme in order to make it catalytically active) in a number of enzymatic reactions, particularly those involved in phosphorylation, cholesterol and fatty acid synthesis\textsuperscript{94}.

1.6 SIGNIFICANCE OF STABILITY CONSTANTS

In studying the formation of complexes in solution, two kinds of stability have to be distinguished, namely thermodynamic stability and kinetic stability. The former is a measure of the extent of formation of a complex species (under certain conditions) when the system has reached equilibrium. The latter refers to speed with which transformation leading to the attainment of equilibrium will occur.

The fact that stability constant\textsuperscript{95} has been found to be appreciably greater than zero is perhaps one of the most convincing pieces of evidence for the existence of the complex in solution. Moreover, if, all the stability constants for a given system have been determined, it is possible,
in principle, to calculate the equilibrium concentration or activity of each of the species present under a known set of experimental conditions. Such exact knowledge of the composition of a solution is essential for a correct interpretation of its optical and kinetic properties, of its partition equilibria and of its biological behavior.

The values of the stability constants can also be used to predict the conditions required for complete or maximal formation of a given complex. Relative information of this type may be of great importance in planning analytical and separative procedures. For example, in cases where the species in question is highly colored or can be precipitated from solution extracted into an organic solvent, or sorbed on an ion exchange or chromatographic column. It is also important in the study of metal chelates in biological systems.

The value of free energy associated with the reaction can be calculated by stability constants. The change in entropy ($\Delta S$) of complex formation can be obtained by stability constants and enthalpy change ($\Delta H$) of complex formation$^{96}$. These parameters are valuable in chemical technology viz., in hydrometallurgy and electrochemistry and in chemical analysis.

1.7 BIOINORGANIC COMPLEXES AND ITS SIGNIFICANCE AGAINST METAL TOXICITY

The term 'antidotes' $^{97,98}$ include the variety of remedies that are anti to action of poison. These are chemical, pharmacological or physiological in nature. They counteract the effect of poison prevent its access to the site of action and enhance its excretion. Specific antidotes are rarely necessary and there are few available, although in appropriate circumstances the administration of an antidote may sometimes be life saving.
Since, the poisons exert their toxic effects by reacting chemically with essential substrate in the cell through biochemical mechanism of toxicity, it is necessary to collect more information about their mechanism of action and more antidotes will be developed.

However, some antidotes have the specific action of their own, which not only affect of the status of the patient but also contributes to fatal outcome\(^9\). Metal intoxication and metal storage diseases are controlled by using antidotes by accelerating the excretion of toxic metals in the form of nontoxic by formation of insoluble compound.

Levine\(^{100}\) has reported the broad and extensive information on the antagonists of antidotes. The antidotes possessing the common property of reacting with metal to form tightly bound complexes. Act by the prevention or by the reversing the binding of toxic metal to body ligands. They form a specific kind of complex called chelate which reduces the free metal ion concentration in the body fluids and capable to promote the dissociation of bonds between metal and tissue enzymes and other functional macromolecules which are generally water soluble, excreted by kidney, thus, total metal is reduced from body.

Till now no suitable antidotes are available for Cd toxicity. At present EDTA and its derivatives are used for Cd toxicity, but initially they all reduce the mortality of Cd but eventually they increase nephrotoxicity. Therefore, the use of these drugs for Cd toxicity is questionable. In case of Zn(II), penicillamine (dimethyl cysteine) has been used for Zn(II) toxicity. Day by day, new suitable antidotes are being prepared.

In our case, antibiotics viz. neomycin, chlortetracycline, oxytetracycline, tetracycline, penicillin-V and penicillin-G and some antipyretics such as vitamin-B\(_2\), vitamin-B\(_X\) and vitamin-B\(_5\) form stable
complexes with Mn(II) and Zn(II) at human blood pH 7.30 ± 0.01, therefore; these antibiotics might be used as antidotes for treating the toxicity of Mn(II) and Zn(II)\textsuperscript{101, 102} in the body. The work in metal intoxication is in progress and in future, it will definitely establish its own platform.

1.8 THEORIES OF COMPLEX FORMATION

(a) Werner's coordination theory

The first successful theory explaining the properties of coordination compound in terms of their structures was proposed by Alfred Werner's (1893).

Werner's\textsuperscript{103} coordination theory, with its concept of primary and secondary valences provides an adequate explanation for the existence of such complexes as [Co(NH\textsubscript{3})\textsubscript{6}] Cl\textsubscript{3}. The properties and stereochemistry of these complexes are also explained by the theory. This theory replaced the older concepts of Brezellius (1819), Grahm (1837), Claus (1856), Blomstrand (1969) and Jorgenson (1878-1894), and become a fundamental part of the theory of valency formulated by G. N. Lewis\textsuperscript{104}. According to Werner,

Every element exhibits two types of valences, namely, primary valency (ionic value) and secondary valency (nonionic valency).

Primary valences are those in which a metal exercise in the formation of its simple salts and the secondary valences are those in which a metal exercises towards a neutral molecule or an anion in the formation of complex ion.

Secondary valences are directed in space and hence compounds are capable of exhibiting the phenomenon of isomerism.

The number of ligands which are arranged around the central metal ion is called the coordination number\textsuperscript{105}. Although this theory explains the structure and stereochemistry of complexes but could not give any
theoretical background for the two types of valences and this was the reason\textsuperscript{106-108} why this theory was not accepted up to 1916.

Later on, Lowry\textsuperscript{109} and Sidgwick\textsuperscript{110} explained wernar’s ideas with the help of electronic theory of valency.

(b) The valence bond theory\textsuperscript{111}

One viewpoint is stressed by the valence bond method chiefly developed for complexes by Pauling\textsuperscript{112}. In this theory, it is considered essential that a number of orbitals of the central metal atom equal to the number of ligands be made available to form coordinate bonds with orbitals of the ligands. Furthermore, by using the criterion that maximum angular overlap of two orbitals forms the strongest covalent bond, it is shown that the original atomic orbitals should be hybridized to form a new set of equivalent bond orbitals with definite directional properties. In this way the familiar set of four tetrahedral orbitals is built from one’s and three ‘p’ orbitals.

It has been postulated by Pauling that, if a ligand has, or can have by resonance, vacant orbitals, and if, the central atoms has d electrons, \(\pi\) bonding from the metal to the ligand will occur. This will strengthen the coordinate bond (making it a double bond) and help to reduce the negative charge formed on the central atoms by the addition of the ligands.

Some of the evidence for the existence of \(\pi\) bonding in metal complexes has been reviewed by Chatt and Nyholm\textsuperscript{113, 114}. This evidence centers about the relative stabilities of certain complexes, changes in infrared absorption frequencies and shortening of bond lengths.

Theoretical accounts of \(\sigma, \pi, \delta\) bonding involving d orbitals have been given by Jaffe\textsuperscript{115, 116} and others\textsuperscript{117, 118}. In order to account for the different magnetics properties of a given metal ion in various complexes
Pauling\textsuperscript{112} postulated that in the case of strong electron donating ligands, such as CN\textsuperscript{-}, covalent bond formation would definitely occur.

One unfortunate result of this historical development of the valence bond theory is that the terms ionic and covalent have come to be used as synonyms for weak and strong respectively.

It has, however, been unable to explain absorption spectra and magnetic properties of complex ions. This shortcoming has led to the development of the crystal field theory.

\textbf{(c) The valence shell electron-pair repulsive theory}

This theory links valence bond theory and electrostatic theory and is very useful to predict the geometry of molecules or complexes of non transition elements and also d\textsuperscript{0}, d\textsuperscript{5} and d\textsuperscript{10} transition metal. This theory is based on the ideas of Sidgwick and Powell\textsuperscript{119} and has been elaborated by Nyholm and Gillespie\textsuperscript{120}. For the non spherically symmetric transition metals, this theory stereochemistry of complexes but dose not deals with other properties such as bond length etc.

\textbf{(d) The electrostatic theory}

Van Arkel and De- Boer\textsuperscript{121}, and Garrick\textsuperscript{122} following the pioneering ideas of Kossel, Magnus and Tajans, showed that a fairly simple electrostatic picture of complexes, assuming point charges and dipoles could account for many of their properties.

The parameters needed were the charges and size of the central ion and the charges, dipole moments, polarizabilties and size of ligands. By using the ordinary potential energy equation of electrostatics, quantitative calculations could be made for various coordination numbers and stereochemistry.
This theory fairly well explains the electrostatic character of complexes but could not explain many forces such as London attraction forces and many properties of complexes.

(e) Crystal field theory

The theory was first introduced by Bethe and Van Vleck and applied mainly to ionic crystals, but Orgel has been largely responsible for developing its general chemical aspects.

On this theory, a complex is regarded as an agglomeration of a central ion surrounded by other ion or molecules with electrical dipoles. The electrical field of the central ion will affect the surrounding ligands, whilst the combined field of the ligands will influence the electrons of the central ion. As will be seen, the effect of the ligands is particularly marked on the d-electrons which play such a large part in complex formation by transition elements. The influence of the ligands depends on the nature, particularly on the strength of their electrical field, and on their geometrical positions in the complex.

In the simplest treatment of the problems concerned the bonding between the central ion and the ligands is regarded as purely ionic so that the forces involved can be limited to electrostatic forces. Such a limited treatment is generally referred to as crystal field theory. A fuller treatment of ligand field theory introduces the possibilities of covalent bonding.

In strong ligands fields, the value of $\Delta_0$ is very large. The tendency of the electrons to go into different orbitals is over-weighed by their tendency to occupy of lower energy level with their spin paired.

The splitting of the five d-orbitals for the octahedral and tetrahedral structure of coordination compound has been explained. The theory takes no account of the partly covalent nature of the metal ligand bond.
The molecular orbital theory

J. H. Vanvleck\textsuperscript{131} was the first to apply this theory in complex formation. The electrons are assumed to move in molecular orbitals which extend over all the nuclei of the system. The molecular orbitals themselves are taken for convenience, as linear combination of atomic orbitals. In the event that a given atomic orbitals (A. O.) overlaps appreciably with only one other (A. O.), the pair may be regarded as forming a localized molecular orbital holding as many as two electrons. This would correspond to the usual conception of a chemical bond. This explains many properties of complexes\textsuperscript{132} but still has some drawbacks. These are:

The usual one of any quantum mechanical approach to complex systems that quantitative calculation of the energy can not be made and

The disappearance of the nice pictures of chemically bonded atoms so useful to the chemists. The later difficulty can be partly avoided by the use of L. M. O. S.
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