CHAPTER 1

Introduction
It is during the past fifty years that one thing has become quite clear and can not escape the notice of any researchers or keen student of chemistry. The development is the coordination among different branches of chemistry. The chemistry of complex compounds has encompassed a number of domains of chemistry and has become a bridge to combine closely and logically the inorganic, organic, physical and other branches of chemistry. In this way, it expresses the unity of chemistry as the science dealing with the structure of matter. The countless theories and methods used here explain the popularity of this domain among the scientists. While the development of coordination science, relatively a few complexes have been proved its valuable utility in industries and other fields\textsuperscript{1-10}.

A wide range of interatomic, interionic and intermolecular reactions in solution\textsuperscript{11-12} as well as in solid phase\textsuperscript{13} embraced under the coordination chemistry. The electronic structures and configuration of the complexes are related to their physical and chemical properties by the progressive development of the valence bond theory\textsuperscript{14-18}, the crystal field theory\textsuperscript{19-27}, ligand field theory and molecular orbital theory\textsuperscript{28-37}.

1.1 General idea about coordination Chemistry

Coordination chemistry has valuable importance in quantitative determinaton viz. volumetrically, gravimetrically and colorimetric determination as well as in polarimetry and microscopy. In addition, coordination compounds are widely used in separating alkali metals, electroplating, techniques for the separation of rare earths, and many other fields. As a consequence of the ability of complexed metal ions to influence many of the complex reactions, upon which the important
process of living organisms depend, coordinated compounds of many varieties are found widely distributed in nature, blood pigment, metallo-proteins, chlorophyll, metallo-enzymes, many vitamins, cytochrome etc. make some important examples of this category.

During the past few decades, coordination compounds also proved their significance in the field of dying. Most dyestuffs are synthetic organic compounds, and of these, the large class of metal dye compounds called "dye-lakes", are of great interest to the coordination chemist.

In the field of analysis, where elements appear more clearly among coordinated components, used to differentiate and sometime to separate the elements that behave similarly in the common ionic reactions.

Coordination phenomenon is used for the softening of water by "tying up" alkaline earth ions in soluble complex ions and removing the formation of precipitates.

Coordination chemistry also proved its significance in pharmaceuticals. If the ligand forms a stable, water soluble metal chelate, it is used as a sequestering agent in sequestration, in which, suppression of property or reaction of a metal is done without removal of that metal from the system or phase by any process of precipitation or extraction by chelation.

This summary indicates theoretical and practical importance of complex formation and explains increasing interest to coordination in recent years.
Studies in the field of coordination chemistry was started by preparing a new type of compound, prusian blue, in 1704 by Dibach. Later on, in 1978, Tassaert prepared orange crystalline hexamine cobalt (III) chloride and gave a new transition in this field and consequently at the end of nineteenth century, a number of compounds of this type containing Co, Pt, Fe, etc. were prepared.

Coordination chemistry has become a fascinating branch and attracts the attention of chemists during the last few decades. This area of chemistry concerned with a compound containing a central metal ion, usually a metal and a cluster of ions or molecules surrounding it. Metal retains its identity in complexes, more or less, even in solution though partial dissociation may occur. The complex may be a cation or anion or non ionic depending the charge carried by the central atom and the coordinated groups.

A magically guidance was originated in this field when Werner gave his coordination theory in inorganic chemistry. Indeed, it might be said to underlie our modern concepts of molecular structures. The current theory of acidity, basicity and hydrolysis given directly from it, and the assumption of the complete ionisation of solid salts is implicit in it.

The utilization of the coordination compounds have also been extended in many important field, viz., industries, labs for determination, identification and separation of elements, preparation of reactor materials, extraction of elements, preparation of fine chemicals etc. and chiral catalysis also the important field in which coordination compounds play important role. New investigation are being made in
coordination chemistry day by day and in future, this branch will prove to open new ways for the scientists.

1.2 Antibiotics and their coordination behaviour

Antibiotics, are natural compounds produced mostly by plant microorganisms, have marked and selective biological activity against microorganisms. They have low toxicity, and are used to destroy microbes in vivo\(^{39}\). These properties make antibiotics powerful drugs applicable in combating infectious diseases, such as tuberculosis, syphilis, gastrointestinal infections, communicable diseases of childhood\(^{40,41}\) and many others\(^{42-53}\).

It has been reported that complexes of antibiotics with metals are most potent and less toxic in many cases than original drug\(^{54}\), therefore, complexes of antibiotics with metal ion have much significance.

Manganese\(^{55,56}\) is an essential component for the reduction of DPN\(^+\) by malate in certain Escherichia coli 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. Pancreatic lipase is inhibited by chlortetracycline only in the presence of divalent ions.

Hunter and lowry\(^ {57}\) have reported that tetracycline uncouple aerobic phosphorylation by interaction with magnesium bound to an enzyme without actually removing it.

Goldman\(^ {58}\) 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 of oxytetracycline is prepared and acts as a actual inhibitor.

Schmid has been reported that selective denaturation of the enzyme in some way, leading to inhibition of the parasite by coordination of antibiotic with enzyme bound metal ions.

Lindenbaum and White reported that certain enzyme system inhibited by metals may be reactivated by tetracycline, such as the beryllium induced inhibition of a rat plasma, alkaline phosphatase is suppressed by the addition of chlortetracycline or other metal complexing agents.

Mullins 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 were reported by many workers.

In complexation, where metal cation combines with a ligand containing two or more donor atoms, more rings are formed in the complex and resulting structure is said to be chelate. The term 'chelation' was originally used by Morgan and Drew, to cover the cases of ring formation in coordination. The nature of bond formed between the metal ion and chelating agent may essentially be ionic or covalent, depends on the metal atom and the donor atoms involved.

Conover have reported that tetracycline possess many sites where metal binding can occur and suggested possible structure of tetracycline which have led to more vigorous attempt to arrive at the most probable coordination sites viz. C₁-C₃ tricarbonylmethane,
C$_4$ dimethylamine and the C$_3$ or C$_{12}$ hydroxyl. C$_{10}$-C$_{11}$ ketophenol, C$_{11}$-C$_{12}$ diketone and multidentate combinations of the C$_{11}$-C$_{12}$ β-diketone and C$_1$-C$_3$ tricarbonylmethane achieved through folding the molecules along the C$_{4a}$ and C$_{12a}$ axis. He concluded on the basis of absorption spectra of metal-oxytetracycline complexes that the binding group is the enolized β-diketone group at C$_{11}$ and C$_{12}$.

On the basis of potentiometrically data and examination of Stuart and Brigglesb models, it was concluded that tetracycline chelation with these metal ions occurs through coordination with the C$_4$ dimethylamino group and either C$_3$ or C$_{12a}$ hydroxyl group.$^{69}$

Baker and Brown$^{70}$ have reported, that tetracycline molecule coordinated through oxygen of the 1,2,3-tricarbonylmethane system, the amide group at C$_2$ and hydroxyl at C$_1$ or C$_3$, on the basis of electronic spectra.

In case of chlortetracycline, oxytetracycline and tetracycline, the oxygen of the carbonyl group and oxygen of amide group take part in bond formation with the metal ion making six membered ring.$^{71,72}$

It has been reported$^{73,74}$ that in case of penicillin-V and penicillin-G, the ring nitrogen of the carboxylic group take part in coordination by making five membered ring.

1.3 **General idea about antipyretics and analgesics**

The analgesic and antipyretic group of drugs includes a small, heterogeneous group of compounds which are used widely for minor aches and pains, headaches and the general feeling of malaria that accompanies febrile illnesses, and to alleviate symptoms of rheumatic fever, arthritis, gout and other musculoskeletal disturbances.$^{75}$ The
salicylate group of analgesics and antipyretics are by far the most commonly employed\textsuperscript{76}. In general, salicylates are contraindicated in hypersensitive individuals and in those with gastrointestinal disturbances, particularly hemorrhaging ulcers\textsuperscript{75}. 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 agents, some of which are clinically while other are largely of theoretical interest\textsuperscript{77–80}. In the present investigation the authors have taken the most common antipyretic and analgesic drugs viz., phenacetin, paracetamol and aspirin as secondary ligands and the complex study of these drugs with manganese and zinc with some antibiotics viz., neomycin, chlorotetracycline, oxytetracycline, tetracycline, penicillin-V, penicillin-G have been studied at 25°C and 35°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 Biological importance of mixed ligand complexes of antibiotics

During the last few decades, it has been observed that human-being suffers from a number of harmful diseases owing to the polluted environment, by factories, vehicles evolving harmful gases, and also a number of bacteria cause different types of very serious diseases. (The drugs that we had, before the discovery of antibiotics in the mid of nineteenth century are not much effective in controlling these diseases.) It is observed that a small dose of antibiotics is capable for combating
the number of diseases. It is evidenced by the study done that antibiotics viz., neomycin, chlorotetracycline, oxytetracycline, tetracycline, penicillin-V and penicillin-G are capable of forming not only the binary complexes but also ternary complexes with metals.

Sundberg and Martin\textsuperscript{81} have reported that in the transport phenomenon across the biological membrane, the ternary complex [Cu(II)-histidine-albumin] plays an important role.

It has been reported by Sarkar and Wigfield\textsuperscript{82} that the [Cu (II)-histidine threonine] system is used in metal ion transfer in biological system.

Mixed ligand complexes of Co, Ni, Cu and Zn with ampicillin, imidazole and bipyridine have reported by pH measurements\textsuperscript{83}. It has been observed that ampicillin, an antibiotic drug of penicillin family, is used for inhibition of microorganisms. Similarly, the selected antibiotics viz., neomycin, chlorotetracycline, oxytetracycline, tetracycline, penicillin-V and penicillin-G and the some analgesics and antipyretics such as aspirin, paracetamol and phenacetin will form ternary complexes with Mn and Zn by polarographic technique.

1.5 Biological aspects of transition metals

Biometals with valuable significance of biochemistry, medicinal chemistry and coordination chemistry, take part in complexation with a number of ligands, therefore, the study related to coordination behaviour of biometals has now become special branch in bioinorganic field.

Some transition metals such as copper, manganese, cobalt, molybdenum and zinc are important components of the biological processes in human body\textsuperscript{84}. Hence, due to these new biochemical
concepts, it, become now necessary to attract the attention of chemists towards the coordination researches and to focus upon metal complexes as being a new wide range of possibilities.

In pharmaceutical, the organomercury compounds in limited dose, are widely used in centuries, however, the excess dose of mercury becomes toxic.

Manganese, is an essential element, presents in all living organisms, are used as antiseptics and germicides. It is also a cofactor (these are non protein constituents 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{85}

The metal ions acting as cofactors in such enzymes may act either by coordination with the reactant species and binding it to the enzyme or they must act as catalyst for the reaction itself.

In a number of enzymatic reaction, it, has been observed that manganese as such is required by all living organisms and its deficiency defects bone reproduction, brain etc. in animals. Manganese is also essential for plant growth and the deficiency of this metal results in poorly growth of plants.\textsuperscript{86}

The metal zinc, which is necessary for normal growth and development in mammals and ubiquitous, is considered as trace element and is present in a number of metalloenzymes including carbonic anhydrase, glutamic dehydrogenase, lactic dehydrogenase and alkaline phosphate.\textsuperscript{85} Therapeutically, zinc has found to be used as topical astringents, dermal products and antiseptics. Zinc is also
used in protein synthesis that makes most of solid matter of the cells. In the blood, liberation of CO₂ from bicarbonates is catalyzed by the enzyme that has zinc metal as its constituent. The large amount of zinc has present in human and animal sperms⁸⁷,⁸⁸.

Furthermore these metals are capable of forming complexes with protein and other biologically active substances, they act as catalyst and they show different oxidation states which are interconvertible in the cell environment, and this interconversion of oxidation states is uniquely situated to biological functions.

1.6 Significance of stability constants

The term “Stability” explains percentage association in the solution of two or more components in equilibrium. More association indicates higher stability of resultant complex in the solution under consideration. The study of complexes in solution state showed two kind of stability namely thermodynamic and kinetic, former describes, the extent at which complex formed at equilibrium, later explains speed of transformation leading to the attainment of equilibrium will occur.

A knowledge of stability constants has systematic route to rationalize our understanding of the behaviour of metal complexes in solution. The stability constants predicting the conditions for the complete formation of complexes, have the values more than zero⁹⁹, showing existance of complex in the solution. If, all the stability constants for a given reaction have been determined, the equilibrium concentration of each species under investigation will also be calculated and this knowledge of composition helps to interprets, its optical and kinetic properties, its partition equilibria and its biological
behaviour. The concentration of different species of metal complexes in equilibrium mixture have valuable information about analytical separation, solvent extraction, ion exchange method and chromatography. It is also important in the study of metal chelate in biological systems.

The value of free energy associated with the reaction can be calculated by stability constants. The change in entropy (ΔS) of complex formation can be obtained by stability constants and enthalpy change (ΔH) of complex formation\(^{90}\). 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”\(^{91,92}\), 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 develop.

However, some antidotes have the specific action of thier own, which not only affect the status of the patient but also contributes to fatal outcome\(^{93}\).
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 compounds.

Levine\textsuperscript{94} have 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 promotes 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, penicillamine (dimethyl cysteine) has been used for Zn toxicity. Day by Day, new suitable antidotes are being prepared.

In our case, antibiotics viz., neomycin, chlotetracycline, oxytetracycline, tetracycline penicillin-V, penicillin-G and some antipyretics such as aspirin, phenacetin and paracetamol form stable complexes with Mn and Zn at human blood pH = 7.30 $\pm$ 0.01, therefore, these antibiotics might be used as antidotes for treating the toxicity of Mn and Zn\textsuperscript{96,97} in the body. The work in metal intoxication is in progress and in future, it will definitely establish its own platform.
1.8 Complex formation theories

A number of theories have been given time to time to explain the formation of complexes between metal and ligands but the most important theories are given below in brief.

(a) Werner's coordination theory

An understanding of coordination compounds and their properties began with the work of Alfred Werner\textsuperscript{98} in 1893. Werner proposed an interpretation of coordination compounds which emphasized the number and nature of groups attached to the central metal ion. This theory replaced the older concepts of Brezellius (1819), Grahm (1837), Claus (1856), Blomstrand (1969) and Jorgenson (1878-1894), and became a fundamental part of the theory of valence formulated by G.N. Lewis\textsuperscript{99}. According to Werner,

1. Most elements show two types of valency
   (a) Primary (i.e. Principal) and
   (b) Auxiliary (i.e. Secondary)

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

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

4. The number of ligands which are arranged around the central metal ion is called the coordination number\textsuperscript{100}. 
Although this theory explains the structure and stereochemistry of complexes but could not give any theoretical background for the two types of valencies and this was the reason\textsuperscript{101-103} why this theory was not accepted up to 1916.

Later on, Lowry\textsuperscript{104} and sidgwick\textsuperscript{105} explained Wernar's ideas with the halp of electronic theory of valency.

(b) The valence bond theory

One viewpoint is stressed by the valence bond theory chiefly developed for complexes by Pauling\textsuperscript{106}. In this theory, it is considered essentially that a number of orbitals on the central metal atom is equal to the number of ligands be made available to form coordinate covalent bonds with orbitals on 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 hybrid orbitals with definite directional properties.

Pauling theory has randered valuable services to the understanding of main features of coordination chemistry and has ability to provide reasonable qualitative explainations but this was criticized by many workers\textsuperscript{107,108} as it fails to,

1. account for the relative energies of different structures and coordination numbers.
2. explain the magnetic properties of covalent and ionic compounds.
3. interpretate absorption aspectra of complexes in the visible reason and reaction paths for substitution reactions.
4. predict the geometry of coordination compounds.
(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^0, d^5 and d^10 transition metal. This theory is based on the ideas of Sidgwick and Powell and has been elaborated by Nyholm and Gillespie. For the non spherically symetrical transition metals, this theory is not so useful, although this theory very well explains the stereochemistry of complexes but does not deal with other properties such as bond length etc.

(d) The electrostatic theory

Van Arkel and D-Boer, and Garrick 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, polarizabilites, and size of ligands. By using the ordinary potential energy equations 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) The crystal field theory

This theory was developed by Bathe, Schapp and Penny and by Van Vleck. Hartmann used this theory to explain d-d spectra of complex in the visible region. Orgel was the first to emphasize the
consequences of the theory for stability of coordination compounds of the transition elements. The essence of the theory is that the five d-orbitals which are degenerated and equal in energy in the gaseous metal ion, become differentiated in the presence of the electrostatic field due to the ligand. It is the symmetry of this field, or its regular geometric properties, which gives the name of this theory. Thought originally applied to crystalline solids, it is equally applicable to any orderly arrangement of the electrically interacting particles such as a single complex. In particular, those orbitals lying in the direction of the ligand are raised in energy with respect to those lying away from the ligand. By preferentially filling the low lying levels, the d-electrons can stabilize the system, as compared to the case of random filling of the d-orbitals. The gain in bonding energy achieved in this way is called the crystal field stabilization energy (C.F.S.E.). It is caused by the distribution of charge around the central atom of the complex not being symmetrical as assumed in the earlier electrostatic calculations. If the d-orbitals were occupied equally, the resulting electron density would have spherical symmetric.

Although crystal field theory explains well many things such as the stereochemistry\textsuperscript{120} of the complexes magnetic properties\textsuperscript{121}, stability, redox potentials\textsuperscript{122}, coordinate bond energy\textsuperscript{123} and effective ionic charges\textsuperscript{124}, but it fails to explain the formation of complex involving bond, the resolution of asymmetric complexes into their optically active modifications and several properties of coordinated compounds\textsuperscript{125}. 
(f) The molecular orbital theory

J.H. Vanvleck\textsuperscript{126} 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 orbital (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{114} but still has some drawbacks. These are:

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

2. 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.
References

1. A. Glazulov, Chem. Listy., 1940, 2, 34.


43. S. Mathur, R.S. Dayal and P.R. Atal, Indian Prediad., 1968, 5, 145.


80. Indian Pharmacopoeia, 1996.


112. F. J. Garrick, Phill Meg., 1930, 9, 131.
      : Ibid, 1932, 14, 914.