CHAPTER-I

INTRODUCTION
Introduction:

Co-ordination compounds have been a challenge to the inorganic chemist right from the time these were identified in the nineteenth century. Complexes are playing important roles in industry ranging from anticorrosion and soil treatment agents to medicinal agents, which certainly testify for their significance in contemporary life.¹ The complex formation has played a vital role in the field of medicinal and biological sciences.²

The versatile field of study found its seed in the work of Alfred Werner, a renowned chemist of 19ᵗʰ century who was attracted to the study of colourful compounds of cobalt and later awarded the prestigious Nobel Prize in chemistry in 1913.³ Coordination compounds are formed by the interaction of a metal ion and ligands molecules and retain their identity in solution. The theory of coordination compounds was modified and developed from time to time by Lewis, Pauling, Bethe, Van-Vleck, Jannik Bjerrum and Carlotte.⁴⁻⁹

Stability constants are fundamental to understanding the behaviour of metal ions in aqueous solution. Such understanding is important in a wide variety of areas, such as metal ions in biology, biomedical applications, metal ions in the environment, extraction metallurgy, food chemistry, and metal ions in many industrial processes. In spite of this importance, it appears that many inorganic chemists have lost an appreciation for the importance of stability constants, and the thermodynamic aspects of complex formation, with attention focused over the last thirty years on newer areas, such as organometallic chemistry.
The knowledge of stability constant is necessary for calculating quantitatively the concentration of free metal ion, ligand and any of its complex formed in the system under different conditions of pH. The stability constant provides the information required to calculate the concentration of complex in solution, which refer to the degree of association between the two species involved in the state of equilibrium. Quantitatively greater the association, the stability of the complex is more.

The method for the determination of the stability constant of the metal amine complexes was first discovered by J.Bjerrum in 1941. Bjerrum, Schwarzenbach and Sillen published immense number of data tabulated in two volumes of stability constant in 1957-58.

Martell have published two volumes on critical stability constant, likewise Sigel has also reported equilibrium data.

Thus substantial work has been done by Martell, Calvin, Beck, Irving, Rossetti. Sigel Schwarzenbach and have given important contribution to the understanding of metal complexes in aqueous and mixed solvent. A.K Mapari et al studied stability constant of binary and ternary metal complexes.

Recently G.V. Mane et al reported pH metric studies in binary and ternary complexes of di carboxylic acids and amino acids with some transition and inner transition metal ions.
Metal chelates in solution

Metal ions get highly solvated in the solvent medium. If it is aqueous medium, water molecules get bound to positive metal ion through negative dipole i.e. oxygen, leading to high solvation of metal ions.

These solvated metal ions are termed as “aquo or solvo complexes” because of the positive charge on metal ion, the electrons in the water molecules are displaced towards the metal resulting in a loss of protons from bound water molecules. The bound water molecule is replaced by the other ligand and metal complexes is formed. The ligands, which combine with metal ion normally contain N, S and O. Some of the electron donor groups are -OH,-SH, =NOH,=NH.

Factors affecting stability of complexes in solution

Stability constant is a measure to know the stability of metal-ligand complex in solution. It could be studied using various techniques. Factors which affect the stability of complexes are as follows-

1. Nature of the central metal ion

The most important characteristic features of the central atom that influence the stability of complex is its degree of oxidation (charge on central metal ion in the case of ionic complexes), radius and the electronic configuration.
The stabilities of transition metal complexes decrease with increasing basicity of the metal. Mellor and Malley\textsuperscript{17} have shown that stabilities of bivalent metal ion complexes follow the order,

\[ \text{Pd}^{2+} > \text{Cu}^{2+} > \text{Ni}^{2+} > \text{Pb}^{2+} > \text{Co}^{2+} > \text{Cd}^{2+} > \text{Fe}^{2+} > \text{Mn}^{2+} > \text{Mg}^{2+} \]

irrespective of the nature of the ligands.

Irving and Williams from the analysis of the stability data for transition metal ions found that the order, \( \text{Mn}^{2+} < \text{Fe}^{2+} < \text{Ni}^{2+} < \text{Cu}^{2+} > \text{Zn}^{2+} \) was obeyed. This order according to them follows logically from the consideration of the reciprocal of the ionic radius and the second ionization potential of the metal.

2. **Nature of donor atom and basic character of the ligand**

Calvin and Wilson\textsuperscript{18} pointed out the correlation between basic strength of the ligand and stability constant of the complexes in connection with the stabilities of cupric chelates of the several enolic compounds.

They demonstrated the analogy between the dissociation constant of a free ligand and the stability constant of its metal complexes. As a consequence, the linear relation \( \log K = pK_a + b \) first suggested by Bjerrum\textsuperscript{19} was put to critical test by many workers.\textsuperscript{20}

According to Sidwick, nitrogen and oxygen atoms were found to be strongly chelating the metal ions and possess almost similar affinities towards them. This coordinating tendency was however found to be greatly influenced for both the elements with increasing substitution in the ligand structures.
3. **Effect of substitution in the ligand**

The substitution of group in the chelating agent may affect the tendency for chelation in one or more of the following ways.

1. It may influence, the acidity of the donor group by inductive and resonance effect

2. The groups in the ligand structures may introduce a purely steric effect, preventing the ligand molecules from acquiring the most favourable orientation for chelation around the central metal ion.

In addition to the above, ring strain due to forced configuration, resonance in chelating ring, occurrence of π bonding and orbital hybridization also affect the stability of a complex.

**Experimental methods of measurements**

Any metal complex is useful in some way or the other has to be sufficiently stable and determination of the stability constants, therefore, assumes significance. Many techniques have been used for this purpose and these have been divided into two groups.

1. Those in which direct determination of the stability constants for one or several types, resulting in the reaction, is possible, such as solubility and potentiometric measurements.
2. Those based on the change in some of the physiochemical properties as a result of complex formation, such as optical density, electrical conductance and colorimetry.

In present investigation two techniques belonging to each of these categories i.e. potentiometric and spectrophotometric have been used for the determination of stability constant.

I. Potentiometric study of chelates

The experimental procedure and methods of calculations of metal-ligands stability constant are given by earlier workers. The techniques followed were mainly potentiometry, spectrophotometry, ion exchange and polarography. An excellent compilation of this work has been done by Martell and Calvin, Dwyer, Beck after the publication of pioneering papers of Irving and Rossotti.

The present work in the solution chemistry is not confined only to the determination of stability constants, but is to investigate the number of important species involved therein. This is for the understanding of energies of metal-ligand bond and the role played by the solvent medium on the complexation equilibria.

pH is one of the popular parameter of modern experimental science. pH–metry has been ably and successfully adopted for the determination of stability constant in the solution.
The simple set up involved in these determination, is possibly one of the reasons for continuous use of this technique. In the present study, this technique has adopted with all measurable precautions which go with it and the stability constants were determined by the standard methods after taking into account the possible error limits in such a type of measurement.

Potentiometric measurements are also being used now a day successfully for the study of mixed-ligand chelates in the solution. Though a large number of phenolic and carboxylic acids\textsuperscript{26-28} in the earlier period was used in the permutation and combination, the present thrust is on the biologically active ligands.\textsuperscript{29}

Scandenevian and coworker’s have, very ably studied all the possible species in ternary complex equilibria and drawn interesting conclusions.

Mention in this regard must be made of an illustrious monograph of Sigel\textsuperscript{30} and Gergely et al.\textsuperscript{31,32} The latter workers have shown that dipeptide behave as tridentate ligand in ternary chelates of Cu(II) with amino acids.

II. Spectrophotometric study of chelates

Colour is one of the most important and characteristic features of a chelate. The absorption spectra can therefore, be used to distinguish the metal ions from their complexes.

Job’s\textsuperscript{33} gave a simplest Colorimetric method for determining the composition of a chelate in solution.
Vosbourgh and coworkers\textsuperscript{34} have modified the Job’s procedure. The composition of the complexes can also be determined by the molar ratio and slope ratio methods. Varielle\textsuperscript{35} has given a procedure of studying coloured complexes with the knowledge of isobestic points. Other method used for the study of metal chelates, are solubility measurement, ion exchange, optical activity, oxidation potential, electromagnetic studies, electrical conductance, polarography and x-ray diffraction.

**Modern trends in solution equilibria**

In many cases, transition metal ions and their complexes play a central role in controlling the reactivity and mechanism of the chemical reactions of interest.

The unique ability of transition metal ions and their complexes to control the chemistry of environmental, industrial, and biological processes has increased the importance of clarifying their mechanistic behaviour in simple and complex chemical processes.

While the knowledge of coordination chemistry is essential to the understanding of the structural and functional features of various biomolecules like metalloproteinase, its medical applications ranges from the development of MRI contrasting agents, radiopharmaceutical chemotherapeutics to the treatment of metal toxicity.\textsuperscript{36}
Studies on the complex formation of metal ions with a number of biomolecules or biologically active ligands have, in fact, attracted a lot of interest during the last few years because they act as models for the interactions of metalloenzymes and other complicated proteins in the biological systems.

**Applications of stability constant.**

Coordination chemistry right from the time of Werner has found applications in many branches of science i.e. analytical chemistry, biology, catalysis, medicinal chemistry, pharmacology and metabolic activities. Several chelating agents are used for qualitative, quantitative and volumetric determination of certain metal ions. The metals Na, K, Mg, V, Cr, Mn, Sn, Fe, Co, Ni, Zn, and non-metals H, C, Si, N, O, P, S, Se, F, Cl, Br and I have found almost essential for healthy human life. The principle ligands present in the living system could be simple like H\(^-\), OH\(^-\), Cl\(^-\), CO\(_3\)\(^-\) or complex ones like protein based amino acids, carbohydrates, carboxylic acid, nucleic acids, lipids, cytochrome and blood pigments.

The majority of elements present in the biological systems except Na, K, and Ca do not occur in the form of free ions and are present in the system as coordination complexes. Various chelating agents like citrate, tartarate, maleate and amino acids are present in the living systems and have complexation with the metal ion. Iron complexes for example contain Fe as central metal ion (heme) and related iron binding groups such as catalases, peroxidase, ferritin, transferrine and hemosiderin as ligands. In case of plants, chlorophyll i.e. a magnesium complex plays a very vital role in the process of photosynthesis.
Insulin, an important hormone contains zinc in the form of a complexed ion. Co is an essential metal in vitamin B\textsubscript{12}. The copper containing proteins such as cerelloplasmin, plastocyanine and its several other coordination complexes play a major role in biological systems and acts as catalysts in many metabolic processes of living bodies, which involve,

a) Redox reaction that change the valency of the metal in the complex.

b) Reactions where these compounds act as Lewis acids to combine with ligands and accelerate the reaction rate.

These compounds also serve the purpose of storage and transportation of either the metal ions or donor molecules and thus function as agents for transmission of energy in animal and plant systems.

Apart from these, life processes also involve a large number of metal ligand complex equilibria, some of which are given below,

1. **Sodium-Potassium pump**

In biological systems the transport of metal ions across the biological membranes takes place by forming complexes with the substrate of the membrane. These complexes are then transported across the membrane.In living body concentration of K\textsuperscript{+} ions inside the cell is relatively higher than the outside, while the concentration of Na\textsuperscript{+} ion is greater outside the cell wall than on the inside.
However, both Na\(^{+}\) and K\(^{+}\) ions diffuse through the cell wall until their concentration on each side of the cell wall becomes equal. This generates electrical potential.

This process of the movement of the Na\(^{+}\) and K\(^{+}\) ions is known as sodium–potassium pump, the formation of which is necessary to take the ions from a region of lower concentration to region of higher concentration. The process naturally depends on co-ordination chemistry of sodium and potassium ions.\(^{53-54}\)

Certain macro cyclic compounds also acts as carriers for the metal ions and carry them across the cell membrane. Thus, while the K\(^{+}\) is transported by formation of complex with macro cyclic ligand having holes located in hydrophobic environment, the Na\(^{+}\) ions is transported in hydrophilic environment with the help of carriers that form coordination complex with it.

2. **Transport of oxygen**

The process of oxygen transport depends on the metal-ligand complex equilibria. The four essential oxygen-carrying proteins for this type of transport are haemoglobin, myoglobin, hemeerythrin and hemocyanin. The former two are complexes of iron, while the latter are non heme proteins. Haemoglobin and myoglobin are responsible for the storage of oxygen and its transport from lungs to the muscles and inside the muscles.\(^{55-56}\)
The partial pressure of oxygen being high in the lungs, it coordinates with haemoglobin and is subsequently transported in the blood. It is only with the help of theories, concepts and techniques developed by inorganic chemist this could be done.

Recent developments in analytical techniques allow the quantitative determination of the trace elements and their compounds present in the living organism. And therefore, bioinorganic chemistry could be in nutshell defined as the chemistry that recognizes the dependence of life on metal ions and brings inorganic chemistry into life processes.

3. Medical Research

When new drug is synthesized, its proton and metal ion stability constants are determined. It is then possible to determine the effect of administering a given dose of that drug along with all the other components of the blood stream.

4. Pollution

Complex formation finds one of the major applications to remove pollutants from environment.

5. Analytical chemistry

The formation of complex is widely used in analytical chemistry in areas such as complexometric titration, metal ion indicators, colorimetric analysis, precipitants and reagents for extracting metal ions from solutions.
6. Electrochemistry

Anticorrosion liquids, pickling agents and rust eaters generally involve phosphoric acid, in one or the other form, which being very strong ligand for iron form an inert protective layer. The metal ions in solution are coordinated with ligands to maintain low metal ion concentration, to obtain an even surface coating in the electroplating.

Determination of stability constants

According to Bjerrum,\textsuperscript{57} the formation of complex at equilibrium can be represented in general as

\[ M^+ + L \rightleftharpoons ML \]  \hspace{1cm} (1)

Where M and L are metal and ligand respectively (charges are omitted, here and elsewhere, for simplicity).

Ligand L is a weak acid (HL), dissociated

\[ HL \rightleftharpoons H^+ + L \]  \hspace{1cm} (2)

The reaction of ligand with metal takes place as

\[ HL + M \rightleftharpoons H^+ + ML \]  \hspace{1cm} (3)

Which is a measure of hydrogen ion concentration in solution, in general for polyprotic acid HiL (i is any positive integer) in solution, the stepwise equilibrium constant are:
\[ \text{L + H } \rightleftharpoons \text{HL} \quad (4) \]

\[ \text{HL + H } \rightleftharpoons \text{H}_2\text{L} \quad (5) \]

\[ \vdots \]

\[ \text{H}_{i-1}\text{L} + \text{H} \rightleftharpoons \text{H}_i\text{L} \quad (6) \]

The \( i \)th thermodynamic proton – ligand stability constant \( K^H_i (T) \) is given as

\[
K^H_i (T) = \frac{a_H^i a_L}{a_{H_{i-1}} a_L a_H} \quad (7)
\]

Which is the reciprocal of thermodynamic dissociation constant of acid \( \text{H}_i\text{L} \) dissociating as

\[ \text{H}_i\text{L} \rightleftharpoons \text{H}_{i-1}\text{L} + \text{H} \quad (8) \]

‘a’ terms are the activities of the respective species.

The free L reacts with the metal ions according the equation (1). Applying the law of mass action to this equation

\[
K_1 = \frac{[\text{ML}]}{[\text{M}][\text{L}]} \quad (9)
\]

Where \( K \) is the equilibrium constant, [M] and [L] are the metal and ligand concentrations respectively.
Several complexes with different ratios of metal to ligand ranging from ML to $ML_N$ are formed in solution. Their stabilities could be described by the following set of equilibrium constants.

$$K_1 = \frac{[ML]}{[M][L]}$$  \hspace{1cm} (10)

$$K_2 = \frac{[ML_2]}{[ML][L]}$$  \hspace{1cm} (11)

$$\vdots$$

$$\vdots$$

$$K_N = \frac{[ML_N]}{[ML_{N-1}][L]}$$  \hspace{1cm} (12)

Quantities in the brackets are the concentration terms.

The thermodynamic metal ligand stability constants are obtained by replacing the concentration terms by activity.

$$K_N(T) = \frac{a_{ML_N}}{a_{ML_{N-1}} a_L}$$  \hspace{1cm} (13)

Determination of the stability constant of every type of complex species is not straightforward. Each of them has different stability while the protons replaced by metal ion during formation of one complex species cannot be distinguished from those liberated during the formation of the others.
We can get total number of protons in the system. In order to overcome this difficulty, Bjerrum introduced a term called ligand number $\bar{n}$. He defined $\bar{n}$ as the average number of ligands bound per metal ion present in different complexes in the same solution.

$$\bar{n} = \frac{\sum_{i=0}^{N} i(ML_i)}{\sum_{i=0}^{N} (ML_i)}$$

(14)

For the proton – ligand association similar function $\bar{n}_A$ is given as

$$\bar{n}_A = \frac{\sum_{i=0}^{N} i\beta_H^i(H)^i}{\sum_{i=0}^{N} \beta_H^i(H)^i}$$

(15)

Where $\bar{n}_A$ is the mean of protons bound per non-complex bound ligand molecules. The total concentration $T_M^0$ of the metal ion M is the sum of concentrations of the different species containing, it is given by the expression

$$T_M = [M]+[ML]+ \cdots + [ML_{i-1}]$$

$$= \sum_{i=0}^{N} i(ML_i)$$

(16)

Similarly, the total concentration of ligand is the sum of the concentrations of the species containing, it is given by the expression;
The total concentrations $T_M$ and $T_L$ are given by the expression:

$$T_M = \sum_{i=0}^{N} \beta_i [L]^i$$  \hspace{1cm} (18)

And

$$T_L = [L] + [M] \sum_{i=0}^{N} i \beta_i [L]^i$$  \hspace{1cm} (19)

The total extent of complex formation is characterized by the ligand number $\bar{n}$, given by

$$\bar{n} = \frac{[ML] + 2[ML_2] + \cdots + N[ML_N]}{[M] + [ML] + \cdots + N[ML]}$$

$$= \frac{T_L - [L]}{T_M}$$  \hspace{1cm} (20)

From this equation, we have

$$\bar{n} = \frac{\sum_{i=0}^{N} i \beta_i [L]^i}{\sum_{i=0}^{N} \beta_i [L]^i} = \frac{\sum_{i=0}^{N} i \beta_i [L]^i}{1 + \sum_{i=0}^{N} \beta_i [L]^i}$$  \hspace{1cm} (21)

The measurement of the free ligand concentration permits the calculations of the complete set of stability constants. The ligand number $n$ is independent of the total concentrations of both the metal ion and ligand.
Experimental method for the determination of stability constant:

The determination of stability constants from experimental data consists of three steps:

1. The construction of formation curve of the system. This is expressed by plotting $\overline{n}$ against pL.
2. The calculation of the values of $K$ by solving the formation function of the system,
3. The conversion of the stoichiometric constants in to the thermodynamic ones.

Irving and Rossotti$^{58}$ and Hearon and Gilbert$^{59}$ have described general method for solving the formation functions.

Irving – Rossotti made use of the potentiometric titration technique used by Calvin – Melchior$^{60}$ and known as Calvin–Bjerrum titration technique. In the present investigation the method of Irving- Rossotti has been used.

The experimental procedure involves following three titrations with standard NaOH.

I. Free HClO$_4$ (A) $\rightarrow$ A

II. Free HClO$_4$ (A) + ligand (L) $\rightarrow$ A + L

III. Free HClO$_4$ (A) + ligand (L) + metal ion (M) $\rightarrow$ A+L+M
The ionic strength of the solution was maintained constant at 0.1 M by the addition of NaClO₄ solution. The temperature of titration solution was kept constant at 30°C. For the same volume of alkali, the ligand curve will indicate lower values of pH than the acid curve if it contains more titrable hydrogen ions as it would happen when the chelating agent is an acid. If the metal chelate is formed in the reaction, the protons attached to the ligand must be displaced so that the metal complex titration curve will indicate pH values lower than the ligand titration curve.

**Calculation of \( \bar{n}_A \) values**

The proton-ligand formation number \( \bar{n}_A \), can be calculated from the volume of alkali required to obtain the same pH value in the acid and ligand titrations. The values of \( \bar{n}_A \) for various pH values can be calculated from the equation.

\[
\bar{n}_A = \gamma - \frac{(V_2 - V_1)(N + \varepsilon^0)}{(V_0 + V_1)T_L^0} \tag{I}
\]

where \( \gamma \) is the number of replaceable hydrogen ions in the ligand, \( V_0 \) is the initial volume of the solution, \( V_1 \) and \( V_2 \) are the volumes of alkali of a known normality \( N \) required during the acid (A) and acid + ligand (A+L) titrations respectively at a particular pH, \( \varepsilon^0 \) and \( T_L^0 \) are the initial concentrations of the perchloric acid and ligand respectively.

The horizontal difference \( (V_2 - V_1) \) was taken from the graph accurately up to the second place of decimal.
Calculations of pK values

The proton-ligand stability constants pKa, were calculated by following method:

1. **Half integral method:**

Approximate pKa values were calculated from the formation curve. The values of pH at $\bar{n}_A$=1.5 and $\bar{n}_A$= 0.5 corresponds to the values of pK$_1$ and pK$_2$ respectively.

2. **Method of pointwise calculations:**

The accurate pK values were determined by the method of point wise calculations. For the calculation of pK$_1$, the expression

$$\log \frac{\bar{n}_A - 1}{2 - \bar{n}_A} = pK_1 - pH \quad (for \ \bar{n}_A = 1.2 \ to \ 1.8) \quad (II)$$

was solved for $\bar{n}_A$ values between 1.2 and 1.8.

For the calculation of pK$_2$, the expression

$$\log \frac{\bar{n}_A}{1 - \bar{n}_A} = pK_2 - pH \quad (for \ \bar{n}_A = 0.2 \ to \ 0.8) \quad (III)$$

was solved for $\bar{n}_A$ values between 0.2 and 0.8.

The calculations for $\bar{n}_A$ values for representative systems are given in table 2.2 and 2.3. The pK values obtained from the formation curves and pointwise calculations are in good agreement.
Calculations of $\bar{n}$ values

The metal-ligand formation number, $\bar{n}$ is given by the expression

$$\bar{n} = \frac{(V_3 - V_2)(N + \varepsilon^0)}{(V_0 + V_2)\bar{n}_A T_M^0}$$  \hspace{1cm} (IV)

where $V_3$ represents the volume of alkali required to obtain the same pH for (A+L+M) system as per the acid and acid + ligand titrations, $T_M^0$ is the initial concentration of metal ions, $\bar{n}_A$ is the proton-ligand formation number of the same pH, and all the other notations have been the same meanings as given earlier.

Calculations of pL values

pL = -log [L] (free ligand concentration)

The free ligand concentration was calculated by the following expression:

$$pL = \log \left[ \frac{1 + \frac{H^+}{K}}{\frac{1}{T_L^0 - \bar{n} T_M^0} \times \frac{V_0 + V_3}{V_0}} \right]$$  \hspace{1cm} (V)

And if the ligand have two pK values

$$pL = \log \left[ \frac{1 + \frac{H^+}{K_2} + \left(\frac{H^+}{K_2}\right)^2}{\frac{1}{T_L^0 - \bar{n} T_M^0} \times \frac{V_0 + V_3}{V_0}} \right]$$  \hspace{1cm} (VI)

Where $T_L^0$ and $T_M^0$ are the stoichiometric concentrations of ligand and metal ion respectively. $V_3$ is the volume of alkali at a particular pH in (A+L+M) titration, $\bar{n}$ is the metal-ligand formation number at a particular pH and $H^+$ is the hydrogen ion concentration at that particular pH.
Calculations of logK values

The following methods were used for the calculations of metal-ligand stability constants.

1. **Half integral method**

The values of $\bar{n}$ have been plotted against pL to get the formation curve for metal ligand complexes. The approximate logK$^1$ and logK$^2$ values were calculated from the formation curves by the known value of pL at which $\bar{n} = 0.5$ and $\bar{n} = 1.5$ respectively.

2. **Method of point wise calculations**

The accurate logK values were calculated by this method. The metal ligand stability constant for 1:1 complex i.e. for calculations of logK$^1$, the expression-

$$\log \frac{\bar{n}}{1 - \bar{n}} = logK_1 - pL \text{ (for } \bar{n} = 0.2 \text{ to } 0.8) \quad \text{(VII)}$$

was solved for $\bar{n}$ values between 0.2 to 0.8.

The metal ligand stability constant for 1:2 complex i.e. for calculations of logK$^2$, the expression

$$\log \frac{\bar{n} - 1}{2 - \bar{n}} = logK_2 - pL \text{ (for } \bar{n} = 1.2 \text{ to } 1.8) \quad \text{(VIII)}$$

was solved for $\bar{n}$ values between 1.2 to 1.8.
3. Method of least squares

For the solution of formation function the methods suggested by Bjerrum\textsuperscript{57} and Irving and Rossotti\textsuperscript{24} have been widely used. Bjerrum\textsuperscript{57} equates the half-integral values to appropriate logK values, where K is a formation constant, as the first step in a series of successive approximations.

This method has been criticized by Irving and Rossotti\textsuperscript{24} on the grounds that it uses only two points on the formation curve and it holds only when \( \log (K_1/K_2) \geq 2.5 \), for system where only 1:1 and 1:2 complexes are formed. However, when a Calvin – Bjerrum pH titration technique is used to obtain the formation curve data, the logK values cannot be more accurate than observed pH values i.e. the accuracy cannot be greater than about \( \pm 0.02 \) log unit. In such cases half integral method give reasonably accurate values for even much lower value of \( \log(K_1/K_2) \).\textsuperscript{61}

The method of least squares was, therefore, worked out for all those systems where in \( \log (K_1/K_2) \) was less than 2.10 because the accuracy of our pH meter is \( \pm 0.01 \).

Since most of the systems in the present investigation fall into this criteria, that method of least squares was used for all the system studied. The mathematical expression for method of least squares when the complexes present are only 1:1 and 1:2 can be written as

\[
\frac{\bar{n}}{(\bar{n} - 1) \times L} = \frac{(2 - \bar{n}) \times (L)}{(\bar{n} - 1)} \times K_1 K_2 - K_1
\]
This is an equation for the best straight line. The method is also adopted to confirm the presence or absence of 1:2 complex\textsuperscript{62} by comparing $\bar{n}$ values obtained from the expressions VII and VIII with the experimental value.

**Limitations of Calvin-Bjerrum titration technique:**

This method is widely used for the determination of metal chelate stability, but it becomes not applicable in presence of very strong or very weak complexes. In the former case, the concentration of the ligand required for the formation of a complex is so small that the complex formation is complete even at very low pH values, irrespective of whether the ligand is a free base or the anion of an acid. Under these conditions the effect of released protons on the pH values of solution would be too small to be detected on any potentiometer.

Such systems have recently been studied by employing the method which uses the principles of (i) replacement of one metal by another and (ii) replacement of one ligand by another. Nayan and Dey\textsuperscript{63} recently have attempted to simplify the approach for calculating the various parameters required to calculate the association constants.

It is shown that there is no necessity to know the exact concentrations of either the mineral acid added to the system or of the alkali used as titrant. The expressions for $\bar{n}_A$, $\bar{n}$, pL for the Irving-Rossotti equations can be obtained involving only the concentration of the total metal ion, total ligand and hydrogen ion (H\textsuperscript{+}) as well as the volume of alkali as titrant.
The protonation constants and the metal ligand association constants can then be calculated from these expressions.

The advantage of this technique is that the determination of the protonation constant of the protonated ligand is also not required for the evaluation of stepwise metal-ligand formation constants.

**SCOG’S programme:**

Computerized methods of evaluation have become very important procedure in the calculation of the complex equilibria. Specially, the identification and characterization of species present in bio-fluids, surface and underground waters effluents etc. constitute an important present day problem, which demands the use of sophisticated computer programmers that can be used to determine the formation constants of all the species present in the systems. More importantly, these computational methods also permit the treatment of complex systems with known numerical and graphical methods. The procedures of computer evaluation also yield valuable information from the experimental data, which cannot be obtained by non-computerized methods.

Since the last four decade, a number of sophisticated mathematical algorithms and computer programmes have been developed for calculating protonation and formation constants from potentiometric data provided the degree of complex formation is pH dependent.
Presently we used developed software package, ‘Stability Constant of Generalized Species’ (SCOG’S) for the calculation of dissociation constants of ligands and stability constant of binary and ternary metal complexes.

The nature and function of drug molecules is important to determine how the collection of these lifeless molecules found in living system interact with each other to constitute and maintain the living state. Investigation on the complex forming properties and important chemical reactions of the naturally occurring amino acids and drug have been carried out by several workers\textsuperscript{64-70} and very scientifically studied the possible species present in binary and ternary complex equilibria.

Literature survey reveals that the study of stability constant of some bivalent and trivalent metal ions with amino acids and drugs to see the effect of substituent ion pK and log K values of metal complexes at 30\textdegree{} C to confirm exact complexation equilibria, the nature of bonding sites and the variation in the mixed ligand stability constant.

Among the wide variety of drug molecules, Amitriptyline HCl, Furosemide, Metoclopramide HCl, Naproxen, Propyl paraben have been studied extensively because of their ready accessibility, diverse chemical activities, broad spectrum of biological significance and variety of industrial applications.
Following is the brief review on the applications of these drug molecules.

**Amitriptyline HCl**

It is tricyclic antidepressant drug and chemically known as 3 - (10, 11, dihydric-5-H-dibenzo [a, d] cycloheptene-5-ylidine)-N,N-dimethyl-1-propanamine hydrochloride. It is used for the treatment of several psychiatric disorder. These types of tricyclics also ease migraines, tension, headaches, anxiety attacks and some schizophrenic symptoms.

![Amitriptyline HCl (1.1)](image)

**Furosemide**

It is loop diuretic (water pill). Furosemide was being developed in the Hoechst laboratories in Germany. Investigation of a series of 5-sulfamoylanthranilic acid, substituted on the aromatic amino group, showed that these compounds were effective diuretics.
It is 4-chloro-N-Furfuryl-5-sulphamoylanthranilic acid. This drug is excreted primarily in changed a small amount of metabolism, however can take place on the furan ring which is substituted on the aromatic amino group. Furosemide has a Saluretic effect. clinically toxicity of furosemide involves abnormalities.

It is effective for the treatment of edmas connected with cardiac, hepatic and renal sites. One of the use of this drug is for the treatment of hypertension.

![Furosemide (1.2)]

Metoclopramide HCl

It is 4-amino-5-chloro-N-[2-(diethyl amino) ethyl]-2-methoxybenzamide HCl. Metoclopramide is antiemetic drug. Experimental and clinical evidences indicate that metoclopramide is potent antiemetic agent with least systematic side effects. This drug has recently been introduced clinically to treat vomiting and other dyspeptic syndromes.
Naproxen

Naproxen is chemically 2-(6-methoxynaphthalen-2-yl) propanoic acid. It is used in the treatment of inflammations, rheumatoid arthritis, musculoskeletal disorders and gout. It is a member of aryl acetic acid group of non-steroidal anti-inflammatory drug used as analgesic (pain reliever) and antipyretic (fever reducing compound).

Non-steroidal anti-inflammatory drugs (NSAID) are compound used to reduce pain, fever and inflammation without the use of steroid.

Naproxen is also sometimes used to treat Paget’s disease of bone. Naproxen can be used to treat osteoarthritis, rheumatoid arthritis, and spondylitis.
Propyl paraben:

Propyl paraben are effective antimicrobial and antifungal agents, which are among the most important preservative agents, commonly used in foods, beverages, cosmetics and pharmaceuticals.

Drugs have various functional groups present in their structure which can bind to metal ions present in human body. Metal complexes of drugs are found to be more potent than parent drug.

Chemistry of drugs attracts many researchers because of its application in medicinal study. Interesting results have been reported earlier on complex.
AMINO ACIDS

Amino acids are very important ligands and play major role in biological and chemical system.\textsuperscript{85-86} Amino acids are organic molecules containing amino groups (-NH\textsubscript{2}) and carboxylic acid group (-COOH) both attached to the same carbon atom. Amino acids play central role both as building blocks of protein and as intermediates in metabolism.

The twenty amino acids that are found within proteins convey a vast array of chemical versatility. Proteins not only catalyse most of the reactions in living cell, but they also control virtually all the cellular process.

The complexes of amino acids are important in the study of bio fluids, particularly when hyper accumulated metal ions are present for physiological or pathological reason. The inherent tendency of amino acids for coordination is due to the presence of potential donor groups such as –COOH, -NH\textsubscript{2},=NH, -OH, and –SH sites in their molecules.\textsuperscript{87-93}

Amino acids and their metal complexes are equally important compound, since they have frequent utilization in biological and chemical applications.\textsuperscript{94-95} The biological importance of some proposed amino acids is as follows:
GLYCINE

Glycine is the neutral, aliphatic, optically inactive, non-essential, glycogenic aminoacid.\textsuperscript{96-101} Glycine is an amino acid, a building block for protein. It is “non-essential amino acid” because the body can make it from other chemicals. A typical diet contains about 2 grams of glycine daily.

The primary sources are protein-rich foods including meat, fish, dairy, and legumes. Glycine is used for treating schizophrenia, stroke, Benign Prostatic Pyperplasia (BPH), and some rare inherited metabolic disorders. It is also used to protect kidneys from the harmful side effects of certain drugs used after organ transplantation as well as the liver from harmful effects of alcohol. Other uses include cancer prevention and memory enhancement.

Some people apply glycine directly to the skin to treat leg ulcers and heal other wounds.

![Glycine structure](image)
LEUCINE

Leucine\textsuperscript{102} is a neutral essential ketogenic amino acid. Leucine works with other amino acids isoleucine and Valine to repair muscles, regulate blood sugar, and provide energy. It also increases production of growth hormones, and helps to burn visceral fat, which is located in the deepest layers of the body and the least responsive to dieting and exercise. Natural sources of Leucine include brown rice, beans, meat, nuts, soy flour, and whole wheat.

Leucine is an essential amino acid, which means that it cannot be manufactured in the body and must be obtained through dietary sources. People that exercise a lot, or have a low-protein diet, or are seriously trying to build muscle mass should consider Leucine supplementation.

Leucine is also available in stand-alone supplemental form, but should always be taken together with the other two branched-chain amino acids, isoleucine and Valine. The ideal balance is 2 milligrams of Leucine and Valine for each 1 milligram of isoleucine.

An excessively high intake of Leucine has also been linked to the development of pellagra, a deficiency of the vitamin niacin that causes dermatitis, diarrhoea, and mental disorders. Too much Leucine in the diet can disrupt liver and kidney function and increase the amount of ammonia in the body. People with impaired liver or kidney function should not take isoleucine without first consulting a physician, as large doses of amino acids may aggravate these conditions.
Valine is essential amino acid. Valine is a branched-chain amino acid (BCAA) that works with the other two BCAAs, isoleucine and Leucine, to promote normal growth, repair tissues, regulate blood sugar, and provide the body with energy.

Valine helps to stimulate the central nervous system, and is needed for proper mental functioning. Valine helps to prevent the breakdown of muscle by supplying the muscles with extra glucose for energy production during intense physical activity. Valine also helps to remove potentially toxic excess nitrogen from the liver, and is able to transport nitrogen to other tissues in the body as needed. Valine may help to treat liver and gallbladder disease, as well as damage to these organs caused by alcoholism and drug abuse.

Valine may help to treat or even to reverse hepatic encephalopathy, or alcohol-related brain damage. Valine is an essential amino acid, which means that it cannot be manufactured in the body and must be obtained through dietary sources.
Natural sources of Valine include meats, dairy products, mushrooms, peanuts, and soya proteins. Although most people get enough Valine from their diet, there have been recorded cases of Valine deficiency. Maple Syrup Urine Disease (MSUD) is caused by the inability to metabolize Leucine, isoleucine, and Valine.

The disease is so named because urine from affected people smells like maple syrup. A deficiency of Valine may also affect the myelin covering of the nerves, and cause degenerative neurological conditions. An excessively high intake of Valine may cause a skin crawling sensation and even hallucinations. Too much Valine in the diet can also disrupt liver and kidney function and increase the amount of ammonia in the body.

![Structure of Valine](image)

Valine (1.8)

**PHENYLALANINE**

Phenylalanine\(^{105}\) is aromatic, essential glucogenic and ketogenic amino acid. Phenylalanine is an essential amino acid that is needed for normal functioning of the central nervous system. It has been used successfully to control symptoms of depression and chronic pain, as well as other diseases linked to a malfunctioning of central nervous system.
Phenylalanine is especially effective for treating brain disorders because it is able to penetrate the blood-brain barrier. The blood-brain barrier is a protective barrier formed by the red blood cells and the glia of the brain that protects the brain from any toxins, bacteria, and viruses, etc. that are circulating through the bloodstream. Only chemicals that are able to cross this barrier can directly affect brain function.

The body needs phenylalanine to make epinephrine, dopamine, and norepinephrine, three neurotransmitters that basically control the way you perceive and interact with your environment. Phenylalanine supplementation may help you feel happier, less hungry and more alert; it has also used to treat chronic pain and improve memory and concentration.

Recent research indicates that phenylalanine, which aids in melatonin production, may be effective for treatment of vitiligo, a condition that causes white patches on the skin. Subjects treated by these researchers took 50 to 100 milligrams oral L-phenylalanine and applied topical 10 percent phenylalanine gel each day and reported an average improvement rate of 83 percent.

Phenylalanine is an essential amino acid, which means it must be obtained from dietary sources. People that suffer from arthritis, obesity, severe menstrual cramps or mild depression may want to speak to their doctor about trying phenylalanine supplementation.
Phenylalanine supplements come in capsule, tablet, and powder form. Phenylalanine has also been used to treat Parkinson’s disease, and schizophrenia, but anyone with a serious health condition should not take any form of supplementation without first consulting their physician about proper dosage and possible side effects.

![DL-phenylalanine](image)

**DL-phenylalanine (1.9)**

**ALANINE**

Alanine[^1] is a non-essential, glycogenic amino acid. Alanine, is an amino acid that helps the body to convert the simple sugar glucose into energy and eliminate excess toxins from the liver. Amino acids are the building blocks of protein, and are key to building strong, healthy muscles. Alanine has been shown to help to protect cells from being damaged during intense aerobic activity, when the body cannibalizes muscle protein to help produce energy.

Alanine is crucial for preserving balanced levels of nitrogen and glucose in the body, which it does through a series of chemical actions called the alanine cycle.
During the alanine cycle, any excess amino acids (proteins) in cells or tissues are transferred to a receptor molecule called pyruvate, which is produced by the breakdown of glucose. The pyruvate is then converted to alanine and transferred to the liver. The liver extracts nitrogen from alanine and converts some of it back into pyruvate, which can then be used to produce more glucose.

Any excess nitrogen is then converted into urea and passed out of the body during urination.

![Alanine (2.0)](image)

**ISOLEUCINE**

Deficiency of isoleucine is only found in people deficient in dietary protein but symptoms may include headache, dizziness, fatigue, depression & confusion. Isoleucine has also several significant applications in biological systems.\(^{107-115}\) Isoleucine is an amino acid that is best known for its ability to increase endurance and help heal and repair muscle tissue and encourage clotting at the site of injury. This amino acid is especially important to serious athletes and body builders because its primary function in the body is to boost energy and help the body to recover from strenuous physical activity. Isoleucine is a branched-chain amino acid (BCAA).
There are three branched-chain amino acids in the body, Isoleucine, Valine, and Leucine, and all of them help to promote muscle recovery after exercise.

Isoleucine is actually broken down for energy within the muscle tissue. It also keeps energy levels stable by helping to regulate blood sugar; a deficiency of isoleucine produces symptoms similar to those of hypoglycaemia, and may include headaches, dizziness, fatigue, depression, confusion, and irritability. Isoleucine is an essential amino acid, which means that it cannot be manufactured in the body and must be obtained through dietary sources. Good sources of isoleucine include high-protein foods, such as nuts, seeds, meat, eggs, fish, lentils, peas, and soy protein. People that exercise a lot or that have a low-protein diet should consider supplementation.

Isoleucine is also available in stand-alone supplemental form, but should always be taken together with the other two branched-chain amino acids, Leucine and Valine. The ideal balance is 2 milligrams of Leucine and Valine for each 1 milligram of isoleucine. Combination supplements that provide all three of the BCAAs may be more convenient. People with impaired liver or kidney function should not take isoleucine without first consulting a physician, as large doses of amino acids may aggravate these conditions. Especially vitamin B₅ (pantothenic acid) and vitamin B₆ (pyridoxine)
L-Isoleucine (2.1)

Complexation studies are very important from the point of view of analytical and biochemical research, include compounds composed of metal atom or ion and one or more ligands (atoms, ions or molecules) that formally donate electron to the metal.\(^{116}\)

Complexes\(^{117}\) are the compounds containing coordinate bond between electron pair donor as the ligand and electron pair acceptor as the metal atoms or ions.

The number of electron pairs donated to the metal is known as its coordination number and thereby many complexes exhibits coordination numbers of two, four or six. In order for a pair of electrons to be donated from ligand to a metal ion, there must be an empty orbital on the metal ion to accept the pair of electrons.

In complexes,\(^{118}\) a central atom or ion is coordinated by one or more molecules or ions (ligands) which act as Lewis bases forming coordinate bonds with the central atom or ion which acts as Lewis acid. The coordination behaviour of biomolecules containing oxygen, nitrogen and sulphur as donor atoms has been studied extensively during last few decades.
Drugs and amino acids are the ligands containing oxygen, nitrogen and sulphur donor atoms.

The complexing properties of these biomolecules with metals have led to the formation of various complexes. Therefore, there is a considerable interest in the coordination chemistry of drugs and amino acids, particularly because of their capability of acting as multi-dentate N – N and N – O donors for the formation of mono or polynuclear metal complexes.

The complexation is easily possible in case of bi, tri and tetradentate ligands. Thus it is well known fact that the biomolecules containing multiple donor sites play a key role in the formation of geometrical structure of the complexes. The class of coordination compounds play crucial role in inorganic chemistry. Many coordination compounds have great importance in living organisms, among them chlorophyll and haemoglobin are important.

Chlorophyll is chief constituent of green plants which is formed by the combination of magnesium and porphyrine and it is useful for the synthesis of carbohydrates. Haemoglobin is a constituent of blood formed by the combination of iron and porphyrin and has importance in the transportation of carbon dioxide and oxygen in animal.

Metal complexes have been reported to play an important part in the biological activity of drugs, as the complex formation has been suggested as one of the important mechanism for the drug action.
Although, the study of metal complexes with many therapeutic drugs have been reported including streptomycin and tetracycline. Many authors have also studied model mixed ligand complexes to understand the nature of metal ion complexation in biological process. These studies involve the complex formation between transition metal ions and various sulphur containing amino acids, imidazole and dipeptides.

Metal ions play an important role in coordination chemistry. They are widely used in biological process. Many of them are essential for all living systems and present an interesting study of the way in which they are involved in life process. Some of these metal ions are distributed selectively in biological system and metal ion concentration. Their selectivity is essential to an understanding of their biological function.

Furthermore, it has been suggested that the presence of metal ions in biological fluids, could have a significant effect on the therapeutic action of drug. All transition metals exhibit a characteristic property of complex formation. These compounds are widely present in minerals, plants and animals and are known to play many important biological functions. The respiration process is regulated by the blood pigment (haemoglobin), which is a coordination compound of iron. A variety of metallurgical processes, industrial catalysts and analytical reagents involve the use of coordination compounds. Many complex metal oxides and sulphides which constitute minerals are solid state coordination compounds.
Following is the brief review on the biological importance of metals copper, zinc, nickel and cobalt used in present investigation.

**Copper**

Copper is present in a large number of enzymes, many involved in electron transfer, activation of oxygen and other small molecules such as oxides of nitrogen, methane and carbon monoxide, superoxide dismutation and even invertebrates, oxygen transport. The copper binding proteins in serum that play an important role in iron metabolism and by the terminal oxidase of the mitochondrial respiratory chain. Cytochrome oxidase which requires both heam iron and copper for its activity. Copper levels are maintained at extremely low levels by a series of copper chaperone proteins in mammals.

**Zinc**

Zinc is an essential element for the normal functioning of most organism and its deficiency can lead to reduction of normal growth.

It is a major regulatory ion in the metabolism of cells the fell for this role comes from cross biological consideration through their molecular nature begins to appear in zinc fingers and in the link to amino acid, nucleotide and heam syntheses. Today it is difficult to know where all the zinc inside cellular system is located. Zinc is found to be associated with DNA and RNA. It is very important in the activity of many enzymes, bacteria and is toxic in excess.
Nickel

Nickel is a rare metal in biology. The activity of nickel is confined to one enzyme, urease, acts in redox processes, although the symbiotic anaerobic bacteria still use nickel in some dihydrogen reaction. Free anaerobic bacteria, especially methanogens, have also kept the nickel hydrogenase and other nickel enzymes, but the methanogens belong to the special class of bacteria. In many microorganisms its transport is highly regulated by the cell.

Cobalt

Cobalt is the essential metal for many organisms including mammals. The activity of cobalt is confined to functions of vitamin B\textsubscript{12} and enzyme. The use of vitamin B\textsubscript{12} in biology required in archaeo bacteria and this association of cobalt with early anaerobic organisms.

Cobalt used as catalysts to handle compounds such as CH\textsubscript{4}, H\textsubscript{2}, H\textsubscript{2}S in atmosphere. Cobalt is toxic moderately when injected intravenously to mammals. During last few years considerable research work has been done on the study of coordination complexes. The studies in metal-ligand complexes in solution of a number of metal ions with carboxylic acids, oximes, phenols etc. is interesting which throw light on the mode of storage and transport of metal ions in biological kingdom.
With the view to understand the bioinorganic chemistry of metal ions, Banerjee et al.\textsuperscript{134} have synthesized number of mixed - ligand alkaline earth metal complexes. Metal complexation not only brings the reacting molecule together to give activated complex\textsuperscript{135} but also polarised electron from the ligands towards the metal. The relation between stability and basicity of the ligands is indicated by the formation constant and free energy change value.

The stability of complexes is determined by the nature of central metal atom and ligands. The stability of complexes is influenced by the most important characteristics like degree of oxidation, radius and electronic configuration. Irving and Williams\textsuperscript{136} had studied the order of stability of metal complexes of transition metal ions by comparing the ionic radius and second ionisation potential of metal ions, as it is valid for most nitrogen and oxygen donor ligands. Narwade et al.\textsuperscript{137} have investigated metal-ligand stability constants of some lanthanides with some substituted sulphonic acids. Many workers\textsuperscript{138-151} have reported their results on metal – ligand stability constants. Bodkhe et al.\textsuperscript{152} have reported the metal ligand stability constants of some β-diketones. Tekade et al.\textsuperscript{153} reported stability constants of some substituted pyrazolines and diketone. Binary complexes of Ca(II), Mg(II) and Zn(II) with L-glutamic acid in DMSO-water has been studied.\textsuperscript{154}
Thakur et al.\textsuperscript{155-156} have studied the influence of ionic strength of medium on the complex equilibria of substituted hydroxy-1,3-propandiones with Cr(III) and La(III) metal ions and the metal-ligand stability constants of Th(III), Sm(III), Nd(III) and Pr(III) metal ion complexes with 2-mercapto-4-substituted phenyl-6-substituted phenyl pyrimidines pH metrically.

Narwade et al.\textsuperscript{157} have studied the metal - ligand stability constant of Cu(II) complexes and measured their viscosity, refractivity index. Shivraj et al.\textsuperscript{158} have studied formation constants and thermodynamic parameters of bivalent metal ion complexes with 3-amino-5-ethyl isoxazole Shiff bases and N - N; N - O and O - O donor ligands in solution.

The above literature survey indicated that, drugs and amino acids having sulphur, oxygen and nitrogen donor atoms play vital role in the medicinal chemistry as well as in coordination chemistry. Metal complexes of drugs and amino acids are found to be more potent parent drugs. Therefore, considerable attention is paid on the study of coordination behaviour of drugs and amino acids with transition metal ions in solution. Recently number of researchers have studied, stability constants of mixed ligand complexes using potentiometric measurement technique. Mixed ligand complex formation equilibria of Cu(II) with biguanide in presence of glycine as the auxiliary ligand has been studied.\textsuperscript{159}
Parihar et al. has been studied the stability constant and thermodynamic parameters of Cadmium complexes with sulfonamides and cephapirin. Mixed ligand complexes of caffeine and cyanate with some metal ions studied by Shaker and his co-workers.

Protonating and chelating efficiencies of some biologically important thiocarbonohydrazides in 60% (v/v) ethanol-water system by potentiometric and spectrophotometric methods studied by Sridhar et al.

The result shows the chelating tendencies in terms of stability constants and distribution nature of the species. Ca(II) complexes with drug ciprofloxacin and leucine and phenylalanine has been studied. Thermodynamic studies of rare earth metal complexes with rifampicin in mixed solvent system has been studied. Solution behaviour of Cu(II) complexes with antibacterial drugs and amino acids studied by Magare et al. Stability of Zn(II), Mn(II),V(II) and Co(II) binary and ternary complexes with 2,3- dimercaptosuccinic acid as a primary ligand and some biologically important amino acids as secondary ligands studied by N. Agrawal et al. The stability of ternary complexes was quantitatively compared with their corresponding binary complexes in terms of ΔlogK. Synthesis and spectroscopic studies of mixed ligand complexes of transition and inner transition metals with a substituted benzimidazole derivatives and RNA bases have been studied by Verma et al.
The metal complexes have been screened for their antifungal activity towards Aspergillus niger fungi. The result obtained is compared with that of parent drug.

Faroqui et al.\textsuperscript{168} reported the stability constant of some medicinal compounds and glycine in aqueous solution. Equilibrium studies on mixed ligand complexes of drug phenylpropanolamine hydrochloride with Cr(II) and Co(II) metal ions has been studied by Arbad \textit{et al.}\textsuperscript{169}

Formation of complex species with respect to pH have been discussed by Irving - Rossotti technique and evaluated by SCOG’S computer program. Stability of binary and ternary complexes of nicotinamide in aqueous solution with Cu(II) metal ion has been studied.\textsuperscript{170}

The proton ligand stability constants and stability constant of binary and mixed ligand complexes of Zn(II) with pyridoxine, nicotinic acid, tetracycline, gentamycin, benzylpenicillin, ampicillin, streptomycin and ranitidine have been studied potentiometrically at 25°C and $\mu =0.1$ M (KNO$_3$) in aqueous medium.\textsuperscript{171} Zinc forms 1:1 and 1:2 complexes with all the chelating agents except for nicotinic acid - ranitidine, nicotinic acid-ampicillin and nicotinic acid-gentamycin for which 1:2 complex species does not exist in the solution. Equilibrium study and stability constant of mixed ligand complexes of biomolecules and Amino acids with metal ions by potentiometric method has studied by Krishna Vijay \textit{et al.}\textsuperscript{172} Thermal stability of complexes can be predicted from their melting point.\textsuperscript{173}
Keeping in view the pharmacological significance of drugs, amino acids, metal ions and utility of coordination compounds it was decided to study the stability constant of some bivalent metal ions with amino acid and drugs. Therefore the present work entitled, “STUDIES ON METAL COMPLEXES OF DRUG MOLECULES” has been undertaken and presented in the form of thesis.
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