1.1. Introduction:

The coordination complexes with stoichiometries other than the simple 1:1 ML type, exist in biological and environmental systems. This results in the existence of multiple equilibria in these systems. The finding on the participation of coordination complexes of different stoichiometry depending on the characteristics of the chelating ligand and metal ion has fundamental implications for the interpretation of immobilized metal ion affinity. The knowledge of distribution of various species in particular equilibria is of great significance.

There are many factors which assist the formation of a complex and sometimes hidden factors are working against the same. The capacity of a metal ion to form a complex with a ligand is mainly decided by its environment, which decides the stability of the complex. Some of the factors, which affect the stability of the complexes are solvents, tempreture, ionic strengths and nature of metal ions and ligands.

The transition and inner transition metal ions are known to have the small radii and variable coordination number, which make them excellent spacers in assembling fascinating metal organic frameworks.[1-14] Further their complexes are of continuing interest mainly due to their structural and catalytical properties and their application in diagnostic pharmaceutical and laser technology. They have been found to exhibit anti-cancer, anti-diabetic, anti-tuberculosis, anti-ulcer plastic stabilizers and fungicidal properties.[15-28]

Synthesis, characterization and antimicrobial studies of transition and inner transition metal complexes have been an active field of research.

However solution studies which explore the multiple equilibria existing between metal(s) and ligand(s) still needs much attention. The present piece of work is based on potentiometric investigation of metal-ligand equilibria of binary and ternary systems in aqueous medium at different temperatures and ionic strengths. The objective of the work is to explore the multiple equilibria existing between the selected metals and ligands. This can serve as a tool to understand the complexation behavior of these species and the related analogues in biological and environmental systems and can serve as valuable addition to chemical literature.

1.2. Brief review:

1.2(a). Significant work in related field:

Existing literature reveals that the initial work in the field of metal-ligand equilibria was started in early ninteens. The pioneers in this field include the names of Bjerrum-Calvin,[29-30] Irving-Rossotti,[31-32] and Martell-Chaberek.[33-34] Bhattacharya and coworkers extended Bjerrum and Calvin's technique for investigation of mixed ligand systems.[35-36] Dey et al. modified Martell-Chaberek method for investigation of multiple equilibria.[37-39] Rammamorthy and Santappa developed the alternative approach for calculation of equilibrium constants of the mixed ligand complexes where two or more ligands coordinates with the metal ions simultaneously.[40-41] With the advancement of time, several computer programs were developed by different group of workers which made it possible to obtain the percent distribution of individual species formed in a particular equilibrium.[42-43]

The equilibrium studies with variety of metal ions and ligands particularly those which are often involved in biological system have been studied by several group of workers.[44-66] Such studies serve to

determine the interactions of biological molecules serving as ligands with metal ions in biochemical reactions. Further chemical speciation of metals is important to understand their distribution, mobility, bioavailability, toxicity and for setting environmental quality standards.[67] A number of studies has been reported on ternary stability constants in different media. Investigations of multiple equilibria involving various ligands, and their interaction with metal ions in media of varying ionic strength, temperature and dielectric constant throw light on the mechanism of enzyme-catalyzed reactions. Bioavailability of a particular metal depends on its complex chemical reactions of dissolution, binding and complexation with the constituents of the environmental aquatic phase.[68-70] Hence the equilibrium studies became the most fascinating field of research for inorganic chemists which can be seen in the form of several monographs and reviews which incorporates the significant work done from the initial period to the present time. [71-80]

1.2(b). Recent publications in the related field:

Literature survey reveals that, over the last decade tremendous work has been done on the study of metal complexes. The studies on metal-ligand complexes in solution with number of metal ions and ligands such as carboxylic acids, oximes, phenols etc. are interesting which throw light on the mode of storage and transport of metal ions in biological kingdom. Jahagirdar et al. have studied stability constants of Al(III), Cr(III) and Fe(III) metal ion complexes with substituted sulphonic acid.[81] Recently, M.M. Shoukry et al. have reported the mixed-ligand complex formation of Cu(II) with 1,2- diphenylethylenediamine as primary ligand and amino acids as secondary ligands, some transition metal ions with hydrazone and phenylalanine complex formation reactions of palladium(II)-1,3-diaminopropane with various biologically relevant ligands. Kinetics of

hydrolysis of glycine methyl ester through complex formation is also investigated.[82-84] Investigations based on mixed-ligand complex formation of cadmium(II) with some amino acids and drug efavirenz and study of stability constant of binary and ternary complexes of enalapril with transition metal ions in aqueous solution has been reported by Farooqui and co-workers.[85-86] Research work on pyridoxine, gabapentin, atenolol, nicotinamide, nicotinic acid, mandelic acid, isoniazid, imipramine, gallic acid and adenosine drug is also carried out by them.[87-98] Binary complexes of transition metal ions with β - diketone and interaction between La(III) and Nd(III) metal ions and 1-(4-hydroxy-6-methylpyrimidine)-3- substituted thiacarbamide is investigated pH-metrically.[99-100] Reports on speciation studies of binary complexes of Ca(II), Mg(II) and Zn(II) with L-glutamic acid in DMSO-water mixtures is also reported.[101] Interaction of Mn(II), Co(II), Ni(II), Cu(II) and Zn(II) metal ions with penicillamine (PEN) has been studied by pH-metric technique at 0.1 M (KNO_3) ionic strength and at 302 ± 0.5 K temperature in aqueous medium.[102] Research work on dipeptides (biomolecules) is carried out by several workers.[103-105] Studies on mixed ligand complexes of bivalent metal ions with 4,6–diamino–2–mercapto pyrimidine is reported by A. More et al.[106] Synthesis and characterization of mixed ligand complexes of Co(II) and Fe(III) ions with malic acid and heterocyclic amines and an over view of potentiometric determination of stability constants of metal complexes are reported in literature.[107-108] Equilibrium based computer studies of heterobinuclear complexes of toxic metal ions involving biologically significant ligands and the synthesis, characterization and antibacterial activity of mixed ligand dioxouranium complexes of 8-hydroxyquinoline and some amino acids are studied in the recent past.[109-110] Lanthanide(III) complex formation with diethylenetriamine in anhydrous *N*,*N*-dimethylformamide is studied

by Clara Comuzzi et al.[111] The synthesis of Ce(III) and Nd(III) inner transition metal complexes of allopurinol as a heterocyclic ligand is reported very recently.[112] Equilibrium studies of binary and mixed-ligand complexes of Zinc(II) involving (aminomethyl)-benzimidazole and some bio-relevant ligands reported by M. Aljahdali.[113]

An exhaustive survey of the existing literature reveals that much work is carried on metal complexes which involve their synthesis, structural analysis and their properties such as anti-bacterial, anti-cancer/anti-tumor, ant-diabetic, anti-tuberculosis, and anti-ulcer etc. However, the role of metals and their complexes in biochemical/environmental/industrial reactions can be understood by carrying the solution equilibrium studies. The availability of sophisticated computer program and rigorous mathematical treatment has made the investigation of multiple equilibria a significant field of research.

1.3. Present work:

1.3(a). Ligands and metals selected for present work:

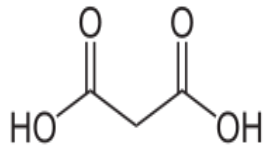
The metals used in present work are simple cations i.e. Cd(II), Gd(III) and oxocations i.e. UO_2(II), VO(II).

Ligands chosen for the present work are listed below:

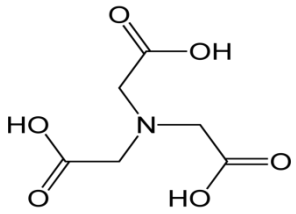
1. Malonic acid(MAL)
2. Nitrilotriacetic acid(NTA)
3. Iminodiacetic acid(IMDA)
4. Tyrosine(TYR)
5. 3,4-dihydroxyphenylalanine(DOPA)
6. Dopamine(DOPM)

1.3(b). Structures of these ligands are shown in scheme 1:

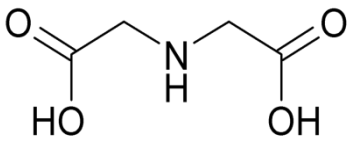
Scheme 1:



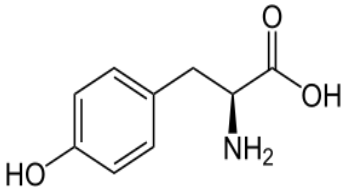
Malonic acid (MAL)



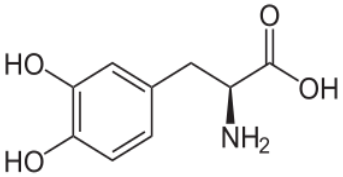
Nitrilotriacetic acid(NTA)



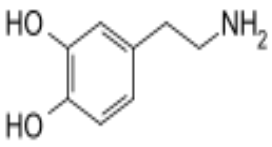
Iminodiacetic acid (IMDA)



Tyrosine(TYR)



3,4-dihydroxyphenylalanine(DOPA)



Dopamine(DOPM)

Role of the selected ligands and metals in biological, environmental, industrial and other fields is discussed in subsequent chapters. Present work includes the investigation of several binary and ternary systems involving selected ligands and metal ions. The objective is to explore the multiple equilibria with the aid of mathematical and computational analysis. The idea for choosing the work is based on the fact that multiple equilibria often occur in analytical, environmental and biological systems.

The following 1:1 binary and 1:1:1 ternary equilibria have been investigated by pH-metric method in aqueous medium at three different temperatures (i.e. 20±1°C, 30±1°C and 40±1°C) and three different ionic strengths (μ= 0.05M, 0.10M, 0.15M) maintained by $NaNO_3$:

a). Metal-Ligand binary systems:

- M-Malonic acid(MAL)
- M-Nitrilotriacetic acid(NTA)
- M-Iminodiacetic acid(IMDA)
- M-L-Tyrosine
- M-L-3,4-dihydroxyphenylalanine (DOPA)
- M-Dopamine (DOPM)

Where,

M = UO_2(II), VO(II), Gd(III) and Cd(II).

b). Metal-Ligand ternary systems:

- M-Malonic acid-Nitrilotriacetic acid
- M-Malonic acid- Iminodiacetic acid

- M-Malonic acid-Tyrosine
- M-Malonic acid-DOPA
- M-Malonic acid-DOPM

Various 1:1binary systems involving all the metals and all the ligands used in present studies were also examined under similar experimental conditions in order to get information on relative complexing tendencies of metal ions in binary and ternary systems. Ternary systems investigated in the present work are being reported for the first time.

1.4. Experimental:

1.4(a). Materials

Water

Distilled water was redistilled over alkaline potassium permanganate. The resulting distillate was cooled and kept in a well stoppered bottle. The pH of this water was found to be ≈6.9.

Sodium hydroxide solution

10.0 gm. of sodium hydroxide (Merck) was dissolved in 15ml CO_2-free double distilled water in a Pyrex flask. The flask was corked and left overnight. The clear supernatant liquid was decanted. A suitable volume of this solution was diluted with doubly distilled water to obtain a solution of 0.10M solution and this was standardized accurately by titrating potentiometrically against standard oxalic acid solution. The concentration of this alkali solution was checked from time to time.

Oxalic acid solution

Oxalic acid (Merck) was used to prepare 0.10M solution in doubly distilled water.

Sodium nitrate solution

Sodium nitrate (Merck) was used to prepare the stock solution of 1.0M in double distilled water.

Nitric acid solution

Nitric acid (Merck) was used to prepare stock solution of 2.0M, the stock solution was diluted to the desired strength (0.01M). The strength of this solution was checked by potentiometric titration against standard sodium hydroxide solution from time to time.

Metal nitrate solution

0.01M solutions of Uranyl(II), Vanadyl(II), Gadolinium(III) and Cadmium(II) (Aldrich) were prepared by dissolving respective nitrates/sulphate in 0.01M nitric acid solution .

Ligand solution

0.01M solution of DOPA (Aldrich) was prepared at the time of experiments by dissolving its accurately weighed amount in double distilled CO_2 free water. Solution of DOPA, being light sensitive, was freshly prepared for experiment and kept in covered flask in dark place.

Solutions of other selected ligands were prepared by dissolving accurately weighed amounts in double distilled water to get 0.01M solution of each. The solution of NTA was neutralized with one equivalent of alkali to make it dibasic. All the ligands were of analytical grade.

1.4(b). Instrument:

An Elico digital pH-meter model LI-127 with ATC probe and combined electrode type (CL-51B- Glass Body; range 0-14 pH units; 0-100ºC Automatic/Manual) with accuracy ±0.01 was employed for pH-measurement throughout the present work. Before starting each set of

observation, the pH meter was calibrated with standard buffer solutions of pH = 4.00 and pH = 9.20.

1.4(c). Titration and titration curves:

For mixed ligand systems following sets of titration mixture were prepared by keeping total volume to be 50.0mL and titrated against 0.10 M NaOH solution, ionic strengths (μ=0.05M,0.10M,0.15M) being maintained by adding different concentration of $NaNO_3$ solution to each titration mixture at temperatures 20±1°C, 30±1°C and 40±1°C.

1). Acid titration: HNO_3 (2.0×10^{-3}M).

2). Ligand 'A' titration:HNO_3(2.0×10^{-3}M) + Ligand 'A' (1.0×10^{-3}M).

3). Metal-Ligand 'A' (1:1) titration: HNO_3 (2.0×10^{-3}M) + Ligand 'A' (1.0×10^{-3}M) + Metal nitrate (1.0×10^{-3}M) .

4). Ligand 'B' titration:HNO_3(2.0×10^{-3}M) + Ligand 'B'(1.0×10^{-3}M).

5). Metal-Ligand'B' (1:1) titration: HNO_3 (2.0×10^{-3}M) + Ligand 'B' (1.0×10^{-3}M) + Metal nitrate (1.0×10^{-3}M).

6). Metal-Ligand 'A' –Ligand 'B'(1:1:1) titration: HNO_3 (2.0×10^{-3}M) + Ligand 'A'(1.0×10^{-3}M) + Ligand 'B' (1.0×10^{-3}M) + Metal nitrate (1.0×10^{-3}M)

All the binary and ternary systems were investigated under equimolar concentration ratios.

By plotting values of pH vs. volume of alkali added, titration curves were obtained for various systems. These curves were examined to understand multiple equilibria existing in solution

1.5. Theoretical treatment of various possible equilibria:

The stability constant of complex in the solution is usually determined by the knowledge of measurement of equilibrium constants for complex forming reaction. Knowledge of stability constant, therefore, is of immense help to rationalize our understanding of the behavior of metal complex in the solution.

Several approaches have been developed to obtain the equilibrium constants by theoretical treatment of various possible equilibria in a particular system.[29-32,35,36,40,41] The theoretical treatment for the calculation of equilibrium constant in accordance with the method of Chaberek and Martell.[33-34] as modified by Dey et al.[37.39] is more informative. The modified method was developed by adding mineral acid to the titration mixture before titration against the standard alkali solution. This served to reveal the state of affair at low pH values and may be applied to evaluate the formation and dissociation of protonated complex, non-protonated metal complex, hydroxo complex species and mixed ligand species as well. This modified method has been used in the present work for investigating of various equilibria and is given here under.

1.6. Proton-ligand equilibria:

The proton dissociation constants K_{a1}, K_{a2},….., K_{an} for the ligand H_nA can be calculated using pH vs. '*a*' curves. The dissociation of ligand H_nA is shown here under:

$$H_nA \rightleftharpoons H_{n-1}A + H; \quad K_{a1} \qquad \text{------(i)}$$

$$K_{a1} = \frac{[H_{n-1}A][H]}{[H_nA]} \qquad \text{-----(1.1)a}$$

$$H_{n-1}A \rightleftharpoons H_{n-2}A + H \; ; \; K_{a2} \qquad \text{----------(ii)}$$

$$K_{a2} = \frac{[H_{n-2}A][H]}{[H_{n-1}A]} \qquad \text{--------(1.1)b}$$

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$$HA \rightleftharpoons A + H \; ; \; K_{an} \qquad \text{----------(iii)}$$

$$K_{an} = \frac{[A][H]}{[HA]} \qquad \text{------(1.1)n}$$

[Charges have been omitted for the sake of simplicity.]

The total ligand concentration which can be obtained using the initial concentration and the total volume at each pH is given by following equation:

$$C_A = [H_nA] + [H_{n-1}A] + [H_{n-2}A] + \ldots\ldots\ldots + [HA] + [A] \qquad \text{-------(1.2)}$$

Applying mass and charge balance:

$$aC_A = [H_{n-1}A] + 2[H_{n-2}A] + \ldots\ldots\ldots + (n-1)[HA] + n[A] \qquad \text{--------(1.3)}$$

From Eqs. 1.3 and 1.4:

$$C_A(n-a) = n[H_nA] + (n-1)[H_{n-1}A] + (n-2)[H_{n-2}A] + \ldots + [HA] \qquad \text{--------(1.4)}$$

Where, '*a*' is the moles of alkali added per mole of ligand/metal.

For the dissociation of first two protons of H_nA showing inflections at a =1 and 2,

$$C_A = [H_nA] + [H_{n-1}A] \qquad \text{--------(1.5)}$$

(between a = 0 and a =1)

For mass and charge balance relation:

$$aC_A = [H_{n-1}A] \qquad \text{----------(1.6)}$$

In the higher buffer region i.e between a =1 and 2, ignoring the existence of other species.

$$C_A = [H_{n-1}A] + [H_{n-2}A] \qquad \text{----------(1.7)}$$

(between a =1 and a=2)

From mass and charge balance relation:

$$aC_A = [H_{n-1}A] + 2[H_{n-2}A] \qquad \text{----------(1.8)}$$

Therefore, the values of K_{a1}, K_{a2} ,…, K_{an} are given as:

$$K_{a1} = \frac{a[H]}{(1-a)} \qquad \text{--------(1.9)a}$$

$$K_{a2} = \frac{(a-1)[H]}{(2-a)} \qquad \text{--------(1.9)b}$$

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$$K_{an} = \frac{(a+(1-n))[H]}{(n-a)} \qquad \text{--------(1.9)n}$$

The relation between dissociation constants and protonation constants is represented as:

$$H + A \overset{\beta_{HA}}{\rightleftharpoons} HA \qquad \text{----------(iv)}$$

$$\beta_{HA} = K_{an} \qquad \text{--------(1.10)a}$$

$$HA + A \overset{\beta_{H_2A}}{\rightleftharpoons} H_2A \qquad \text{----------(v)}$$

$$\beta_{H_2A} = K_{a2} \cdot K_{an} \qquad \text{-------(1.10)b}$$

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$$H_{n-1}A + A \overset{\beta_{H_nA}}{\rightleftharpoons} H_nA \qquad \text{----------(vi)}$$

$$\beta_{HnA} = K_{a1}\ldots\ldots\ldots K_{a2} \,.\, K_{an} \qquad \text{-------(1.10)n}$$

Protonation constants of ligands were calculated by using following expressions:

$$\log \beta_{HA} = pK_{an} \qquad \text{----------(1.11)a}$$

$$\log \beta_{H_2A} = pK_{a2} + pK_{an} \qquad \text{----------(1.11)b}$$

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$$\log \beta_{H_nA} = pK_{a1} + \ldots\ldots + pK_{a2} + pK_{an} \qquad \text{----(1.11)n}$$

1.7. Metal-ligand equilibria:

a). Nonprotonated species:

The titration curves plotted between '*a*' (*a* = moles of alkali per mole of metal ions) and pH for reaction between M and H_nA consisting of inflections at *a* =1, 2n etc. corresponds for 1:1, 1:2 etc. metal to ligand ratios.

In the present studies, since the equilibria involving metal - ligand 1:1 ratio are only investigated, thus theoretical treatment for this equilibria is given here under:

$$M + A \rightleftharpoons MA \qquad \text{----------(vii)}$$

(between *a* = 0 and n)

$$K_{MA}^{M} = \frac{[MA]}{[M][A]} \quad \text{---------(1.12)}$$

[Charges have been omitted for the sake of simplicity.]

Now after calculating the values of [M], [A] and [MA] the value of K_{MA}^{M} can be evaluated.

$C_A = [H_nA] + [H_{n-1}A] + [H_{n-2}A] + \ldots\ldots + [A] + [MA]$ ---------(1.13)

$C_M = [M] + [MA]$ ---------(1.14)

[M] is the concentration of uncomplexed metal ion.

$$aC_A = [H_{n-1}A] + 2[H_{n-2}A] + \ldots\ldots\ldots + n[A] + n[MA] \quad \text{---------(1.15)}$$

Introducing the dissociation constants of the ligand and substituting the value of [MA] from Eq. 1.14 in to Eq. 1.16 we get:

$$[A] = \frac{(n-a)C_A}{\left(\frac{n[H]^n}{K_{a1}K_{a2}\ldots.K_{an}} + \frac{(n-1)[H]^{n-1}}{K_{a2}K_{a3}\ldots.K_{an}} + \cdots + \frac{[H]}{K_{an}}\right)} \quad \text{------(1.16)}$$

Therefore,

$$[MA] = C_A - Y_1[A] \quad \text{---------(1.17)}$$

$$[M] = Y_1[A] \quad \text{---------(1.18)}$$

Where,

$$Y_1 = \frac{[H]^n}{K_{a1}K_{a2}\ldots.K_{an}} + \frac{[H]^{n-1}}{K_{a2}K_{a3}\ldots.K_{an}} + \cdots + \frac{[H]}{K_{an}} + 1 \quad \text{--------(1.19)}$$

b). Protonated species:

The interaction between metal ion and protonated ligands having more than one proton can result in the formation of protonated metal-

ligand species due to the fact that one or more protons remain undissociated.

In the present work 1:1 metal-ligand equilibria are investigated. Hence considering the 1:1 metal to ligand interaction between M and H_nA forming the protonated species MAH_x showing inflection at $a = (n-x)$, can be given as:

$$M + H_xA \rightleftharpoons MAH_x \qquad \text{----------(viii)}$$

(between $a = 0$ and $n-x$)

$$K^{M}_{MAH_x} = \frac{[MAH_x]}{[M][H_xA]} \qquad \text{--------(1.20)}$$

[Charges have been omitted for the sake of simplicity.]

The stepwise dissociation of protons from the protonated complex can be shown as:

$$MAH_x \rightleftharpoons MAH_{x-1} + H \qquad \text{----------(ix)a}$$

(between $a = n-x$ and $n-x+1$)

$$K^{H}_{MAH_x} = \frac{[MAH_{x-1}][H]}{[MAH_x]} \qquad \text{--------(1.21)a}$$

$$MAH_{x-1} \rightleftharpoons MAH_{x-2} + H \qquad \text{----------(ix)b}$$

(between $a = n-x+1$ and $n-x+2$)

$$K^{H}_{MAH_{x-1}} = \frac{[MAH_{x-2}][H]}{[MAH_{x-1}]} \qquad \text{--------(1.21)b}$$

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$$MAH \rightleftharpoons MA + H \qquad \text{----------(ix)x}$$

(between a = n-1 and n)

$$K^{H}_{MAH} = \frac{[MA][H]}{[MAH]} \qquad \text{--------(1.21)x}$$

The stability constant $K^{M}_{MAH_X}$ can be evaluated similar to 1:1 species, ignoring the existence of other species which are obtained after proton dissociation from MAH_x .

When the value of 'a' is between a = 0 and n-x the equilibria that exist are given here under:

$$C_M = [M] + [MAH_x] \qquad \text{----------(1.22)}$$

$$C_A = [H_nA] + [H_{n-1}A] + [H_{n-2}A] + \ldots + [A] + [MAH_x] \qquad \text{-------(1.23)}$$

By mass and charge balance relation:

$$aC_A = [H_{n-1}A] + 2[H_{n-2}A + \ldots + n[A] + (n-x)[MAH_x] \qquad \text{---------(1.24)}$$

Introducing the proton dissociation constants of ligands and substituting the value of $[MAH_x]$ from Eq.1.24 in Eq.1.25 we get:

$$[A] = \frac{(n-a)C_A}{\left(\frac{n[H]^n}{K_{a1}K_{a2}\ldots K_{an}} + \frac{(n-1)[H]^{n-1}}{K_{a2}K_{a3}\ldots K_{an}} + \cdots + \frac{[H]}{K_{an}}\right)} \qquad \text{-----(1.25)}$$

Therefore,

$$[MAH_x] = C_A - Y_1[A] \qquad \text{--------(1.26)}$$

$$[M] = Y_1[A] \qquad \text{------(1.27)}$$

Where,

$$Y_1 = \frac{[H]^n}{K_{a1}K_{a2}....K_{an}} + \frac{[H]^{n-1}}{K_{a2}K_{a3}....K_{an}} + \cdots + \frac{[H]}{K_{an}} + 1 \quad \text{-----(1.28)}$$

Eq.1.26 provides the value for [A] and [M] is calculated from Eq.1.27 and $[MAH_x]$ from Eq.1.26.The value for $K^M_{MAH_x}$ can be obtained from Eq.1.20.

Alternatively, in case where, *a* > (n-x), the following equilibria will also exist:

$$M + H_{x-1}A \rightleftharpoons MAH_{x-1} \quad \text{---------(x)a}$$

$$K^M_{MAH_{x-1}} = \frac{[MAH_{x-1}]}{[M][H_{x-1}A]} \quad \text{----------(1.29)a}$$

$$M + H_{x-2}A \rightleftharpoons MAH_{x-2} \quad \text{----------(x)b}$$

$$K^M_{MAH_{x-2}} = \frac{[MAH_{x-2}]}{[M][H_{x-2}A]} \quad \text{--------(1.29)b}$$

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$$M + A \rightleftharpoons MA \quad \text{----------(x)x}$$

$$K^M_{MA} = \frac{[MA]}{[M][A]} \quad \text{----------(1.29)x}$$

The values of $K^M_{MAH_{x-1}}$, $K^M_{MAH_{x-2}}$,....., K^M_{MA} can be evaluated from the following relations introducing the value of stability constant of MAH_x.

When the value of '*a*' is between (n-x) and (n+1-x):

$$C_M = [M] + [MAH_x] + [MAH_{x-1}] \quad \text{----------(1.30)}$$

$$C_A = [H_nA] + [H_{n-1}A] + [H_{n-2}A] + \ldots + [A] + [MAH_x] + [MAH_{x-1}] \quad \text{--(1.31)}$$

The following expression is obtained by mass and charge balance relation:

$$aC_A = [H_{n-1}A] + 2[H_{n-2}A + \ldots + n[A] + (n-x)[MAH_x] + (n+1-x)[MAH_{x-1}] \quad \text{---------(1.32)}$$

From Eq. 1.21:

$$[MAH_x] = \frac{K^M_{MA\,H_x}[M][H]^x[A]}{K_{a(n-x+1)}K_{a(n-x+2)}\ldots K_{an}} \quad \text{------(1.33)}$$

By using Eqs. 1.9, 1.27, 1.31 and 1.21 Eq. 1.32 can be written as:

$$N_1[A]^2 + N_2[A] + N_3 = 0 \quad \text{------(1.34)}$$

Where,

$$N_1 = \frac{K^M_{MA\,H_x}Y_1[H]^x}{K_{a(n-x+1)}K_{a(n-x+2)}\ldots K_{an}}$$

$$N_2 = \frac{(n+1-x)[H]^n}{K_{a1}K_{a2}\ldots K_{an}} + \frac{(n-x)[H]^{n-1}}{K_{a2}K_{a3}\ldots K_{an}} + \cdots - \frac{(x-2)[H]}{K_{an}} - (x-1)$$

And $$N_3 = -\ C_A\ (\ n + 1 - x - a)$$

Eq. 1.34 will give the value of [A].

Thus,

$$[MAH_{x-1}] = C_A - Y_1[A] - \frac{K^M_{MAH_x} Y_1 [H]^x [A]^2}{K_{a(n-x+1)} K_{a(n-x+2)} \ldots K_{an}} \qquad \text{-----(1.35)}$$

then $K^M_{MAH_x}$ can be evaluated.

Further, assuming the whole of the metal ion and ligand to be consumed in the formation of MAH_x species, the dissociation constants $K^M_{MAH_x}$, $K^M_{MAH_{x-1}}$, …., K^M_{MAH} can be evaluated by either of the two ways:

- By treating the equilibria (x)a, (x)b, …., (x)x as proton dissociation of the ligand.
- Considering concentrations of involved species as obtained by above treatment.

Overall formation constants of various binary complex species were calculated by using following expression:

$$\log \beta_{MAH_{(n-x-1)}} = \log K^M_{MAH_{(n-x)}} + \log \beta_{MAH_{(n-x)}} \qquad \text{-----(1.36)}$$

1.8. Mixed ligand equilibria:

(Protonated and Nonprotonated Biligand Systems)

Depending upon the affinity of the ligands involved (say A and B), two types of the complexation behaviour are found in the solution.

a). Stepwise equilibria:

The coordination of secondary ligand(H_yB) to the metal primary ligand complex(MAH_x) can be represented by following equilibrium in the stepwise ternary complex formation.

Step I. $M + H_xA \rightleftharpoons MAH_x$

(between *a* = (n-x-1) and (n-x))

StepII. $MAH_x + H_yB \rightleftharpoons MAH_xBH_y$ ----------(xi)

(between *a* = (n-x) and (n+m-x-y))

$$K^{MAH_x}_{MAH_xBH_y} = \frac{[MAH_xBH_y]}{[MAH_x]\,[H_yB]} \qquad \text{----------(1.37)}$$

Here, H_nA and H_mB are recognized as primary and secondary ligands respectively. Where 'n' and 'm' are the number of dissociable protons in ligand A and B respectively and H_xA and H_yB are the primary and secondary ligands with undissociated protons.

b). Simultaneous equilibria:

When the affinity of two ligands is comparable, both H_nA and H_mB combine with metal ion simultaneously. This type of equilibria is more complicated and may be represented as:

$$M + H_xA + H_yB \rightleftharpoons MAH_xBH_y \qquad \text{----------(xii)}$$

(between a = 0 and (n+m-x-y))

$$K^{M}_{MAH_xBH_y} = \frac{[MAH_xBH_y]}{[M]\,[H_xA]\,[H_yB]} \qquad \text{----------(1.38)}$$

A number of mathematical approaches have been developed to calculate the stability constants in mixed systems.[31-41] Mathematical treatment for (1:1:1) ternary system, based on the method of Chaberek and Martell, is given here under:

$$C_M = [M] + [MAH_x] + [MBH_y] + [MAH_xBH_y] \qquad \text{--------(1.39)}$$

$$C_A = [H_nA] + [H_{n-1}A] + [H_{n-2}A] + \ldots\ldots + [HA] + [A] + [MAH_x] + [MAH_xBH_y] \qquad \text{--------(1.40)}$$

$$C_B = [H_mB] + [H_{m-1}B] + [H_{m-2}B] + \ldots\ldots + [HB] + [B] + [MBH_y] + [MAH_xBH_y] \qquad \text{--------(1.41)}$$

[Only major species have been considered to simplify the treatment and the charges have been omitted for the sake of simplicity.]

For equimolar systems:

$$aC_M = [H_{n-1}A] + 2[H_{n-2}A] + \ldots\ldots + (n-1)[HA] + n[A] + (n-x)[MAH_x] + [H_{m-1}B] + 2[H_{m-2}B] + \ldots\ldots + (m-1)[HB] + m[B] + (m-y)[MBH_y] + (n+m-x-y)[MAH_xBH_y] \text{----(1.42)}$$

From Eqs. 1.40, 1.41 and 1.42:

$$aC_M = (n+m-x-y)C_M - ((n-x)[H_nA] + (n-x-1)[H_{n-1}A] + \ldots\ldots - x[A] + (m-y)[H_mB] + (m-y-1)[H_{m-1}B] + \ldots\ldots - y[B] \quad \text{-----(1.43)}$$

or,

$$C_M(n+m-x-y-a) = a_1[A] + b_1[B] \quad \text{--------(1.44)}$$

Where,

$$a_1 = \frac{(n-x)[H]^n}{K_{a1}K_{a2}....K_{an}} + \frac{(n-x-1)[H]^{n-1}}{K_{a2}K_{a3}....K_{an}} + \ldots\ldots - \frac{(x-1)[H]}{K_{an}} - x \quad \text{------(1.45)}$$

$$b_1 = \frac{(m-y)[H]^m}{K_{b1}K_{b2}....K_{bm}} + \frac{(m-y-1)[H]^{m-1}}{K_{b2}K_{b3}....K_{bm}} + \ldots\ldots - \frac{(y-1)[H]}{K_{bm}} - y \quad \text{-------(1.46)}$$

Further,

$$C_M - C_A = [M] + [MBH_y] - [H_nA] - [H_{n-1}A] - [H_{n-2}A] - \ldots\ldots - [A] = 0 \quad \text{---------(1.47)}$$

$$C_M - C_B = [M] + [MAH_x] - [H_mB] - [H_{m-1}B] - [H_{m-2}B] - \ldots\ldots - [B] = 0 \quad \text{-------(1.48)}$$

Introducing the dissociation constants of ligands and the stability constants of the mono-ligand complexes from Eqs. 1.09 and 1.20, Eqs. 1.47 and 1.48 can be written as :

$$[M] = \frac{a_2[A]}{\left\{1+\frac{K^{M}_{MB\,H_y}[H]^{y}[B]}{K_{b(m-y+1)}K_{b(m-y+2)}\ldots K_{bm}}\right\}} \qquad \text{-------(1.59)}$$

$$[M] = \frac{b_2[B]}{\left\{1+\frac{K^{M}_{MA\,H_x}[H]^{x}[A]}{K_{a(n-x+1)}K_{a(n-x+2)}\ldots K_{an}}\right\}} \qquad \text{-----(1.50)}$$

$$a_2 = \frac{[H]^n}{K_{a1}K_{a2}\ldots K_{an}} + \frac{[H]^{n-1}}{K_{a2}K_{a3}\ldots K_{an}} + \ldots + \frac{[H]}{K_{an}} + 1 \qquad \text{------(1.51)}$$

$$b_2 = \frac{[H]^m}{K_{b1}K_{b2}\ldots K_{bm}} + \frac{[H]^{m-1}}{K_{b2}K_{b3}\ldots K_{bm}} + \ldots + \frac{[H]}{K_{bm}} + 1 \qquad \text{------(1.52)}$$

Combination of Eq. 1.49 and 1.50 gives:

$$\frac{a_2[A]}{\left\{1+\frac{K^{M}_{MB\,H_y}[H]^{y}[B]}{K_{b(m-y+1)}K_{b(m-y+2)}\ldots K_{bm}}\right\}} = \frac{b_2[B]}{\left\{1+\frac{K^{M}_{MA\,H_x}[H]^{x}[A]}{K_{a(n-x+1)}K_{a(n-x+2)}\ldots K_{an}}\right\}} \qquad \text{-------(1.53)}$$

From Eq. 1.44:

$$[B] = e_1 - d\,[A] \qquad \text{----(1.54)}$$

Where,

$$e_1 = \frac{C_M(n+m-x-y-a)}{b_1} \qquad \text{and} \qquad d = \frac{a_1}{b_1}$$

Substituting the value of [B] in Eq.1.53:

$$P_1[A]^2 + P_2[A] - P_3 = 0 \qquad \text{-------(1.55)}$$

$$P_1 = \left\{\frac{a_2 K^{M}_{MA\,H_x}[H]^x}{K_{a(n-x+1)}K_{a(n-x+2)} \ldots . K_{an}}\right\} - \left\{\frac{b_2 K^{M}_{MB\,H_y}[H]^y d^2}{K_{b(m-y+1)}K_{b(m-y+2)} \ldots . K_{bm}}\right\}$$

-----(1.56)

$$P_2 = \left\{a_2 + b_2 d + \frac{2b_2 e_1 d K^{M}_{MB\,H_y}[H]^y}{K_{b(m-y+1)}K_{b(m-y+2)} \ldots . K_{bm}}\right\} \qquad \text{-----(1.57)}$$

$$P_3 = \left\{b_2 e_1 + \frac{b_2 e_1^2 K^{M}_{MB\,H_y}[H]^y}{K_{b(m-y+1)}K_{b(m-y+2)} \ldots . K_{bm}}\right\} \qquad \text{-----(1.58)}$$

Solution of quadratic Eq. 1.55 will give the value of [A], which on substitution in Eq. 1.54 would give [B]. Then [M] can be obtained from Eq. 1.49 or 1.50. [MAH_xBH_y] can be determined, considering [A], [B], [M] and stability constants of corresponding binary species.

Dissociation of the protonated mixed ligand complexes was treated in the same manner as the ligand dissociation. Values of formation constants of various mixed ligand complex species were calculated by using following expression:

$$\log \beta_{MAB\,H_{(n-x+m-y-1)}} = \log K^{M}_{MAB\,H_{(n-x+m-y)}} + \log \beta_{HA/HB} \qquad \text{--- (1.59)}$$

1.9. Computation of equilibrium constants:

Various computer programs for the treatment of equilibria in aqueous medium have been developed for calculating the stability constants of metal complexes, from pH titration data. Anderegg published a program that could deal with protonated, hydrolysed or polynuclear metal complexes, hydrolysed metal ions and protonated ligands.[114] I.G. Sayce developed a computer program named as SCOGS (Stability constant of

generalized species) which employs the conventional non linear least square approach.[115-117] The program is written in FORTRAN IV. It is capable of calculating simultaneously or individually, association constants for any of the species formed in the system containing up to two metals and two ligands, provided that the degree of complex formation is pH-dependent. Thus, SCOGS may be utilized to analyse appropriate pH titration data to yield metal-ion hydrolytic constants, stability constants of simple complexes (MA, MB and MA2 etc.). SCOGS may also be used to calculate constants for "mixed" complexes containing two different metals and two different ligands resulting the formation of MAB and M1M2 AB types of complexes. The main program deals with input of data, the setting up and solution of the least-squares equations and output of the results and used successfully in the refinement of binary and ternary data.

Thereafter several computer programs were developed, mainly so as to be able to use microcomputers for computation. The programs: **MINIQUAD**, **MINIQUAD -75**[118-119] and **BEST** [120] are commonly used to determine equilibrium constant from potentiometric data. Although **MINIQUAD** is considered to be a robust program for the computation of equilibrium constants, it has obtained criticism that the function minimized did not involve experimentally observed quantities directly. This has been put right in **SUPERQUAD.**[121] Many programs follow standard approach, in which the sum of squares is minimized by means of the Gauss – Newton – Marquardt algorithm. The derivatives required by this algorithm are originally obtained numerically, some programs use derivatives calculated analytically. The free concentrations are calculated by solving the non linear simultaneous equations of mass balance using the Newton – Raphson method.[122] Rainforcement in the

field of computation of equilibrium constants from experimental data are reviewed[42-43]. Determination of equilibrium constants with **HYPERQUAD**[123-124] has been described clearly in the publication made by Peter Gans and co-workers. All of these programs use a least square approach [125].

In the present work computation of equilibrium constants is done by using experimental data obtained by potentiometric technique. Computation of data was done by using **SCOGS** computer program. The complex formation equilibria were elucidated with the help of speciation curves.

1.10. Calculation of thermodynamic parameters:

From the curve plotted between the stability constants (log K) and square root of ionic strength ($\sqrt{\mu}$), the thermodynamic values of the stability constant have been obtained by extrapolation of log K values to zero ionic strength. The values of the thermodynamic stability constant $K^{\mu\rightarrow 0}$ are used to determine the ligational standard free energy change ($\Delta G°$) for the complexation reaction from Van't Hoff isotherm:

$$\Delta G° = -2.303RT \log K^{\mu\rightarrow 0} \qquad \text{------- (1.60)}$$

The Gibb's Helmholtz equation is:

$$\Delta G° = \Delta H° - T\Delta S° \qquad \text{------- (1.61)}$$

This can be written as equation (1.62) by putting $\Delta G° = -2.303RT \log K^{\mu\rightarrow 0}$

$$\log K^{\mu\rightarrow 0} = \frac{-\Delta H°}{2.303R}\ \frac{1}{T} + \frac{\Delta S°}{2.303R} \qquad \text{----- (1.62)}$$

The standard enthalpy change (ΔH°) and entropy change (ΔS°) have been determined by linear least square fit method by plotting a graph between $\frac{1}{T}$ vs $\log K^{\mu \to 0}$ [126]. In equation (1.62)

Slope = $\frac{-\Delta H^\circ}{2.303R}$ and Intercept = $\frac{\Delta S^\circ}{2.303R}$

1.11. References:

1. H. Sigel, 'Metal Ions in Biological System', 1-44, Marcel Dekker, New York **(1971-2009)**.
2. A. Sigel, H. Sigel and K.O. Roland Sigel, Nickel and its surprising impact in nature , Metal Ions in Life Sciences, John Wiley & Sons Ltd., 2**(2008)**.
3. T. Kiss, T. Jakusch, D.Hollender, A. Dörnyei, Vanadium: The Versatile Metal; K. Kustin, J. Costa Pessoa, D.C. Crans, (Eds) Am. Chem. Soc., Washington DC, 974, 323**(2007)**.
4. H. Sigel, A.Sigel and K.O. Ronald Sigel; Metal Ions in Life Science, John Willey & Sons Ltd., Chichester, U.K., 44, **(2006)**.
5. S. Aime, S. Geninatti Crich, E. Gianolio, G.B. Giovenzana ,L. Tei and E. Terreno Coord. Chem. Rev., 250, 1562(**2006).**
6. D.C. Crans, J. J. Smee, E. Gaidamauskas, L.Yang, Chem. Rev., 104, 849(**2004)**.
7. F. A. Cotton, Advance Inorganic Chemistry, 6th Eds., John Wiley, New York, (**1999)**.
8. M.T. Beck and I. Nagypal, 'Chemistry of Complex Equilibria', Eillis Harwood Ltd., Chichester, Hastald Press, New York, **(1990)**.
9. G. Wilkinson, Comprehensive Coordination Chemistry. Pergamon Press, Oxford, **(1987).**

10. M.N. Hughes, 'The Inorganic Chemistry of Biological Process', 2nd Eds., Wiley Chicheser **(1981)**.

11. A.E. Martell; 'Inorganic Chemistry in Biology and Medicine', Am. Chem. Soc., Washington D.C., **(1980)**.

12. A.W. Addison, W.R. Cullen, D. Dolphin and B.R. James; 'Biological Aspect of Inorganic Chemistry', Wiley, New York, **(1977)**.

13. B.L. Valle, J.E. Coleman, Compr. Biochem, 8, 1458(**1968).**

14. L. Halleman, C.C Stock, J. Biochem , 77, 125**(1938).**

15. S.I. Habib, M.A. Baseer, P.A. Kulkarni, Der Chemica Sinica, 2(1), 27(**2011).**

16. S. Sharma, J. Ramania, J. Bhalodiaa, N. Patela, K. Thakkara and R. Patel, Pelagia Research Library, Advances in Applied Science Research, 2(4), 374(**2011)**.

17. M. E. Mohamed, Der Chemica Sinica, 2(4), 274(**2011)**.

18. S. Verma, S. Shrivastva and P. Rani, Der Chemica Sinica, 2(5), 12 **(2011)**.

19. P. Mittal, V. Uma, Der Chemica Sinica, 1(3), 124(**2010).**

20. H. Kumar, R. Chaudhary, Der Chemica Sinica, 1(2), 55(**2010)**.

21. C. Picard, N. Geum, I. Nasso, B. Mestre, P. Tisnès, S. Laurent, R.N. Muller. and L.Vander Elst ,Bioorganic & Medicinal Chemistry Letters, 16, 5309(**2006).**

22. T. Kiss and T. Jakusch, 'Metal Therapeutic Drugs and Metal Based Diagnostic Agents' The use of Metals in Medicine Eds. by Gielen and Tiekinik, John Wiley and Sons Ltd.**, (2005).**

23. R. Aydin and U. Ozer; Chem. Pharm. Bull. (Tokyo), 52(1), 33 **(2004)**.

24. J. Nishikido, M. Kamishima, H. Matsuzawa and K. Mikami, Tetrahedron, 58, 8345(**2002).**

25. S. J. Franklin, Current Opinion in Chemical Biology, 5, 201(**2001).**

26. A. Louie Etal, Nat. Biotechno., 18321(**2000)**.

27. M. Farewell, 'Transition Metal Complexes as Drugs and Chemotherapeutic Agents', Dordrecht, Netherlands, **(1989)**.

28. R. Reisfeld and C.K. Jorgensen, Lasers and Excited States of Rare Earths, Springer-Verlag, Berlin Heidelberg, New-York (**1977)**.

29. N. Bjerrum, Kgl. Danske Videnskab. Selskab. Naturvidenskab. Math. Ajdel, 12(7), 147 **(1915)** ; Z. Anorg. Chem., 118, 131 **(1921)**.

30. J. Bjerrum, G. Schwarzenbach and L.G. Sillen, 'Stability Constants' Part-I Organic Ligands, Part-II Inorganic Ligands, Chemical Society London, **(1957).**

31. H. Irving and H.S. Rossotti, J. Chem. Soc., 3397 **(1953)**.

32. H. Irving and H.S Rossotti, J. Chem. Soc., 2904 **(1954)**.

33. S. Chaberek and A.E. Martell, J. Am. Chem. Soc., 74, 5052 **(1952)**.

34. S. Chaberek and A.E. Martell, J. Am. Chem. Soc., 77, 1477**(1955)**.

35. M.V. Chidambaram and P.K. Bhattacharya, Indian J. Chem., 8, 941 (1970); 9, 1294 **(1971)**.

36. M.V. Chidambaram and P.K. Bhattacharya, Acta. Chem., Hungary, 75, 123 **(1973)**.

37. R. Nayan and A.K. Dey, Indian J. Chem., 14(A), 892 **(1976)**.

38. R. Nayan and A.K. Dey, Transition Metal Chem., 1, 61 **(1976)**.

39. R. Nayan and A.K. Dey, J. Inorg. Nucl. Chem., 36, 2545 **(1974)**.

40. S. Ramamoorthy and M. Santappa, Indian J. Chem., 9,381**(1971)**.

41. S. Ramamoorthy and M. Santappa, J. Inorg. Nucl. Chem., 33, 1775 **(1971)**.

42. D. J. Leggett, 'Computational Methods for the Determination of Formation Constants', Plenum press, New York **(1985).**

43. M. Meloum, J. Havel and E. Hogfeldt, 'Computation of Solution Equilibria', Ellis Horwood, Chichester **(1994).**

44. I. Erden, N. Demirhan and U. Avciata, Indian J. Chem., 45A, 1395 **(2006).**

45. E. Lodyga-Ehruscinska, D. Sanna, G. Micera, L. Chruscinski, K.J. Olegni, R.J. Nachman and J.Zobrok, Acta Biochim. Polonica, 53(1), 65 **(2006)**.

46. A. Miličević and N. Raos, Croat. Chim. Acta.,79(2), 281 **(2006).**

47. J. Wang and Y. Fang, Biomed. Chromatogr., 29(9), 904 **(2006)**.

48. I. Correia, J.C. Pessoa, M.T. Duarte, M.F.M. Piedade, T. Jakusch, T. Kiss, M.M.C.A. Castro, C.F.G.C. Geraldes and F. Avecilla, Eur. J. Inorg. Chem., 732 **(2005).**

49. M.V. Katariya, Asian J. Chem., 17(2), 707 **(2005).**

50. S. Belaid, S. Djebbar, O. Benali-Baitich, S. Ghalem, M.A. Khan and H. Bouet, Asian J. Chem. 17(2), 811**(2005).**

51. P. Narender, R. Rani, M. Reddy P. and B. Satyanarayana, Proc. Nat. Sci. Acad., India, 75(2), 85 **(2005)**.

52. J.D. Joshi, A.D. Patel, L.S. Bhutadia, J.J. Bora and S. Sharma, Asian J. Chem., 17(4), 2347 **(2005)**.

53. D.S. Reddy, B.K. Rao, P. Pallavi, N. Navneeta and S. Satyanarayana, Indian J. Chem., 44(A), 678 **(2005)**

54. Z. Arkosi, Z. Paksi, L. Korecz, T. Gajda, B. Henry and A. Rockenbauer, J. Inorg. Biochem., 98(12), 1995 **(2004)**.

55. A. Doğan and E. Kilic, Indian J. Chem. 42(A), 1632 **(2003)**.

56. R.N. Patel, R.P. Shrivastava, N. Singh and S. Kumar, Indian J. Chem., 40(A), 361 **(2001).**

57. A.K. Das, Trans. Metal Chem., 16(1), 108 **(1991)**.

58. R. Ahuja and K. Dwivedi, Indian Chem. Soc., 68, 643 **(1991)**.

59. R. Ahuja and K. Dwivedi, J. Indian Chem., 30(7), 614 **(1991)**.

60. T.P.I and G.H. Nancollas, Inorg. Chem., 11, 2414 **(1972).**

61. R. Năsănen and M. Koskinen, Suomenkemistilehti, 340, 23 **(1967).**

62. L.G. Sillen, Acta Chem. Scand., 18, 1085 **(1964)**.

63. D.L. Leussing, Talanta, 11, 189 **(1964).**

64. N. Ingri and L.G. Sillen, Acta Chem. Scand., 16,173 **(1962)**.

65. R. Năsănen, P. Merilainen and S. Lukkari, Acta Chem. Scand., 16, 2384, **(1962)**.

66. L.G. Sillen, Acta Chem. Scand., 16, 159 **(1962)**.

67. S. Teigen and R. Andersen Trace Metals in the Marine Environment: State of The Art and Research Needs. Programme on Marine Pollution. Zagreb. Croatian Society of Chemical Engineers (**1992)**.

68. P.S. Rao, B. Srikanth, V.S. Rao, C. Kamala Sastry and G.N. Rao, E-J. Chem. 6, 561**(2009**).

69. P.R. Paquin, R.C. Santore, K.B. Wu, C.D. Kavvadas and D.M. Di Toro, Environ. Sci. Policy., 3, 175**(2000)**.

70. S. Raju, B. A. Kumar, K. B. K. Naik and G. N. Rao, Asian J. Res. Chem. 4(12), 1908**(2011)**.

71. A. Bianchi ,, L. Calabi , F. Corana , S. Fontana , P. Losi , A. Maiocchi, L. Paleari ,and B. Valtancoli, Coord. Chem. Rev. 204 309**(2000).**

72. O. Hornykiewicz, Pharmacol. Rev., 18, 925(**1966)**.

73. Nitrilotriaccetic Acid and its Salt, IARC Monograph, 73 **(1990).**

74. A. Butler, J. V. Walker, Chem. Rev., 93, 1937(**1993).**

75. K. H. Thompson, J. H. McNeill, C. Orvig, Chem. Rev., 99, 2561**(1999)**.

76. N. Hnasko, R. Ben-Jonathan, Endocr. Rev., 22, 724(**2001)**

77. K.V. S. Devi, B. R. Raju and G. N. Rao, Res. and Rev., J. Chem., 1(1), 13**(2012).**

78. D. C.Crans, J. J. Smee, E. Gaidamauskas, L. Yang, Chem. Rev., 104, 849(**2004)**.

79. T. Kiss, T. Jakusch, B. Gyurcsik, A. Lakatos, É. A. Enyedy, É. Sija, Coord. Chem. Rev., 256, 125**(2012).**

80. T. Jakusch, J. Costa Pessoa, T. Kiss, Coord. Chem. Rev., 255, 2218**(2011)**.

81. S.D. Deosarkar, H.G. Jahagirdar, M.L. Narwade, Acta Ciencia Indica**,** 2**,** 277(**2009)**.

82. S.A. Lahsasni, R.A. Ammar, M.F. Amin and E.M. Shoukry, Int. J. Electrochem. Sci., 7, 7699 (**2012)**.

83. M.M. Mahrouka, A.T. Abdulkarim, A.A. El Sherif, M.M. Shoukry, Int. J. Electrochem. Sci., 10, 456**(2015)**.

84. A.A. El-Sherifa, M.M. Shoukry, R.M. El-Bahnasawyb, D.M. Ahmed, Cent. Eur. J. Chem. 8(4), 919 **(2010).**

85. R.L. Ware, S. Peerzade, S.D. Naikwade and M. Farooqui, J. Chem. and Pharma. Res., 5(8), 59**(2013)**.

86. A. Qasem, M. Farooqui, and S. Hussain J. Chem. and Pharm. Res., 7(3), 741**(2015)**.

87. A. A. Zaid, M. Farooqui and D. M. Janrao, J. Saudi Chem. Soc., 10, 1016**(2011)**.

88. D. D. Kayande, A. A. Zaid, V. Pradhan and M. Farooqui, Int. J. Sci. Nat., 3(2), 438**(2012)**.

89. S. Hussain, A. Rahim and M. Farooqui, J. Adv. Scientific Res., 3, 68 **(2012)**.

90. S. Hussain, A. Rahim and M. Farooqui, Chem. J., 2, 206 **(2012)**.

91. S.V. Thakur, M. Farooqui and S. D. Naikwade, Thermodyn. Aspect, Int. J. Res. Inorg. Chem., 1, 5**(2012)**.

92. S.V. Thakur, M. Farooqui and S.D. Naikwade, J. Chem. Pharma. Res., 4, 4412**(2012)**.

93. S.V. Thakur, R.L. Ware, M. Farooqui and S.D. Naikwade, Asian J. Res. Chem., 5, 1465**(2012)**.

94. S. Thakur, M. Farooqui and S. Naikwade, Int. J. Emerging Technol. Computational & Appl. Sci., 342 **(2013)**.

95. S. Hussain, M. Farooqui and S.A. Rahim, Int. J. Emerging Technol. Computational Appl. Sci., 276**(2013)**.

96. S.V. Thakur, M. Farooqui and S.D. Naikwade, Acta Chim. Pharma. Indica, 3, 35**(2013)**.

97. S. Husain, M. Farooqui, S.A. Rahim, Int. J. Emerging Tech. Comp. Appl. Sci., 276**(2013)**.

98. S.V. Thakur, M. Farooqui, S.D. Naikwade, Acta Chim. Pharma. Indica. 3(1)**,** 35**(2013)**.

99. Dr. S.R. Vaidya, Dr. M.R. Bagal, Dr. V.A. Shelke, Dr. S.M. Jadhav, Dr. T.K. Chondhekar Am. Int. J. Res. in Formal, Applied and Natural Sci. 15, 123**(2015)**.

100. D.A. Pund Bhagawatkar, D.T. Tayade, R.B. Rathod, J. Ind. Chem. Soc., 3(2**),** 246(**2010)**.

101. A. B. Kumar, S. Raju, B. K. Kumar Naik, B.B.V. Sailaja, G. N. Rao, Der Pharma Chemica, 3(5), 155(**2011)**.

102. A.B. Patil, Rasayan J. chem., 5(4), 490(**2012)**.

103. G.N. Mukherji, P.K. Chakraborty, J. Indian. Chem. Soc., 78, 565(**2001)**.

104. S. Sharifi, D. Nori-shargh and A. Bahadory J. Braz. Chem. Soc., 18(5), 1011**(2007)**.

105. P.M. Deore. B.C. Khade and B.R. Arbad, Int. J. Chem. Tech. Res. 4(1), 425**(2012)**.

106. A. More, K.V. Reddy, V. Ravindra and K. Kankanala, Int. J. Chem. Tech. Res., 6(7), 3509**(2014)**.

107. Md. B. Hossain, M.A. Yousuf, M. Rafiqul Islam, Md. A. Salam, M.A. Rahman and Md. A. Akbor, Bangladesh Pharma. J. 15(2), 177**(2012)**.

108. D.M. Janrao, J. Pathan, D.D. Kaynade and J.J. Mulla, Sci. Rev. Chem. Commun., 4(1), 11**(2014)**.

109. K. Kumar, D.K. Dwivedi, Int. J. Innovative Res. in Sci., Eng. and Tech., 3(7), 14711**(2014)**.

110. S. S. Patil, and M.M. Shaikh Acta Poloniae Pharmaceutica - Drug Res., 69(4), 679**(2012)**.

111. C. Comuzzi, P. Di Bernardo, P. Polese, R. Portanova, M. Tolazzi, P.L. Zanonato, Polyhedron 19, 2427**(2000)**.

112. K.L. Kendre, G. Pande1 and S.R. Pingalkar, Der Pharmacia Lettre, 6(4), 38**(2014)**.

113. M. Aljahdali, A.A. El-Sherif, J. Solution Chem. 41, 1759 **(2012).**

114. G. Anderegg, Helv. Chim. Acta., 45, 901**(1962)**.

115. I. G. Sayce, Talanta, 15, 1397 **(1968).**

116. I. G. Sayce, Talanta, 18, 653 **(1971).**

117. I. G. Sayce and V.S. Sharma, Talanta, 19, 831 **(1972) .**

118. A. Sabatini, A. Vacca and P. Gans, Talanta, 21, 53 **(1974).**

119. P. Gans, A. Sabatini and A. Vacca, Inorg. Chim. Acta, 18, 239 **(1976).**

120. R. J. Motekaitis and A. E. Martell, Can. J. Chem., 60,168**(1982).**

121. P. Gans, A. Sabatini and A.Vacca, J. Chem. Soc., Dalton Trans, 195**(1985).**

122. I. Nagypal, I. Paka and L. Zekany, Talanta, 25, 549**(1978).**

123. A. Sabatini, A. Vacca and P. Gans, Coord. Chem. Rev., 120, 389**(1992).**

124. L. Alderighi, P. Gans, A. Ienco, D. Peters, A. Sabatini and A. Vacca, Coord. Chem. Rev., 184, 311**(1999).**

125. P. Gans, 'Data Fitting in The Chemical Sciences', Wiley, Chichester **(1992).**

126. D.A. Skoog, D.M. West, F.J. Holler and S.R. Crouch, 'Fundamentals of Analytical Chemistry', Ed. 8, Thomson Publication, 194**(2005).**