SUMMARY
SUMMARY

Quinazolinones and their derivatives are well known for their biological activity. Besides biological activity these compounds have donor atoms, so they also act as good chelating agents. A survey of literature shows that these compounds have been synthesized and characterized based on spectral data. However little work has been done on chelating tendencies of these compounds with the metal ions in solution. Ternary complexes play vital role in the biological systems. The ternary metal complexes in solution using amino acids and aminopolycarboxylic acids were also little bit reported in the literature survey. Therefore in order to understand the chelating tendencies of these compounds, it was thought worthwhile to determine the formation constants of 3-hydroxy-2-chloromethyl quinazolin-4-one (cmhqo), 3-hydroxy-quinazolin-2,4(3H)-dione (hqdo), 2-(o-carboxy phenyl)-3-hydroxy-4(3H) quinazolinone (cphqo) and 2-carboxy ethyl-3-hydroxy-4(3H)-quinazolinone (cehqo) with Co(II), Ni(II), Cu(II) and Zn(II) ions. In view of the importance of ternary complexes in biological systems, further prompted us to determine the mixed ligand complexes of cmhqo, hqdo, cphqo and cehqo in presence of ligands such as Glycine (gly), Alanine (ala), Proline (pro), Nitrilotriacetic acid (NTA), Histidine (hist), Iminodiacetic acid (IMDA), Ethylenedimine (en) and Bipyridal (bipy) with Co(II), Ni(II), Cu(II) and Zn(II). The above mentioned factors prompted us to carry out a systematic study on binary and ternary complexes in solution.

CHAPTER - 1

This chapter is a brief introduction to the concept of metal chelates in solution, characteristics of complexes, their stoichiometry and stability. The various methods employed to study the thermodynamic stabilities of complexes in solution are
given along with the necessary details regarding the techniques used in the present work. The important applications of cyclic hydroxamic acid and their derivatives in biological, analytical, industrial and other chemical fields are outlined to show the significance of these ligands. The scope and aim of the present work is also presented.

CHAPTER - 2

This chapter deals with the survey of literature of cyclic hydroxamic acids and their derivatives including their biological activities and coordination tendencies towards various metal ions.

CHAPTER - 3

This chapter deals with the experimental details which includes the apparatus, instruments, reagents and preparation of solutions. It also deals with the synthesis of ligands (cmqho, hqdo, ephqo, eehqo), purification and standardization of different chemicals used in the present study. The titration methods are described in this section. This part also deals with the methods for the determination of stability constants of the binary and ternary complexes. The experimental data along with the graphs and figures are also presented.

CHAPTER - 4

This chapter deals with the determination of dissociation constants of the ligands cmqho, hqdo, ephqo, eehqo and formation of binary metal complexes, effect of ionic strength on proton ligand dissociation constants, stability constants of binary metal complexes and distribution of various species in solutions as a function of pH. Irving-Rossotti potentiometric technique is used to determine the constants. The results and discussions are presented under six heads of 4.1, 4.2, 4.3, 4.4, 4.5 and 4.6.
4.1. Structure of the ligands

This part deals with the structure of the ligands chosen for the present investigation.

4.2 Determination of acid dissociation constants of the ligands

The acid dissociation constants (pKa) values of the ligands cmhqo, hqdo, ephqo and cehqo chosen for the present investigation are listed in Tables. The acid dissociation constant values of the ligands [L] [where L = cmhqo, hqdo, ephqo and cehqo] show that all these ligands have one dissociable proton.

The basicity order of these ligands are cmhqo > hqdo> ephqo> cehqo may be explained in the light of electronic effects. It may be mentioned that the basicity values of these ligands are lower than 3-hydroxy quinazolin-4-one (hqo) i.e. unsubstituted cyclic hydroxamic acid. The lower basicities of these ligands when compared to hqo may be due to −I or −M effect of substituents present at the 2nd position of the cyclic hydroxamic acids. The lower value of cmhqo when compared to hqo is due to −I effect of chloromethyl group. The lower pKa value of hqdo when compared to cmhqo is due to −M effect of oxygen atom. Further, the lower pKa values of ephqo and cehqo are due to the strong −M effect of −C₄H₄COOH and −COOC₂H₅ groups. The acid dissociation constants of gly, ala, pro, hist, IMDA, NTA, en and bipy have been determined under similar experimental conditions. The pKa values are found to be in good agreement with the values reported in the literature under similar conditions.

4.3. Formation constants of Binary Metal Complexes

The formation constants of binary complexes have been determined at 30°C and I = 0.1M KNO₃ 10% (v/v) aqueous Ethanol medium. It has been observed that ligands cmhqo, hqdo, ephqo and cehqo form 1:1 and 1:2 complexes[M:L] with
bivalent transition metal ions. It has been observed that the metal-ligand stability order is found to be cemhqo>hqdo>ephqo>cehqo. This is in accordance with their relative basicities. The order of stability constants with respect to metal ions has been found to be Co(II)<Ni(II)<Cu(II)>Zn(II). This is in accordance with the Irving-Williams natural order of stability. The stability constants of binary metal complexes of other ligands viz. gly, ala, pro, hist, IMDA, NTA, en and bipy have been determined under present experimental conditions. Their stability constant values are in good agreement with literature values.

4.4. Effect of Ionic strength on proton-ligand and metal-ligand stability constants

The binary stability constants of cemhqo, hqdo, ephqo and cehqo have been determined at I = 0.1, 0.2 and 0.3 M KNO₃ at 30°C. The results showed a regular and slow decrease in the values of binary formation constants, with increase in ionic strength, which is also in agreement with the trend in variation of pKa values of these ligands. Since the ligands are O-O' donors, the observed trend is in accordance with the theoretical expectations.

4.5. Effect of Temperature and Thermodynamic factors associated with binary metal complexes

The binary formation constants of cemhqo, hqdo, ephqo and cehqo have also been determined at 20, 30 and 40°C at I = 0.1M KNO₃. A decrease in pKa and formation constant values are observed with increase in temperature. The negative free energy values indicate the spontaneity of the complex formation. The negative ΔH values indicate the metal ligand interactions are exothermic, reflecting the formation of stronger metal ligand covalent bonds. The positive entropy (ΔS) values indicate the release of water bound molecules from the metal ion on complexation. Thus the formation of binary complexes are thermodynamically favoured.
4.6. Distribution of Complexes species in solution.

The formation of various metal ligand species in solutions with the variation of pH has been calculated by using the computer program BEST. These diagrams gives an idea of the formation of different species in significant properties in solutions.

CHAPTER - 5

This chapter deals with the formation constants of ternary complexes, description of ternary formation curves. The relevant data is listed in Tables. The results and discussion and the conclusions drawn regarding the different aspects of formation and stability of complexes are dealt under four heads 5.1, 5.2, 5.3 and 5.4.

5.1. Determination of stability constants of ternary complexes

The interaction of two different ligands with metal ion can either occur in step-wise or in simultaneous fashion. When the affinities of the two ligands and the range of pH of their complexation are largely different, the ligands react in two distinct regions, such type of ternary systems are referred to as a stepwise process (equations- 5.1 to 5.4). (charges are omitted for the sake of clarity)

\[
\begin{align*}
M + A & \rightleftharpoons MA \quad \text{---} \quad 5.1 \\
MA + L & \rightleftharpoons MAL \quad \text{---} \quad 5.2 \\
M + L & \rightleftharpoons ML \quad \text{---} \quad 5.3 \\
ML + A & \rightleftharpoons MLA \quad \text{---} \quad 5.4
\end{align*}
\]

The ligands with comparable affinities co-ordinate with metal ions simultaneously as shown below (equation- 5.5)

\[
M + A + L \rightleftharpoons MAL \quad \text{---} \quad 5.5
\]
In the present investigation, formation of ternary metal complexes of cmhqo, hqdo, cphqo and cehqo in presence of gly, als, pro, en, NTA, hist, IMDA and bipy with Cu(II), Ni(II), Co(II), Zn(II) have been studied.

5.2. Description of ternary formation curves

5.2.1 Ternary complexes of bivalent metal ions [MAL]

In the case of ternary complexes [MAL] (Where M = Co(II), Ni(II), Cu(II) and Zn(II)); A = hist, bipy, IMDA and NTA; L = hqdo, cphqo and cehqo), the divergence of ternary titration curve from both [MA] and [ML], shows that the complex formation takes place by simultaneous equilibrium.

\[ M + A + L \rightleftharpoons [MAL] \]

(Where L = hqdo, cphqo and cehqo; A = hist, bipy, IMDA and NTA; M = Co(II), Ni(II), Cu(II) and Zn(II))

5.2.2 Ternary complexes of bivalent metal ions [MAL]

In the case of ternary complexes [MAL] (Where A = hist and IMDA; L = cmhqo; M = Co(II), Ni(II), Cu(II) and Zn(II)), the divergence of ternary titration curve from both [MA] and [ML], shows that the complex formation takes place by simultaneous equilibrium.

\[ M + A + L \rightleftharpoons [MAL] \]

(Where L = cmhqo; A = hist and IMDA; M = Co(II), Ni(II), Cu(II) and Zn(II))
5.2.3 Ternary complexes of bivalent metal ions [MAL]

In the case of ternary complexes [MAL] (where M = Co(II), Ni(II), Cu(II) and Zn(II), A = bipy and NTA; L = cmhfo), the ternary curve followed [MA] curve in the lower pH range and deviated from [MA] curve in the higher pH range. This indicates the ternary complex formation occurs in a step-wise equilibrium in which [A] is acting as primary ligand and [L] is acting as secondary ligand.

\[
M + A \rightleftharpoons [MA] \\
[MA] + L \rightleftharpoons [MAL]
\]

(Where A = bipy and NTA; L = cmhfo; M = Co(II), Ni(II), Cu(II) and Zn(II))

5.2.4 Ternary complexes of bivalent metal ions [MLA]

In the case of ternary complexes [MLA] (where M = Co(II), Ni(II), Cu(II), and Zn(II); L = cmhfo, hqdo, cphqo and cehqo; A = gly, ala, pro and en) the ternary curve followed [ML] curve in the lower pH range and deviated in the higher pH range (where L = cmhfo, hqdo, cphqo and cehqo) which indicate that ternary complex formation takes place in stepwise equilibrium in which [L] is acting as primary ligand and [A] is acting as secondary ligand. (charges are omitted for the sake of clarity.)

\[
M + L \rightleftharpoons [ML] \\
[ML] + A \rightleftharpoons [MLA]
\]

(Where A = gly, ala, pro and en; L = cmhfo, hqdo, cphqo and cehqo; M = Co(II), Ni(II), Cu(II) and Zn(II)).

247
The formation of ternary complexes is further supported by non-superimposable nature of experimental curve with theoretically calculated curve and also shift in the pH of hydrolysis/precipitate formation.

The distribution of the total metal among the various metal ligand species as a function of pH has been discussed. The typical species distribution curves also supported the ternary complex formation.

5.3 Factors that influence the formation of ternary complexes

The factors which are responsible for the formation of ternary complexes have been discussed under different headings.

5.3.1 Statistical Aspects

The extent of ternary complex formation and their relative stabilities over those of binary systems have been measured in terms of statistical parameters such as $\Delta \log K$ which is the difference between the formation constants of a ternary complex and its corresponding binary complexes. The negative $\Delta \log K$ values obtained in the present investigations indicate that the formation of ternary complexes are less favored over those of binary complexes.

5.3.2 Ligand Basicity

The order of stability constants of ternary complexes with respect to ligands $A$ are $\text{IMDA} > \text{NTA}$, while with respect to ligands $[L]$ are $\text{hqdo} > \text{cphqo} > \text{cehqo}$. These trends are almost in conformity with the general basicity sequence of the ligands hqdo, cphqo and cehqo. These complexes are formed by the simultaneous equilibria. When the complexes [MAL] are formed by stepwise equilibria (where $M = \text{Co(II)}, \text{Ni(II)}, \text{Cu(II)}$ and $\text{Zn(II)}$; $A = \text{gly, als, pro and en}; L = \text{cmhqo, hqdo, cphqo, cehqo}$). The order of stabilities with respect to $[L]$ are $\text{cmhqo} > \text{hqdo} > \text{cphqo} > \text{cehqo}$, while
with respect to [A] are pro > gly > ala > en. The order of stabilities were explained. Since the basicities of all the ligands are not of the same order, a mere comparison of the stabilities with those basicities may not throw any light on the factors like stereochemical, electrostatic and $\Pi$ interaction. The stabilities of ternary complexes were explained in terms of a more useful parameter known as stability per unit base strength (SUBS). In the present investigation, the SUBS values of ternary complexes are less than those of corresponding binary complexes revealing that the ternary complexes are less favoured over those of binary complexes. A stereo chemical distortion in ternary complexes may be responsible for their de stabilization over those of binary chelates.

5.3.3 Ligand-Ligand interactions

The formation constants and $\Delta \log K$ values of [M-hist-L] ternary complexes (where $L = \text{cmhquo, hqdo, cphquo and cehquo}$) reveal that the ternary complex formation is less favoured over their binary complexes. In all the systems studied, hist acts as neither primary nor secondary ligand and coordinated simultaneously along with ligand [L] (where $L = \text{cmhquo, hqdo, cphquo and cehquo}$). Positive $\Delta \log K$ values are expected in complexes of [MAL] (where $A = \text{hist}$ and $L = \text{cmhquo, hqdo, cphquo, cehquo}$) which can be attributed to the $\pi-\pi$ interactions between aromatic ring of hist and $L = \text{cmhquo/hqdo/cphquo/cehquo}$ of the ternary systems.

However, the negative $\Delta \log K$ values for [M-hist- cmhquo/hqdo/cphquo/cehquo] indicates that $\pi-\pi$ interactions/stacking interactions between ligands are absent. Hence the ternary complexes of cmhquo/hqdo/cphquo/cehquo in presence of hist with bivalent metal ions are less favoured over their binary complexes.
5.3.4 Stereo chemical factors

The perusal of $\Delta \log K$ values for [MAL] complexes (where $L = hqdo$, ephqo and $A = bipy, hist$ and IMDA) $\Delta \log K$ values indicates that bipy complexes are less stable over hist which in turn less stable over IMDA complexes. The higher stability of IMDA over that of bipy and hist may be explained in the light of stereo chemical factors. The bulkier bipy and hist may destabilize the formation of ternary complexes.

gly forms more stable mixed ligand complexes when compared to ala complexes because of the absence of any alkly side chain, which may produce an unfavourable steric effect in ala. Hence more negative $\Delta \log K$ values are observed in ala systems.

5.3.5 Electrostatic interactions

It has been inferred from the formation constants and negative $\Delta \log K$ values, that the ternary complexes are not favoured over binary complexes. This is due to the charge neutralization effect, which is involved in the formation of the mixed chelates which is turn depend upon the denticity of the ligands.

In the case of IMDA the equilibrium

$$M(II) + \text{IMDA} \rightleftharpoons [M-\text{IMDA}]$$

$$[M-\text{IMDA}] + L^- \rightleftharpoons [M-\text{IMDA-L}]^-$$

(where $L = cmhqo$ and eehqo)

In the case of NTA the equilibrium

$$M(II) + \text{NTA} \rightleftharpoons [M-\text{NTA}]^-$$

$$[M-\text{NTA}]^- + [L]^+ \rightleftharpoons [M-\text{NTA-L}]^{2-}$$
Therefore, more electrostatic attraction is expected between \([L]\)^- and neutral [M-IMDA] which in turn more than between \([L]\)^- and uninegative [M-NTA]^-. Hence the order is IMDA > NTA

### 5.3.6 Nature of metal ions (Bivalent metal ions)

The formation constants of the ternary complexes with respect to metal ions are in the order: Co(II) < Ni(II) < Cu(II) > Zn(II). This is in conformity with the Irving-Williams natural order of stabilities. The order of stabilities found in the ternary systems are similar to that of binary complexes.

### 5.3.7 Effect of Ionic Strength

The formation constants were found to decrease with increase in ionic strengths in all the ternary systems studied. The observed trend is in accordance with the theoretical expectations. To find out whether the ligands are combining with the metal ions in dissociated form or undissociated form and also to know the mechanism of complexation equilibria, the formation constants obtained at different ionic strengths were plotted against \(\sqrt{\mu}\).

### 5.3.8 Effect of temperature

The formation constants are found to decrease with an increase in temperature. This suggests that the interaction of metal ions with the given ligands is exothermic in nature. It can be seen that the negative values of free energy change \((\Delta G)\) suggest that the mixed ligand formation reactions are spontaneous in nature. The negative values of enthalpy changes for all the [M-A-L] complexes indicate the liberation of heat during the formation of ternary chelates. The positive \(\Delta S\) values indicates that the formation of ternary complexes are also entropy favoured.

251
5.4 Conclusion

It can be concluded that

i). All the four cyclic hydroxamic acids contain one dissociable proton.

ii). These ligands are O-O' donors. i.e. these are coordinating with the metal through oxygen atoms.

iii). These are forming most stable binary and ternary complexes with bivalent metal ions.

iv). The ternary complexes are less stable than their corresponding binary complexes.

v). Thermodynamic studies have shown that the reactions are exothermic in nature and favoured by enthalpy as well as entropy.

vi). The results of the present study would go a long way in contributing biologically important ligands and metal complexes in the field of bio-inorganic chemistry.