CHAPTER II

BINARY COMPLEXES
Introduction

In recent years, in spite of extremely rapid development of co-ordination chemistry, the equilibrium studies of drugs with metal ions have not yet reached maturity. Metal complexes show their importance in various field of scientific interest like pollution control, medicine, industries, analytical chemistry, pharmacology, pathology, biochemistry, metallurgy, etc.

Co-ordination behaviour of metals has played an important role in the extreme fast development of inorganic chemistry. It will not be an exaggeration to say that metal complexes have vital role in modern scientific age to achieve advancement in any chosen field of science. The outstanding development in the field of co-ordination chemistry is due to Jannik Bjerrum for his work in 1941. In his work, he has elaborated the general method of calculation of stability constant of metal-amine complexes.

Martell et al have published two monographs entitled, “Critical Stability Constants” The first part of it includes the metal complexes of biological ligands. The latter monograph published in 1976 is an ample proof of the intensive research on the biologically active molecules as complex forming ligands. ‘Metal ions in biological systems’ by Sigel also cover various aspects of bioinorganic chemistry.

Literature survey reveals that some of the ligands containing oxygen, nitrogen and sulphur donors are used as the chelates of metals. Munshi et al have studied the stability constants and thermodynamic functions of iron (III) complexes of some organic ligands. Cefola et al have also shown that the
stability of the complexes of lanthanides and some transition elements decreases as the substituted group changes from –OH to –NH₂.

Metal chelates of large number of carboxylic, phenolic, naphthoic acids have been investigated in an aqueous and mixed solvent media during the last decade⁷–⁳⁰. Transition metal complexes with a variety of ligands have been studied recently by different workers³¹–⁴⁶.

It is now believed that different trace elements serve many critical roles in the living body at a molecular level. The role of inorganic constituents in biological systems has been understood to some extent but unfortunately the utilization of the knowledge already explored has not been done at a comparable rates to design drugs. It is realised that most of the drugs used clinically have been developed by performing the experiments with some trial and error methods. There are only few cases where the drug action can be rationalised in the light of thermodynamic and kinetic aspects. In the development of potential, antibacterial, antiviral agents, bioinorganic chemists can contribute appreciably along with traditional experts.

Many organic and natural products such as aspirin, anticancer drugs, antibiotics etc., which are being used clinically for long time, show that the drug action takes place through the complexation with the available bio-molecules. The action of the drugs to remove toxic metal ions from bodies (metal poisoning) is due to co-ordination behaviour. The effectiveness of any molecule as a drug depends on its co-ordination behaviour at the body temperature and extra cellular fluid pH conditions. The coordination behaviour of a drug can be examined in vitro and mechanism of drug can be explained
through the formation of binary and ternary complexes. Literature survey reveals that no systematic study of drugs has been carried out. In view of these considerations, it is worthwhile to use the pharmaceutically significant drugs as ligands for the study of metal complexes.

**Drugs**

In the present work drugs used are: 1) Enalpril Maleate, 2) Lignocaine HCl 3) Ephedrine HCl 4) Theophylline.

**Enalpril Maleate**

![Enalpril Maleate structure](image)

It is an antihypertensive drug and angiotensin converting enzyme inhibitor. It decreases the after load and preload in congestive heart failure and the exercise capacity of patient is enhanced and decreases the long term mortality in myocardial infarction. It decreases the risk of diabetic nephropathy (Kidney failure) and decreases the rise of BP and deterioration of renal function in scleroderma crises.

It contains not less than 98% and not more than 102% of $\text{C}_{20}\text{H}_{28}\text{N}_{2}\text{O}_{5}$, $\text{C}_{4}\text{H}_{4}\text{O}_{4}$ (Mol. Wt. 492.53). It is soluble in water and ethanol.
**Lignocaine Hydrochloride**

\[
\text{CH}_3 \quad \text{NH} \quad \text{CO} \quad \text{CH}_2 \quad \text{N} \quad \text{CH}_2 \quad \text{CH}_3 , \text{HCl} \quad \text{H}_2\text{O}
\]

It is a versatile local anaesthetic. It is also used for surface application, infiltration, nerve block, epidural, spinal, intravenous regional block anaesthesia. It is used in ventricular tachyarrhythmias especially, which follows acute myocardial infarction. It is given prophylactically to decrease the occurrence of ventricular fibrillation and also used in the treatment of digitalis toxicity.

It contains not less than 99% and not more than 101% of \(\text{C}_{14}\text{H}_{22}\text{N}_2\text{O}\cdot\text{HCl}\) (Mol.Wt. 288.82). It is a white crystalline powder with a slightly bitter taste. It has a melting point 74 – 79°C. It is soluble in water, ethanol and chloroform.

**Ephedrine Hydrochloride**

\[
\text{CH}_3
\]

\[
\text{HO} \quad \text{CH} \quad \text{CH} \quad \text{NHCH}_3 \quad \text{.HCl}
\]

Markedly increasing cardiac output and oxygen consumption of heart uses it in hypotensive states as it increases heart beat rate.
It is used as nasal decongestant and controls local bleeding from skin and mucous membrane. These are potent vasodilators and used in peripheral vascular diseases. It causes dilation of pupil and facilitates fundus examination of eye and decreases intraocular tension. It acts as bronchodilator and used in bronchial asthma and also used in allergic conditions like angioedema.

It occurs as white crystalline powder with a bitter taste. It has melting point of 217 - 220°C. It contains not less than 99% and not more than 101% of C_{10}H_{5}NO.HCl (Mol.Wt. 201.70). It is soluble in water and ethanol

**Theophylline**

![Theophylline molecule](image)

It is a bronchodilator. It is used in bronchial asthma and chronic obstructive pulmonary disease. It acts as central nervous system stimulant. It is used in apnoea in premature infants. It acts as smooth muscle relaxant and relieves biliary spasm.

It is a white crystalline monohydrate substance with melting point 270-274°C. It has a bitter taste. It is soluble in water, alcohol and chloroform.
EXPERIMENTAL DETAILS:

Water-

The distilled water obtained in a steel container was again distilled over alkaline permanganate in a glass quick-fit set up and was always used afresh. The conductivity and pH of this distilled water was found to be $1.60 \times 10^{-6}$ mhos and 6.8 respectively.

Solutions

The nitrates of transition metals were of A.R. grade. The solutions of transition metals were prepared in perchloric acid to avoid the possibility of complex formation of metal ions with anions. The metal perchlorates were prepared by dissolving the corresponding metal nitrates in known volume of perchloric acid\textsuperscript{47}. The concentration of metal ions in solutions was estimated by standard procedures\textsuperscript{48-50}.

All other chemicals like perchloric acid, sodium perchlorate and sodium hydroxide were of analytical reagent grade, obtained either from B.D.H. (London) or E. Merck. Riedel (Germany). The solutions of above reagents were prepared in CO$_2$ free distilled water by taking precautions to avoid errors in their concentrations. Exact normalities were obtained by standard methods.

The transition metal salts of AR grade obtained from B.D.H. (India) and S.D. Fine Chemicals were used.

Standardization of glasswares

Borosil quality glassware’s were used in the experiments. The micro burette was calibrated by the method of Vogel\textsuperscript{51}. Micropipettes with
graduation of 0.02 ml were also calibrated and other glassware’s like measuring cylinders and standard flasks were calibrated by standard burette.

**Digital pH meter**

An Elico model LI-120 Digital pH – meter in conjunction with an Elico combined electrode consisting of glass and reference electrodes in the single entity of the type CK-61/CN-91/CM-51 were used for the pH measurement. The digital pH meter has a built in internal electronic voltage supply. The instrument had built in temperature compensator having the range 0 - 100°C with an accuracy of 0.2°C. The instrument could read pH in the range 0-14 with an accuracy of 0.01 pH units. The pH meter was standardised before each titration by potassium hydrogen phthalate buffer (N/20 with pH of 4.01 at 27°C) tablet.

**Maintenance of Combined Electrode**

A combined electrode consisting of glass and reference electrodes in a single entity was used for the pH measurements. The reference electrode contained 2N potassium chloride solution saturated with silver chloride crystals. After each titration the electrode was cleaned every time by rinsing it with a jet of distilled water. The strong adhering impurities was removed by careful wiping of the bulb and fibro junction with a tissue paper. In order to prevent electrode from developing an asymmetry potential, it was occasionally kept in N/10 HCl for 24 hours and then repeatedly washed with distilled water before reuse. When not in use, electrode was kept immersed in glass distilled water.
All the precautions necessary for smooth working of combined electrode were taken. These were in accordance to the suggestions of Bates\textsuperscript{52} and Albert and Serjeant\textsuperscript{53}.

**Calibration of pH Meter Scale**

It is essential to calibrate the scale of the instrument over the entire range, as the pH of the solution during the course of titration could vary continuously from 1.5 to 12.0. The instrument was switched on at least half an hour prior to use. When a steady standby is recorded, the combined electrode was dipped in the standard buffer solution (pH 4.01) and the reading on the pH meter was adjusted by the standardization knob to the pH of the buffer.

The same type of calibration was also done for pH 9.11 using standard buffer solution. The adjustment was repeated till steady pH values i.e. 4.01 and 9.11 at both the buffer solutions were obtained to secure the calibration in both acidic and alkaline range of pH.

The standard buffer solutions were prepared by dissolving buffer tablets in double distilled water and then making the volume to 100 ml. As the pH of the buffer solution varies with temperature, actual value of pH of the solution at the temperature of measurement was calculated from the following equation.

For buffer solutions of pH 4.01

\[
(1) \quad \text{pH}_{tc} = \text{pH}_{15^\circ} - 0.5 \frac{(t - 15)^2}{100}
\]

For buffer solutions of pH 9.11

\[
(2) \quad \text{pH}_{tc} = \text{pH}_{15^\circ C} - 0.0085 \ (t - 15)
\]
The calibration of the pH meter and standardization of the electrode was checked by titrating 0.025M HClO₄ against NaOH. The pH values measured and calculated from the analytical concentration of HClO₄ and activity coefficient agreed within ± 0.02 pH units.

The pH meter after warming up, was standardized every day prior to the measurements as well as after the completion of measurements for the series of titrations.

**Inert Atmosphere**

All the potentiometric titration’s were carried out in an inert atmosphere by bubbling oxygen free nitrogen gas through an assembly containing the electrodes in order to avoid atmospheric oxidation. The nitrogen gas supplied by Indian Oxygen and Acetylene Company Ltd. Bombay, contained a small amount of oxygen (0.5%) which was removed by passing the gas through alkaline pyrogallol (15 gms in 100 ml of 50% KOH solution). The purified nitrogen was presaturated with 0.1 N sodium perchlorate solution before its passage through the test solution. Bubbling of gas also ensured proper stirring of the solution during the titration.

**Precision and accuracy of the experimental results**

The reproducibility and reliability of any experimental results could be judged from the error limits in the working of the instrument and the mathematical calculation involved in the determination of the final values. Extra precautions were taken throughout this investigation to get the precision and accurate experimental results. The usual sources of errors were, as far as possible, eliminated. The most common of these is the presence of impurities in
the chemicals and solvents used were minimised by using mostly AR grade
pure chemicals and properly purified and freshly distilled solvents.

Another source of error was the pH assembly, where combined glass
electrode was used. The suitability of the instrument was checked as follows:

It was left switched on for one hour and adjusted on a potassium
hydrogen phthalate buffer (pH 4.01). One hour later, it was again checked for
the same buffer. The instrument did not show the change of ± 0.05-pH unit.
The glass electrode used was supplied by Elico Company, Hyderabad. It was
not susceptible to attack by acid. According to the manufacturers, the working
life of the electrode was about three months and whether it is fit for use was
determined by testing it for two buffers, potassium hydrogen phthalate (pH
4.01), the electrode was showing the pH as required for the other borax buffer
(pH 9.11) with a difference less than ± 0.05 pH unit. The glass electrode was
not used for determining pH values higher than 12.0 as it involves the
introduction of additional sources of error viz. (a) the nature of glass electrode
becomes more porous to sodium as the ratio $\text{Na}^+ / \text{H}^+$ increases and (b) the
standardization of the electrode is not possible at a pH higher than that of the
borax buffer.

The precision of the experimental data was checked by (a) determining
the pK value of benzoic acid (4.21) at 25° C, which was a good agreement with
the known literature value (4.21), and (b) performing the same experiment on
two different days with solutions of different concentrations. The observed $\bar{n_A}$
and $\bar{n}$ values for ligand agreed well within the limits of experimental error.
**Experimental procedure**

The Calvin-Bjerrum titration technique has been used in the present study. The experimental procedure involved potentiometric titrations of solutions of

1) Free HClO₄ (A) → (A)
2) Free HClO₄(A)+ ligand (L) → (A+ L)
3) Free HClO₄ (A)+ ligand (L)+ metal ion (M) → (A+L+M)

against standard NaOH solutions in water medium and 0.1 M (NaClO₄) ionic strength. The titration’s were carried out in 100 ml Borosil glass beaker in a water bath maintained at a constant temperature, 27°C. The solutions to be titrated were allowed to attain the bath temperature before commencement of the titrations. Nitrogen gas was continuously bubbled through the solutions to remove the dissolved oxygen and carbon dioxide. Each pH meter reading was recorded after gas bubbling and magnetic stirring were stopped. At the point of inflection in the pH, the rate of gas bubbling was increased so as to get quickly steady readings. Normally each titration requires about 50 minutes for completion.

**Experimental Results**

The data obtained in pH metric titration performed in water medium at 27°C is presented in Table 2.1. The titration curves obtained by plotting the pH against volume of alkali added is shown in Fig. 2.1.

1) Free HClO₄ (A) → (A)
2) Free HClO₄(A)+ ligand (L) → (A+ L)
3) Free HClO₄ (A)+ ligand (L)+ metal ion (M) \( \rightarrow \) (A+L+M)

The curves representing the plots of pH against the volume of standard NaOH solution required are shown in Fig 2.1, 2.2, 2.3 and 2.4.

**Calculations of proton ligand stability constants of drugs.**

The phenolic –OH group and azomethine nitrogen are the bonding sites in the drugs. In the initial stages of titration the ligand curve shows higher pH than the acid curve and intersect the acid curve at about pH 5.01. This indicates the protonation of azomethine nitrogen in the ligands, and then the ligand curve again deviates from acid curve to right side. This deviation represents the deprotonation of phenolic –OH group.

The values of \( \bar{n}_A \) are obtained by equation (I) given in chapter-I. To calculate \( \bar{n}_A \), \( V_1 \) and \( V_2 \) (corresponds to the volume of NaOH required to obtain the same pH of acid and acid + ligand curve) required can be read directly from the curve. All these values for a representative system are given in Table 2.2.

Due to the presence of nitrogen in the ligand, protonation takes place in the initial stages of titration and therefore the proton association constant (pK₁) and proton dissociation constant (pK₂) were determined at \( \bar{n}_A = 1.5 \) and \( \bar{n}_A = 0.5 \) respectively. The values of \( \bar{n}_A \) obtained in the range of 0.2 to 2.0 indicates the presence of two pK values for drug L₁. Whereas drugs L₂ L₃ and L₄ have only one pK due to phenolic –OH. The pK values were calculated by following methods.
1) Point wise Calculation Method

The $\bar{n}_A$ values in the region 1.2 to 1.8 and 0.2 to 0.8 were used to obtain $pK_1$ and $pK_2$ by using equation (I) in Chapter II. The average of these values were taken as the correct values of $pK_1$ and $pK_2$. Straight-line plots of further corroborated these values

$$\log \frac{\bar{n}_A - 1}{2 - \bar{n}_A} \quad \text{and} \quad \log \frac{\bar{n}_A}{1 - \bar{n}_A}$$

versus pH respectively. The representative calculations are given in Table 2.3(A) and Table 2.3(B). This method was used to obtain correct pK values and presented in Table 2.4 for all the drugs.
Table 2.1

**Potentiometric titration of Cu- Enalpril Maleate (L₁) system**

Medium - water

εₒ = 0.011404, TₒL = 0.002, TₒM = 0.0004, N = 0.3141

Vo = 50.00 ml, µ = 0.1 M NaClO₄, Temp. = 27± 0.1°C.

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<th>Titration of free acid A</th>
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<th>Titration of free acid + ligand + metal (A+L+M)</th>
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### Table 2.2

Proton ligand stability constant of Enalpril Maleate (L₁)

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2) Half Integral Method

The graph plotted between $n_A$ against pH is known as formation curve. Approximate values of proton-ligand stability constant can be determined by this method. The values of pH at which $n_A = 1.5$ and $n_A = 0.5$ corresponds to pK$_1$ and pK$_2$ of the ligand respectively.

The values of pK$_1$ and pK$_2$ obtained by half-integral method and point wise calculation method are found to be in good agreement.

The formation curves representative systems are shown in (Fig. 2.5).

Calculation of Metal Ligand Stability Constants

The following conditions should hold for the system for conversion of any Calvin-Bjerrum titration data into stability constant.

1) Formation of complex, under the experimental conditions:

2) Absence of metal ion hydrolysis, polynuclear hydrogen and hydroxyl bearing complexes and anion complexes of metal ions and

3) The absence of complexes of very high and very low stability.

The deviation along the volume axis of metal + ligand titration curve from the ligand titration curve is an indication for chelation in solution. The metal solution used in present investigation is of 2.0 x 10$^{-3}$ M. Therefore, the possibility of formation of polynuclear complexes is not expected. All the metals are used in perchlorate form.

Calculation of $\overline{n}$ and pL

The value of metal ligand formation number $\overline{n}$ was obtained by using equation (IV) in chapter I. To calculate $\overline{n}$, the volume of NaOH required to
obtain the same pH i.e. \( V_2 \) and \( V_3 \) can be directly read from the ligand titration curve and ligand + metal ion titration curve respectively. The calculations of \( \bar{n} \) were done in the pH range where there is no possibility of hydrolysis of metal ions. The values of \( V_2, V_3, \bar{n} \) and pL for a representative system are represented in Table 2.5 and 2.7. The values of pL were calculated using equation (V) and (VI) given in Chapter I. The following methods were used for calculation of metal – ligand stability constants.

1) Point wise calculation method

The metal ligand stability constants \( \log K_1 \) and \( \log K_2 \) were calculated by using this method.

For 1:1 complexation, linear equation (VII) given in chapter-I, was solved for different values of \( \bar{n} \) and pL. The average of these values were taken as the correct value of \( \log K_1 \). The values of \( \bar{n} \) selected were in the range 0.2 to 0.8.

Point–wise calculations for \( \log K_1 \) values are shown in Table 2.6 for a representative system.

The formation constants in the case of 1:2 complexes were calculated using the linear equation (VIII) given in chapter-I, for different values of \( \bar{n} \) and pL. The average of these values were taken as the correct value of \( \log K_2 \). The values of \( \bar{n} \) were selected in the range 1.2 to 1.8.

The calculated values are listed in Table 2.8 for a representative system.
2) Half integral method

To get the formation curves, the values of $\bar{n}$ have been plotted against $pL$. The formation curves for each metal ligand system were drawn separately. The number of complexes formed in the reaction and the values of stability constants can be deduced from the formation curve. From the formation curve the values of $\log K_1$ and $\log K_2$ were calculated by known values of $pL$ at $\bar{n} = 0.5$ and $\bar{n} = 1.5$ respectively. The formation curves of the representative systems are shown in (Fig. 2.6).

(3) Method of Least squares

The metal ligand systems having a ratio of $\log(K_1/K_2)$ less than 1.78 were subjected to the method of least squares to achieve greater accuracy.

The method of least squares was carried out to determine $\log K_1$ and $\log K_2$ values. The equation for it can be written as

$$\frac{\bar{n}}{(\bar{n} - 1)L} = \frac{(2 - \bar{n})}{(\bar{n} - 1)} K_1 K_2 - K_1$$

which is an equation of the best straight line. It is convenient to plot $\bar{n} / (\bar{n} - 1)L$ against $(2 - \bar{n}) / (\bar{n} - 1)$ to obtain the slope $K_1 K_2$ and the intercept $-K_1$ of the straight line. The $\bar{n}$ values between 0.8 to 1.2 were however, not taken for calculation as in this range the values $\bar{n} / (\bar{n} - 1)$ and $(2 - \bar{n}) / (\bar{n} - 1)$ becomes very large in the centre of curve and very sensitive to even experimental errors in $\bar{n}$ points in this small region.

In the present investigation all values of $\log K_1$, $\log K_2$ were calculated by all the methods.
### Table 2.3(A)
**Point wise calculations for pK\(_1\) of Enalpril Maleate (L\(_1\))**

<table>
<thead>
<tr>
<th>pH</th>
<th>$\bar{n}_A$</th>
<th>$\bar{n}_A - 1$</th>
<th>$\log(\frac{\bar{n}_A - 1}{2 - \bar{n}_A})$</th>
<th>pK(_1)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2.60</td>
<td>1.6212</td>
<td>1.6399</td>
<td>0.2148</td>
<td>2.8148</td>
</tr>
<tr>
<td>2.70</td>
<td>1.5585</td>
<td>1.2650</td>
<td>0.1020</td>
<td>2.8020</td>
</tr>
<tr>
<td>2.80</td>
<td>1.4958</td>
<td>0.9833</td>
<td>-0.0073</td>
<td>2.7927</td>
</tr>
<tr>
<td>2.90</td>
<td>1.4952</td>
<td>0.9809</td>
<td>-0.0473</td>
<td>2.8527</td>
</tr>
<tr>
<td>3.00</td>
<td>1.4649</td>
<td>0.8688</td>
<td>-0.0610</td>
<td>2.9839</td>
</tr>
<tr>
<td>3.10</td>
<td>1.4175</td>
<td>0.7167</td>
<td>-0.1446</td>
<td>2.9554</td>
</tr>
<tr>
<td>3.20</td>
<td>1.4022</td>
<td>0.6728</td>
<td>-0.1721</td>
<td>3.0279</td>
</tr>
<tr>
<td>3.30</td>
<td>1.3869</td>
<td>0.6310</td>
<td>-0.1999</td>
<td>3.1000</td>
</tr>
<tr>
<td>3.40</td>
<td>1.3713</td>
<td>0.5905</td>
<td>-0.2287</td>
<td>3.1713</td>
</tr>
<tr>
<td>3.50</td>
<td>1.3557</td>
<td>0.5520</td>
<td>-0.2580</td>
<td>3.2420</td>
</tr>
<tr>
<td>3.60</td>
<td>1.3244</td>
<td>0.4801</td>
<td>-0.3186</td>
<td>3.2814</td>
</tr>
<tr>
<td>3.70</td>
<td>1.2930</td>
<td>0.4144</td>
<td>-0.3825</td>
<td>3.3175</td>
</tr>
</tbody>
</table>

**Mean pK\(_1\) = 3.02**

### Table 2.3(B)
**Point wise calculations for pK\(_2\) of Enalpril Maleate (L\(_1\))**

<table>
<thead>
<tr>
<th>pH</th>
<th>$\bar{n}_A$</th>
<th>$\bar{n}_A - 1$</th>
<th>$\log(\frac{\bar{n}_A}{1 - \bar{n}_A})$</th>
<th>pK(_2)</th>
</tr>
</thead>
<tbody>
<tr>
<td>5.20</td>
<td>0.7746</td>
<td>3.4365</td>
<td>0.5361</td>
<td>5.7361</td>
</tr>
<tr>
<td>5.30</td>
<td>0.7118</td>
<td>2.4698</td>
<td>0.3926</td>
<td>5.6926</td>
</tr>
<tr>
<td>5.40</td>
<td>0.6175</td>
<td>1.6143</td>
<td>0.2079</td>
<td>5.6079</td>
</tr>
<tr>
<td>5.50</td>
<td>0.4918</td>
<td>0.9800</td>
<td>-0.0087</td>
<td>5.4913</td>
</tr>
<tr>
<td>5.60</td>
<td>0.3976</td>
<td>0.6600</td>
<td>-0.1804</td>
<td>5.4196</td>
</tr>
<tr>
<td>5.70</td>
<td>0.3033</td>
<td>0.4353</td>
<td>-0.3612</td>
<td>5.3388</td>
</tr>
<tr>
<td>5.80</td>
<td>0.2176</td>
<td>0.1332</td>
<td>-0.8754</td>
<td>4.9246</td>
</tr>
</tbody>
</table>

**Mean pK\(_2\) = 5.44**
Table 2.4
Formation constants of drugs

Medium - water, Temp. : 27 ± 0.1°C and
μ = 0.1 M NaClO₄

<table>
<thead>
<tr>
<th>Sr. No.</th>
<th>Ligands</th>
<th>pK₁</th>
<th>pK₂</th>
</tr>
</thead>
<tbody>
<tr>
<td>(1)</td>
<td>(S) – 1 – [N-[1-(Ethoxycarbonyl)-3 – phenylpropyl]-L-alanyl]-L-proline. (Enalpril maleate)</td>
<td>3.02 (3.00)a</td>
<td>5.44 (5.40)a</td>
</tr>
<tr>
<td>(2)</td>
<td>2,diethyl amino-2’,6’-acetoxylidide hydrochloride. (Lignocaine HCl)</td>
<td>-</td>
<td>8.21</td>
</tr>
<tr>
<td>(3)</td>
<td>α-[1-(methylamino) ethyl]- benzene-methanol hydrochloride. (Ephedrine HCl)</td>
<td>-</td>
<td>9.22 (9.22)a</td>
</tr>
<tr>
<td>(4)</td>
<td>3,7-Dihydro-1,3-dimethyl-1H-purine-2,6-dione. (Theophylline)</td>
<td>-</td>
<td>8.79 (8.79)a</td>
</tr>
</tbody>
</table>

a- ref. 88
Table 2.5
Determination of $\bar{n}$ and pL values for Cu(II) and Enalpril maleate ($L_1$)

Medium - water

$e^0 = 0.011404$, $T^0_L = 0.002$, $T^0_M = 0.0004$, $N = 0.3141$

$V_0 = 50.00$ ml, $\mu = 0.1$ M NaClO$_4$, Temp. $= 27 \pm 0.1 ^\circ $C.

<table>
<thead>
<tr>
<th>pH</th>
<th>$V_2$ ml</th>
<th>$V_3$ ml</th>
<th>$(V_3 - V_2)$ ml</th>
<th>$\bar{n}$</th>
<th>pL</th>
</tr>
</thead>
<tbody>
<tr>
<td>4.40</td>
<td>2.09</td>
<td>2.11</td>
<td>0.02</td>
<td>0.2869</td>
<td>2.7999</td>
</tr>
<tr>
<td>4.50</td>
<td>2.10</td>
<td>2.12</td>
<td>0.02</td>
<td>0.2955</td>
<td>2.8082</td>
</tr>
<tr>
<td>4.60</td>
<td>2.10</td>
<td>2.14</td>
<td>0.03</td>
<td>0.5247</td>
<td>2.8293</td>
</tr>
<tr>
<td>4.70</td>
<td>2.11</td>
<td>2.145</td>
<td>0.35</td>
<td>0.6088</td>
<td>2.8436</td>
</tr>
<tr>
<td>4.80</td>
<td>2.12</td>
<td>2.16</td>
<td>0.04</td>
<td>0.6279</td>
<td>2.8756</td>
</tr>
<tr>
<td>4.90</td>
<td>2.13</td>
<td>2.175</td>
<td>0.045</td>
<td>0.6766</td>
<td>2.9496</td>
</tr>
<tr>
<td>5.00</td>
<td>2.15</td>
<td>2.20</td>
<td>0.05</td>
<td>0.6932</td>
<td>2.9824</td>
</tr>
<tr>
<td>5.10</td>
<td>2.165</td>
<td>2.22</td>
<td>0.55</td>
<td>0.7182</td>
<td>3.3353</td>
</tr>
<tr>
<td>5.15</td>
<td>2.17</td>
<td>2.23</td>
<td>0.06</td>
<td>0.7996</td>
<td>3.4347</td>
</tr>
</tbody>
</table>

Table 2.6
Determination of metal ligand stability constant for Cu (II) and Enalpril Maleate ($L_1$) system by point wise calculation method

Medium - water, Temp. $= 27 \pm 0.1 ^\circ $C

<table>
<thead>
<tr>
<th>PL</th>
<th>$\bar{n}$</th>
<th>$\frac{\bar{n}}{1 - \bar{n}}$</th>
<th>log $\frac{\bar{n}}{1 - \bar{n}}$</th>
<th>log $K_1$</th>
</tr>
</thead>
<tbody>
<tr>
<td>2.7999</td>
<td>0.2869</td>
<td>0.4023</td>
<td>-0.3954</td>
<td>2.4045</td>
</tr>
<tr>
<td>2.8082</td>
<td>0.2955</td>
<td>0.4192</td>
<td>-0.3775</td>
<td>2.4307</td>
</tr>
<tr>
<td>2.8293</td>
<td>0.5247</td>
<td>1.1039</td>
<td>0.0429</td>
<td>2.8722</td>
</tr>
<tr>
<td>2.8436</td>
<td>0.6088</td>
<td>1.5562</td>
<td>0.1920</td>
<td>3.0356</td>
</tr>
<tr>
<td>2.8756</td>
<td>0.6279</td>
<td>1.6874</td>
<td>0.2272</td>
<td>3.1028</td>
</tr>
<tr>
<td>2.9496</td>
<td>0.6766</td>
<td>2.0921</td>
<td>0.3204</td>
<td>3.2701</td>
</tr>
<tr>
<td>2.9824</td>
<td>0.6932</td>
<td>2.2594</td>
<td>0.3539</td>
<td>3.3063</td>
</tr>
<tr>
<td>3.3353</td>
<td>0.7182</td>
<td>2.5486</td>
<td>0.4063</td>
<td>3.6963</td>
</tr>
<tr>
<td>3.4347</td>
<td>0.7996</td>
<td>3.5766</td>
<td>0.5553</td>
<td>3.9900</td>
</tr>
</tbody>
</table>

Mean log$K_1 = 3.12$
Table 2.7

**Determination of $\bar{n}$ and pL values for Cu(II) and Enalpril maleate (L$_1$)**

Medium - water

$\varepsilon^0 = 0.011404$, $T^0_L = 0.002$, $T^0_M = 0.0004$, $N = 0.3141$

$V_0 = 50.00$ ml, $\mu = 0.1$ M NaClO$_4$, Temp. = 27±0.1°C.

<table>
<thead>
<tr>
<th>pH</th>
<th>$V_2$ ml</th>
<th>$V_3$ ml</th>
<th>$(V_3 - V_2)$ ml</th>
<th>$\bar{n}$</th>
<th>pL</th>
</tr>
</thead>
<tbody>
<tr>
<td>5.20</td>
<td>2.18</td>
<td>2.24</td>
<td>0.06</td>
<td>1.1608</td>
<td>2.8327</td>
</tr>
<tr>
<td>5.25</td>
<td>2.19</td>
<td>2.26</td>
<td>0.07</td>
<td>1.4089</td>
<td>2.8619</td>
</tr>
<tr>
<td>5.30</td>
<td>2.20</td>
<td>2.28</td>
<td>0.08</td>
<td>1.5780</td>
<td>2.8959</td>
</tr>
<tr>
<td>5.35</td>
<td>2.21</td>
<td>2.30</td>
<td>0.09</td>
<td>1.6707</td>
<td>2.9361</td>
</tr>
</tbody>
</table>

Table 2.8

**Determination of metal ligand stability constant for Cu (II) and Enalpril Maleate (L$_1$) system by point wise calculation method**

Medium - water, Temp. = 27 ± 0.1°C

<table>
<thead>
<tr>
<th>$\bar{n}$</th>
<th>pL</th>
<th>$\bar{n} - 1$</th>
<th>$\bar{n} - 1$</th>
<th>log $\bar{n} - 1$</th>
<th>log $K_2$</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.1608</td>
<td>2.8327</td>
<td>0.1916</td>
<td>-0.7176</td>
<td>2.1151</td>
<td></td>
</tr>
<tr>
<td>1.4089</td>
<td>2.8619</td>
<td>0.6883</td>
<td>-0.1622</td>
<td>2.6997</td>
<td></td>
</tr>
<tr>
<td>1.5780</td>
<td>2.8959</td>
<td>1.3696</td>
<td>0.1366</td>
<td>3.0235</td>
<td></td>
</tr>
<tr>
<td>1.6707</td>
<td>2.9361</td>
<td>2.0386</td>
<td>0.3093</td>
<td>3.2454</td>
<td></td>
</tr>
</tbody>
</table>

Mean log$K_2$=2.76
Results and Discussion

The proton – ligand stability constants of drugs have been determined in water medium in presence of 0.1 M sodium perchlorate and presented in Table 2.4. The present ligands are of diverse in nature; hence it is rather difficult to correlate the pK values of one ligand with others. The metal ligand stability constants of various drugs with Co, Ni, Cu and Zn are presented in Table 2.9.

Effect of substituent on pK values

In Enalpril Maleate the two pK values observed are 3.02 and 5.45. These values can be assigned to the dissociation constant of –COOH and deprotonation constant of secondary amine present in the drug molecule. The pK value 3.02 is assigned to the dissociation of carboxylic group. The observed value is lower than any saturated aliphatic acid and higher than amino group present in the structure. The five membered ring of the drug molecule can also be compared with pyrrolidine molecule which has a pK value of 3.11. The observed value is slightly less because of the carbonyl group present near the amine group has the tendency of electron withdrawal by mesomeric effect which makes the carboxylic group more acidic. This effect is also observed for the second pK 5.44 which is the deprotonation constant of secondary amine.

In lignocaine hydrochloride the pK value observed is 8.1 which is the deprotonation of tertiary amine group (pK 9.80). The carbonyl group present near the tertiary amine has a tendency of electron withdrawal by inductive effect which makes the nitrogen of tertiary amine electro positive and hence lowers the pK value.
The pK value which is observed in ephedrine hydrochloride is 9.22 which is the dissociation constant of alcoholic ( -OH) group. The alcoholic group attached to the benzene ring can be compared with bezyl alcohol which has pK value of 9.95. The protonated secondary amine in the drug molecule withdraws the electron by inductive effect and thereby decrease in dessociation constant ..

In theophylline molecule only one pK is observed which is the deprotonation constant of secondary amine (pK 10.77). The 5 membered ring present in the molecule can be compared with the Imidazole molecule which has pK value of 7.09. The tertiary amine present in the ring has inductive and mesomeric effect due to the sp2 hybrid orbitals. Such effect is also enhanced because of the carbonyl group present near the secondary amine thus making it more positive which enhances the pK to 8.79.

In general the pK values determined fore the present drug molecules are in good agreement with the standard literature values except the drug Lignocaine hydrochloride. Therefore considering the co-relation of observed ph values with literature pK values for three drugs. The pK value of the drug must be precise and accurate.

Metal Ligand Stability Constants of Transition Metal Complexes

The calculated values of log $K_1$, log $K_2$ and log $\beta$ of drugs complexes, Co(II), Ni(II), Cu(II) and Zn(II) are presented in Table 2.9.

The influence of various factors on the stability of metal complexes is discussed below.
1) Effect of ligand basicity

The metal ions and hydrogen ions act as Lewis acids. The interaction of metal ion with a base is similar to the neutralization reaction involving hydrogen ion. It is assumed that the ionic and coulombic forces responsible for binding a proton should be the same as those responsible for binding the metal ion in a chelate, provided steric and resonance effect in the ligand remains unaltered. On this basis formal analogy between metal ligand and proton – base system has been developed by J. Bjerrum\textsuperscript{55}, who pointed out that the bases which have the strongest affinity for hydrogen ions form most stable complexes. In general, it may be expected that the more basic ligands form more stable complexes. It is reasonable, therefore, to expect that there should be a similarity in the factors influencing the bonding of hydrogen ion and metal ions to Lewis base. Bjerrum, in his study on silver complexes with various amines showed a relationship between $\log K_{\text{Ag}^+}$ and $\log K_{\text{H}^+}$ for the ligands. Similar linear relationship was shown by several workers \textsuperscript{55-66} between the $\log K$ of a series of metal complexes derived from one metal ion with a set of similar ligands and their pK values.

Calvin and Wilson’s\textsuperscript{67} measurements on the stability constants of the complexes of diketones and hydroxaldehydes with copper (II) show a similarity between the strength of the L- Cu\textsuperscript{2+} and L- H\textsuperscript{+} bonds. In all cases $\log K_1$ and $\log K_2$ were obtained for copper complexes and $K_1 > K_2$ as required by statistical effect. On plotting average value of $\log K_{\text{av}}$ against $\log K_{\text{H}^+}$ concluded that at least two factors influence the strength of the metal ligand bonds. The first includes the effects of charge and charge distribution in the ligand and the
charge and size of the cation. The second is attributed to the double bond character of the bond between metal and the ligand. The co-ordinate bond between metal containing d-electrons and an atom containing a vacant d-orbital of sufficiently low energy always has a certain amount of double bond character. This is due to the tendency of metal to share these electrons with the atoms, which donates an electron pair to it to form the co-ordinate bond.
Table 2.9
Formation constants of transition metal ions with drugs,
Medium -water.
Temp. : (27 ± 0.1°C). μ = 0.1 M NaClO₄

<table>
<thead>
<tr>
<th>Transition metal ions</th>
<th>L1</th>
<th>L2</th>
<th>L3</th>
<th>L4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Co(II) logK₁</td>
<td>3.12</td>
<td>2.75</td>
<td>2.79</td>
<td>2.73</td>
</tr>
<tr>
<td>logK₂</td>
<td>2.76</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>logβ</td>
<td>5.88</td>
<td>2.75</td>
<td>2.79</td>
<td>2.73</td>
</tr>
<tr>
<td>Ni(II) logK₁</td>
<td>2.87</td>
<td>2.79</td>
<td>3.01</td>
<td>2.80</td>
</tr>
<tr>
<td>logK₂</td>
<td>2.72</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>logβ</td>
<td>5.59</td>
<td>2.79</td>
<td>3.01</td>
<td>2.80</td>
</tr>
<tr>
<td>Cu(II) logK₁</td>
<td>3.47</td>
<td>2.86</td>
<td>2.86</td>
<td>2.86</td>
</tr>
<tr>
<td>logK₂</td>
<td>2.85</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>logβ</td>
<td>6.32</td>
<td>2.86</td>
<td>2.86</td>
<td>2.86</td>
</tr>
<tr>
<td>Zn(II) logK₁</td>
<td>2.99</td>
<td>2.72</td>
<td>2.83</td>
<td>2.90</td>
</tr>
<tr>
<td>logK₂</td>
<td>2.74</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>logβ</td>
<td>5.73</td>
<td>2.72</td>
<td>2.83</td>
<td>2.90</td>
</tr>
</tbody>
</table>
The general form of the equation \( \log K = aK + b \) was first proved by Bjerrum. Exceptions to this rule occur in cases where stereo chemical considerations show that the ligand molecules will not get well around the metal ions. There are evidences that the above relation does not hold in same series of ligands.

Calvin and Wilson\(^67\) found but did not comment on the fact that although there was a rough linear relation between \( pK \) and \( \log K \), many salicylaldehyde derivatives gave results deviating strongly from it. For 8-hydroxy-quinoline, use of only one acidic dissociation constant (\( pK_{\text{OH}} \)) did cause the linear relation\(^68\).

A rough linear relation was found between \( \log K \) and \( pK \) for certain types of substituents such as \(-\text{CH}_3\), \( \text{Cl} \) and \(-\text{NO}_2\) groups in salicylaldehyde\(^69\), number of workers stressed that the linear relation fails if the conjugated system of the ligand extended through carbon chain eg. phenyl substituent in acetyl acetone. It is supposed that a substituent such as nitro group interacts with a conjugated hydrocarbon in much the same way as an extension of the conjugation; there should thus be changes in both \( \sigma \) and \( \pi \) electron densities throughout the molecule. Such changes may alter stability of \( \text{HL} \) in manner different from that of \( \text{ML} \).

The validity of linear relation has been examined for the present complexes by plotting \( pK_1 \) vs. \( \log K_1 \). No linearity could be obtained except in some cases, which was expected in the light of above discussion. Ionisation potential of the metal ion and donor atoms have tendency to form \( \pi \)- bonds,
ligand field stabilization of ligand are some of the factors, which affect the linear relationship. The linear relationship depends considerably on the nature of ligands. The direct correlation of stabilities of metal complexes with ligand basicity is based on the assumption that the base strength is a measure of the \( \sigma \)– bonding ability of ligands with metal ions. Since the basicities of the present ligands are not of the same order, these correlations would not throw any light on the steric and \( \pi \)-interactions in the metal ligand system. This can be achieved by comparison of the ‘stability per unit base strength’ defined as the ratio of stability constants to the total basic strength of the ligand, i.e., \( \log \beta / \sum pK \) for various metal complexes. These ratios for the present complexes are presented in Table 2.10.

2) Effect of metal ions

It is known that the stabilities of the complexes of particular ligands vary with the position of the metal in the periodic table, of course, being a function of the electronic structure of the metal. Mellor and Maley reported the stability order of salicylaldehyde-metal complexes as

\[
Pd > Cu > Ni > Pb > Co > Zn > Cd > Mg.
\]

In every case \( K_1 > K_2 \) and no abnormal effects were found. The same workers later showed that a similar order is obtained for the complexes of pyridine and ethylene diamine.
Irving and Williams\textsuperscript{76} reported the relation between atomic number of the metal ions and their stability constants. They plotted $\log K_n$ against atomic number of the metal ions from Mn(II) to Zn(II) and showed that the stabilities increases with the increasing in atomic number upto the end of transition series and then decreases again at zinc. The order of stability was

Mn $<$ Fe $<$ Co $<$ Ni $<$ Cu $>$ Zn

unless special factors such as steric hindrance, which depends only on ionic size and the spatial arrangement of bonds are operative above order is found for all ligands. The explanation of this regularity must be that the metal ligand bond strength depends on the metal to a considerable extent, since it does not matter whether the metal atom is attached to oxygen, nitrogen or sulphur.

The reason for the increase of bond strength with rise of atomic number is not yet clear, but fall from copper to zinc can be explained. In cupric compounds d-orbitals are available for bond formation where as in zinc complexes no d-orbital of low energy are vacant.

Calvin and Melchior\textsuperscript{77} attempted to explain the phenomenon by comparing number of properties of the ions under discussion such as the ionic radius, heat of hydration, partial molar entropy and ionisation potentials. The only obvious correlation was between stability and the second ionisation potentials of the elements. The authors pointed out that except for zinc, this potential measures the energy required for removal of d-electron and they suggest that co-ordination replaces this electron, so that in each case (except Zn), the hybridisation should involve d-orbital.
Table 2.10
Stability constant per unit base strength for various metal ligand systems

\[(\log K_1 + \log K_2 = \log \beta / \Sigma pK)\]

Temp. : \((27 \pm 0.1^\circ C)\) \hspace{1cm} \mu = 0.1 \text{ M NaClO}_4

<table>
<thead>
<tr>
<th>Transition metal ions</th>
<th>L1</th>
<th>L2</th>
<th>L3</th>
<th>L4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Co(II)</td>
<td>0.70</td>
<td>0.33</td>
<td>0.30</td>
<td>0.31</td>
</tr>
<tr>
<td>Ni(II)</td>
<td>0.66</td>
<td>0.33</td>
<td>0.32</td>
<td>0.31</td>
</tr>
<tr>
<td>Cu(II)</td>
<td>0.75</td>
<td>0.34</td>
<td>0.31</td>
<td>0.32</td>
</tr>
<tr>
<td>Zn(II)</td>
<td>0.68</td>
<td>0.33</td>
<td>0.30</td>
<td>0.32</td>
</tr>
</tbody>
</table>
Sahadev et al\textsuperscript{78} reported the order of metal complexes of 2-hydroxy-1-naphthaldehyde monosemicarbazone as

\[ \text{Cu} > \text{Ni} > \text{Co} > \text{Zn} > \text{Pb} > \text{Cd} > \text{Mn} > \text{Mg} \]

which was in good agreement with Mellor and Maley.

Karala and coworkers\textsuperscript{79} studied the 2-amino-3-hydroxy pyridine complexes

\[ \text{Cu(II)} > \text{Zn(II)} > \text{Ni(II)} > \text{Co(II)} > \text{Cd(II)} \]

The order of stability constants of the complexes of some bivalent metals with some Schiffs bases was reported by Maya deo et al \textsuperscript{80} as

\[ \text{Co(II)} < \text{Ni(II)} < \text{Cu(II)} > \text{Zn(II)} \]

The order of stability Cu>Ni>Co>Zn was reported for the transition metal complexes with 2-hydroxy-1-naphthaldehyde thiosemicarbazone in dioxane water medium\textsuperscript{81}.

In order to test the validity of above observations the log K values obtained in the present investigation for Cu(II), Ni(II), Co(II) and Zn(II) complexes show the following order of stability.

\[ \text{L1 : Co} > \text{Zn} > \text{Cu} > \text{Ni} \]
\[ \text{L2 : Cu} > \text{Ni} > \text{Co} > \text{Zn} \]
\[ \text{L3 : Ni} > \text{Cu} > \text{Zn} > \text{Co} \]
\[ \text{L4 : Zn} > \text{Cu} > \text{Ni} > \text{Co} \]

The above order of stabilities of the metal complexes with all the ligands are similar to the observations made by number of workers\textsuperscript{79, 82-84} and are in good agreement with Irving Williams order.
3) The Ligand Effect

The ligand effect is further divided into electrostatic effect and the rest effect. The electrostatic effect represents the effect of any ionic charge on the ligand. This shows the effect of co-ordination of a charged ion on the already charged species of the complex. Magnitude of the electrostatic effect is related to the work done to bring an electrically charged ligand L to a complex MLn to give MLn+1. This can be determined by taking into account the electronic charge, dielectric constant of the medium and distance between the charges.

The rest effect shows that the ligand molecule affects the ability of further ligand molecules to attach themselves to the lower complex already formed.

In the case of bidentate ligands it is supposed that the molecule first attaches itself to one co-ordination position and that the second co-ordinating group then occupies the second position. The log $K_1$ values of the metal complexes are, therefore, found to be greater than log $K_2$. Generally $k_1$ for a bidentate ligand is comparable with ($K_1 \times K_2$) for a monodentate ligand. In ethylenediamine – Cu(II), and ammonia – Cu(II) complexes the ethylenediamine molecules bound more firmly than ammonia to copper. At equilibrium, in the dissociation process of the complex, the neutral monodentate ammonia molecule is free to migrate once it is split off, whereas if one group of the bidentate ligand is freed the other group holds it in the vicinity of that metal ion so that it is readily reattached than in the monodentate ligand molecule. Hence the bidentate ligand having two reactive groups is statistically more liable to co-ordinate than a monodentate ligand.
The ligand or chelate effect has been analysed by Schwarzenbach\textsuperscript{85} and Adamson\textsuperscript{86} model which seems to be simpler since it does not require ligand geometry or the length of the bridge between two or more donor atoms. This approach may be represented by the equation.

\[
\log K_1(\text{bidentate}) = \log K_1(\text{unidentate}) + \log 55.5
\]

The log 55.5 represents the entropy of translation of one mole of solute generated at one molar concentration. The utility of this equation has been shown for several metal chelates\textsuperscript{87}.

This relationship has been tested for all the present metal complexes by plotting \(\log K_1\) vs. \(\log K_{(\text{OH})}\), where \(\log K_{(\text{OH})}\) is the stability constant of the metal hydroxide. All the plots show a linear relationship with the intercept approximately equal to 1.80, which is close to \(\log 55.5\) (i.e. 1.74). This shows that the chelate effect given by Adamson is valid for chelates formed by all the ligands.

The involvement of \(H^+\) ion from OH and not from nitrogen for the formation of 1:1 chelate has been proved earlier potentiometrically. This was also tested by plotting \(\log K_1\) of the metal complex vs. \(\log K_{(\text{ammonia})}\). A linear relationship was found with higher values of intercept. However, this proves non-involvement of the hydrogen ions from >NH group.
References