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# SYNTHESIS, CHARACTERIZATION AND STABILITY CONSTANT STUDY OF TRANSITION METAL COMPLEXES OF CHLOROQUINE PHOSPHATE

**[1]Ayesha Meraj**
Dr. Rafiq Zakaria College for Women, Aurangabad, Maharashtra, India.

**[2]Dr. D. M. Janrao**
Dr. Rafiq Zakaria College for Women, Aurangabad, Maharashtra, India.

## Abstract
This chapter discusses the chloroquine phosphate. The chemical name of chloroquine phosphate in chemical abstracts is found under the heading Quinoline and designated as 7-Chloro- [4-(4-diethylamino-1-methylbutylamino)] quinoline diphosphate. Chloroquine phosphate is a white, odorless, crystalline powder having a bitter taste: it discolors gradually on exposure to light. pH-metric studies of complexes of Co(II), Cu(II), Ni(II) & Zn(II) with Cloroquine phosphate were carried out in aqueous solution and in solid state. Change in potential value suggesting the formation of complex. To calculate the stability constant for binary complexes, Irvin-Rosotti method were used. IR spectra, elemental analysis and Melting point of the complexes indicates the formation of complexes in solid state.
Keywords : Chloroquine phosphate, complex, pH-metric study, Cobalt, Copper, Nickel, Zinc, etc.

## Introduction
A study shows that, organometallic compounds have been utilised in medicine. In both agriculture and the pharmaceutical business, metal complexes are crucial. In biological systems, the intracephalic metallo-elements are essential for molecular functions. Several enzymes depend on transition metal ions to function properly[1]. A large range of peptide-based medications, which are now only administered intravenously due to poor absorption and digestive breakdown, may now be delivered orally due to "Inorganic Pharmaceuticals". When given in combination or combination with copper, several anti-inflammatory and anti-tumor medications are more effective than when taken alone. While the exact chemical mechanism via which chloroquine affects the malarial parasite is still unknown, it has been observed that the medication selectively interacts with the parasite's glycolytic enzyme, lactate dehydrogenase[2-5]. Finding and developing more effective medications to combat diseases is one of the primary objectives of modern inorganic coordination chemists and pharmaceutical research, which has given rise to a plethora of studies on drug-metal complexes [6]. A number of studies have been conducted on the complexation of some commonly used antimalarial medications with metals.

Metallopharmacology is the general term for the application of metals to restore the body's normal, healthy physiology. These methods include direct metal administration, chelating out excess or toxic metals, using them as carriers for targeted drug delivery, and tagging biomolecules for diagnostic purposes[7-13].

However, Rosenberg and Loretta Van Camp's coincidental discovery of cisplatin's anticancer capabilities in 1965 provided the most significant impetus for the study of metal-based medications with therapeutic qualities[14]. Metal complexes are a very adaptable and dependable tool for the creation of

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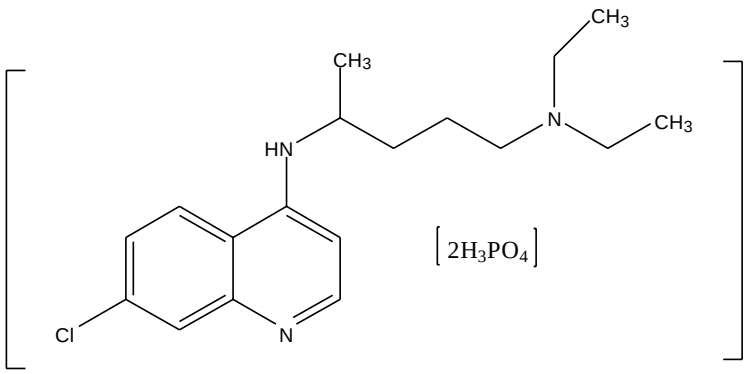
better therapeutic molecules. It is in fact feasible to precisely adjust the chemical characteristics of these complexes by choosing the best ligands for each application and managing the oxidation state of the metal centre. It follows that the difficulty of creating novel and enhanced metal-based medications closely coincides with the creation of novel and enhanced ligands for the functional metal elements[15,16].




**Chloroquine Phosphate**

Chemically, Chloroquine phosphate is a 7-chloro-4-4-diethylamino-1-methylbutyl amino-quinoline diphosphate. It is the phosphate salt of Chloroquine, having anti-inflammatory and antimalarial effects. With the exception of cases brought on by Plasmodium falciparum that is resistant to chloroquine, chloroquine is the most commonly used medication to treat malaria. It has been demonstrated that chloroquine inhibits the parasitic enzyme heme polymerase, which changes toxic heme into non-toxic hemazoin, causing poisonous heme to accumulate inside the parasite, however the exact mode of action is yet unknown. It's possible that chloroquine prevents nucleic acid production from occurring[17-22].

## Experimental

In the present investigation pH metric titration of ligand in the presence and absence of metal ions under experimental conditions were carried out. formation of complex observed due to the change in hydrogen ion concentration of solution. Metal ligand concentration can be estimated by examining pH data. New equilibria can be demonstrated based on the interaction of a metal ion ($M^+$), protons ($H^+$), hydroxide ions ($OH^-$) and ligands. The measurement of the free concentration of the ligand or metal ion at equilibrium serves as the foundation for calculating formation constants.

All chemicals are used for the titration were of AR grade. Perchloric acid, Sodium Perchlorate, NaOH, metals were prepared in double distilled water. The NaOH solution was standardized against oxalic acid solution (0.1M). The drug Choloroquine Phosphate is easily soluble in water pH measurement were carried out by ELICO-LI 120 pH-meter with a combined (glass & calomel) electrode.

A standard procedure were adopted for the titration of binary system. Acid titration (A) were carried out by taking 5ml $HClO_4$ (0.2M) and 5ml $NaClO_4$ (1.0M) solution in 50ml standard flask and diluted up to the mark with doubled distilled water. This was titrated against 0.2N NaOH. Readings was noted as ‘A’.

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1) Free $HClO_4$ (A) …… **A**
2) $HClO_4$ + Ligand (L) …… **X = A+ L**
3) $HClO_4$ + Ligand $(L)_2$ + Metal ion (M) …… **$M_x$ = (A+L+M)**

**Result and Discussion**

The Calvin-Bjerrum pH-metric titration technique was used for determination of proton-ligand stability constant (pK) and metal-ligand stability constant (logK).

**Proton-Ligand stability constant**

The proton-ligand stability constant, $\bar{n}_A$ is the average number of protons associated with one-ligand molecules. The replacement of hydrogen ion with respect to pH calculated by Irving- Rossetti's expression

$$\bar{n}_A = \gamma - \frac{(V_3 - V_2)(N + s^\circ)}{(V_0 + V_1)T^\circ_L} \quad \ldots\ldots\ldots\ldots 1$$

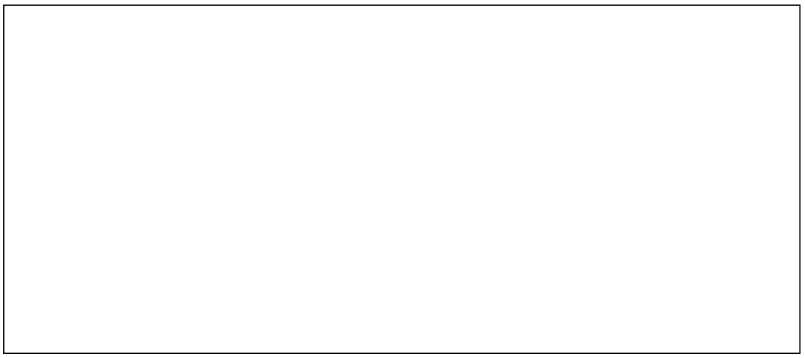
where $\gamma$ is number of replaceable protons per ligand molecule, N is the normality of NaOH used in titration, $V_1$ and $V_2$ are volumes of alkali required in acid and ligand titration at given pH, $\varepsilon^\circ$ and $T^\circ_L$ are initial concentrations of free acid and ligand respectively. The formation curve pK constructed by plotting $\bar{n}_A$ against pH.

**Metal-Ligand stability constant**

To determine metal-ligand stability constant, the value of $\bar{n}$ was calculated which shown by the equation 2. $\bar{n}$ Is the average number of ligand associated with per metal ion at different pH from ligand and metal ion titration curve determined by the equation i.e.

$$\bar{n} = \frac{(V_3 - V_2)\ (N + s^\circ)}{(V_0 + V_2)\ \ \bar{n}_A T^0_M} \quad \ldots\ldots\ldots\ldots 2$$

Where $V_3$ are the volume of NaOH added in metal ion titration to attain given pH reading. $T^0_M$ Is initial concentration of metal ion in reaction mask.



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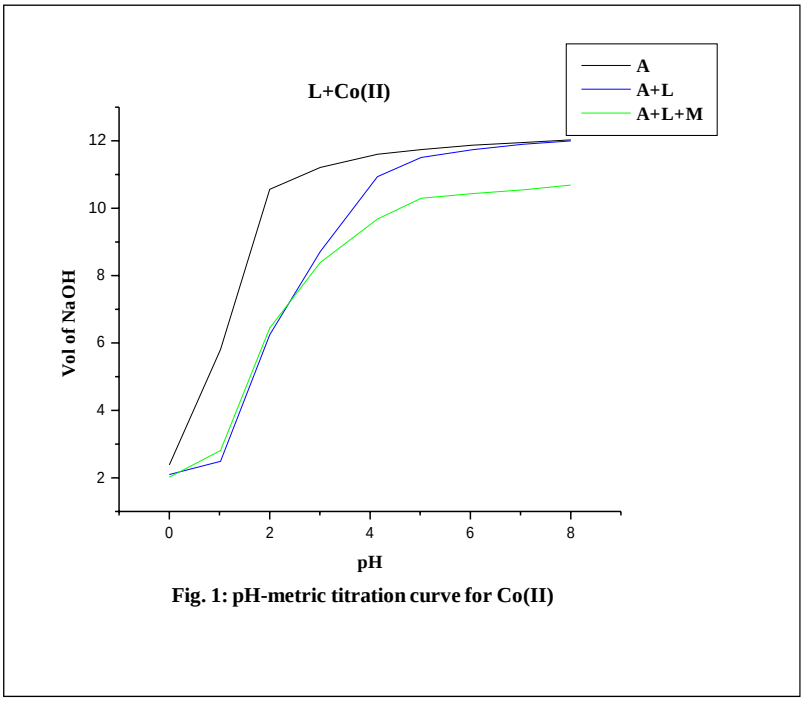


**Fig. 1: pH-metric titration curve for Co(II)**

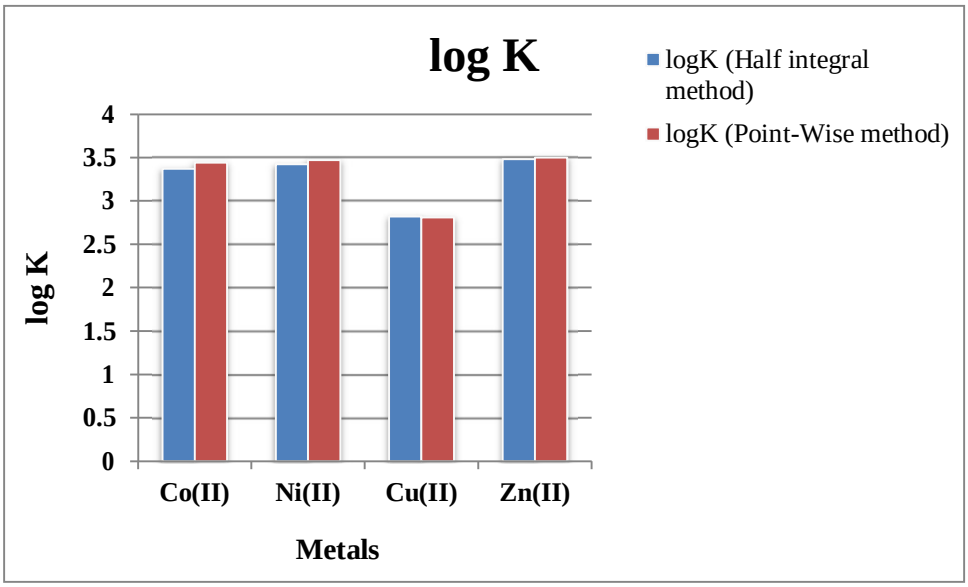


**Fig. 2: Metal-Ligand Stability Constant**

**Table 1: Calculation of Proton-ligand and Metal-ligand Stability constant**

| Ligand | Protonation Constant | | | Metal-Ligand Stability Constant | |
|---|---|---|---|---|---|
| | Metal | pK (Half integral method) | pK (Point-Wise method) | logK (Half integral method) | logK (Point-Wise method) |
| **Chloroquine** | Co(II) | 2.12 | 2.15 | 3.37 | 3.44 |

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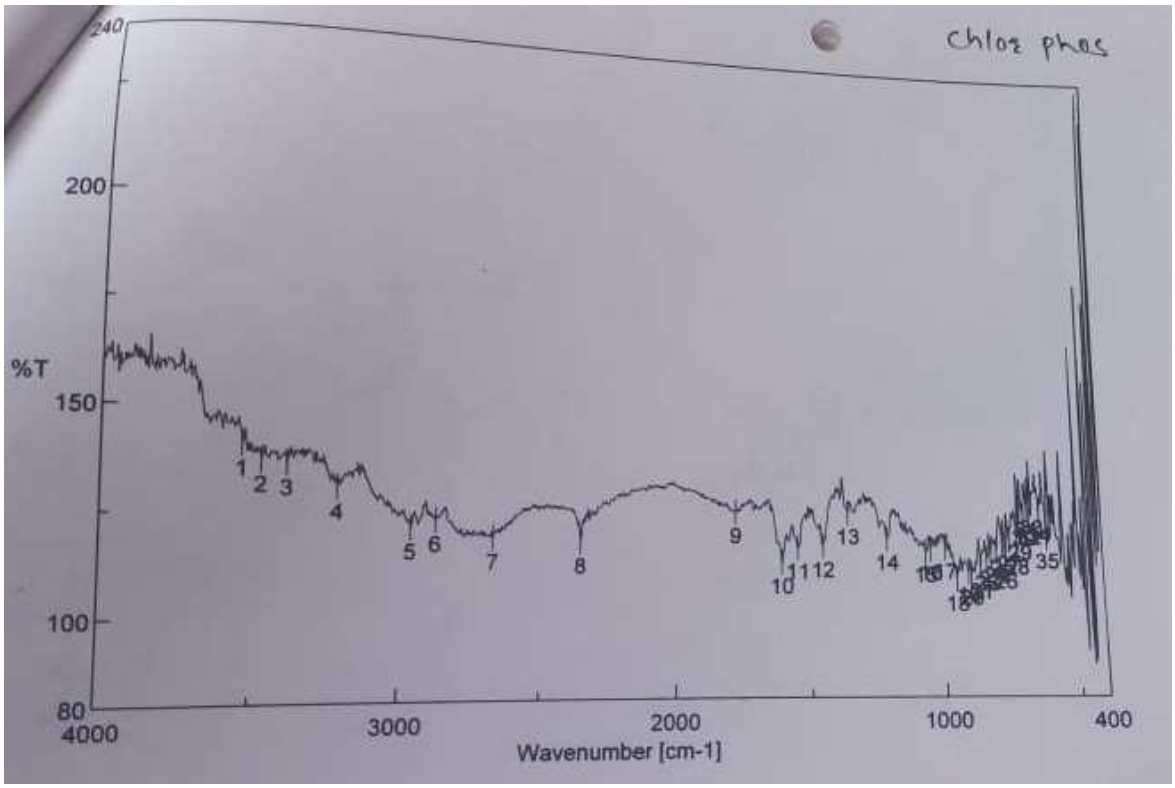
| | | | | | |
|---|---|---|---|---|---|
| **Phosphate** | Ni(II) | 2.12 | 2.15 | 3.42 | 3.47 |
| | Cu(II) | 2.12 | 2.15 | 2.82 | 2.81 |
| | Zn(II) | 2.12 | 2.15 | 3.48 | 3.50 |

| **Compounds** | **Molecular Weight** | **Colour** | **% Analysis Found (Calculated)** | | | | | **M.P. ($^0$C)** | **M:L Ratio** |
|---|---|---|---|---|---|---|---|---|---|
| | | | **C** | **H** | **N** | **O** | **Metal** | | |
| ChloroPh [Co (complex)] | 574.8 | Light Brown | 45.34 | 6.13 | 8.81 | 13.42 | 12.36 | 232 | 1 : 0.140 |
| ChloroPh [Cu (complex)] | 579.41 | Brown | 44.91 | 6.07 | 8.73 | 13.29 | 13.20 | 254 | 1 : 0.065 |
| ChloroPh [Ni (complex)] | 574.56 | Dark Green | 45.37 | 6.13 | 8.82 | 13.43 | 12.32 | 227 | 1 : 0.164 |
| ChloroPh [Zn (complex)] | 581.26 | Green | 44.74 | 6.05 | 8.70 | 13.24 | 13.53 | 246 | 1 : 0.067 |



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## IR spectra of Chloroquine phosphate complex

For the present investigation, A Calvin-Bjerrum titration technique was used for the determination of stability constant with transition metals such as Co(II), Cu(II), Ni(II) & Zn(II) with the medicinal drug Chloroquine Phosphate as a ligand. By plotting the graph of pH against the volume of NaOH, the Acid Curve (A), Ligand Curve (A+L) and the Metal Complex curve (A+L+M) were obtained. The proton-ligand stability constant(pK) of ligand Chloroquine phosphate with transition metals Co(II), Ni(II), Cu(II), Zn(II) were determined by point-wise method and half integral method as shown in table(1).

The observed trend for stability constant with ligands obeys Irving-Williams order $Cu^{+2} < Co^{+2} < Ni^{+2} < Zn^{+2}$. In the ligand, $Zn^{+2}$ has the highest value for stability constant.

The transition metal complexes are coloured. The dark green to brown colour of the compound suggested that the formation of complex. The change in Melting point of all the complex were ranging from 227- $254^0$C. The complex's melting points relative to chloroquine indicate the formation of additional products. Compared to chloroquine, metal complexes of chloroquine had a greater melting point. Studies have demonstrated that complexes have melting temperatures that are greater than those of the corresponding free ligands. Elemental analysis shows the good agreement with the metal complexes.

According to literature survey, infrared spectra of Chloroquine phosphate (CQP), N-H stretching frequency observed at 3260 $cm^{-1}$, while in the (CQP - ) complex, the vibrational frequency observed at 3227 $cm^{-1}$, it indicate that the rise in electron density will lengthen the NH bond and slow down the vibrational frequency, this change suggests that coordination happened through the N-H functional group. The C=N functionality appeared at 1120 in the chloroquine infrared spectrum, whereas in the metal complex spectrum it appear at 1067.41 $cm^{-1}$. This shift suggest that the rise in electron density will lengthen the C-N bond and slow down the vibrational frequency, these alterations indicate that coordination occurred through the C=N functional group. Vibrational frequencies of the [CQP - ] remained constant for the aromatic C-C, aromatic C-H, aliphatic C-H, and C-Cl, indicating that these functionalities were not involved in coordination.

Conclusion

For the present investigation, pH-metric method were used to determine the stability of complexes. the formation of chloroquine and metal binary complexes is supported by the log k value. The Irving-Williams order for the complexes were found $Cu^{+2} < Co^{+2} < Ni^{+2} < Zn^{+2}$. Physical data shows good agreement for the formation of solid complexes.

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