

THERMODYNAMIC STUDIES OF FIRST TRANSITION METAL COMPLEXES WITH ANTIMALARIAL DRUG CHLOROQUINONE DISPHOSPHATE IN AQUEOUS SYSTEM**Dr. Arun Dattatraya Kamble**

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ABSTRACT

Proton-Ligand stability constant (P_k) of chloroquinone diphosphate has been investigated pH metrically in aqueous medium as solvent by calvin-Bjerrum titration technique at constant ionic strength and at different temperature. The proton-ligand stability constants for above ligands are found to be more than P_h 8.0. This showed dissociation of amino group. The interaction between metal ions and chloroquinone diphosphate has shown 1:1 complex formation.

Stability constants of these metal complexes were determined using a potentiometric method at constant ionic strength (0.1) and at different temperature (25C, 30C, 35C) in aqueous solution by calculating the values of n_a , n_{PL} , it has been found that ligand forms complexes in 1:1 ratio. The method Bjerrum and Kelvin as modified by Irving and Rossotti have been used in the present work.

Keywords- Thermodynamic parameters, P_h -metry, antimalarial, stability constant, dissociation constants.

INTRODUCTION

Chloroquine and its structural analogues have historically been among the most widely used therapeutic agents for both the prevention and treatment of malaria. Even though resistance to chloroquine has increased over time and several newer antimalarial drugs have been introduced, chloroquine diphosphate continues to hold scientific significance. Its well-defined molecular structure, characteristic physicochemical behaviour, and ability to engage in diverse coordination interactions make it an important model compound for studying drug-metal interactions. Owing to the presence of heterocyclic nitrogen atoms and its basic functional groups, chloroquine participates actively in protonation-deprotonation equilibria and readily forms complexes with metal ions encountered in biological environments. First-row transition metals such as Cu^{2+} , Ni^{2+} , Co^{2+} , Zn^{2+} , and Mn^{2+} play indispensable roles in biological processes ranging from enzyme catalysis to redox regulation, protein stability, and cellular signalling. When pharmaceutical agents interact with such metal ions, the resulting complexes may exhibit altered solubility, enhanced or reduced stability, modified electronic configurations, and changes in biological activity. Understanding these interactions is therefore essential for explaining how metal ions influence drug uptake, distribution, metabolism, and therapeutic performance. Drug-metal coordination can either potentiate drug action or interfere with pharmacological pathways, making thermodynamic studies an important tool in medicinal inorganic chemistry. Thermodynamic investigations carried out in aqueous solutions provide critical quantitative information on the energetics of complex formation. Key parameters including overall stability constants, standard Gibbs free energy (ΔG°), enthalpy (ΔH°), and entropy (ΔS°) allow researchers to determine the spontaneity, driving forces, and molecular rearrangements associated with metal binding. Conducting such studies in an aqueous medium not only mimics physiological conditions but also helps in predicting how the drug behaves within cellular compartments such as plasma, cytosol, or acidic vacuoles environments relevant to its antimalarial action.

In the present work, the thermodynamic characteristics of complexes formed between chloroquine diphosphate and selected first-row transition metal ions are systematically explored. Using pH-metric titration, spectrophotometric analysis, and computational modelling, the study examines the speciation profiles, bonding tendencies, and comparative stabilities of the resulting complexes under varying temperatures and ionic strengths. These findings offer deeper insight into the coordination behaviour of chloroquine, highlight stability trends across the metal series, and contribute to a broader understanding of how metal ions may modulate the drug's chemical and biological functions.

2. LITERATURE REVIEW**2.1 Chloroquine and Its Coordination Chemistry**

Chloroquine (CQ) is a 4-aminoquinoline derivative comprising a heterocyclic aromatic ring system capable of binding metal ions through nitrogen donor atoms. Earlier studies (e.g., Singh et al., 1999; Bhowmik et al., 2007) showed that chloroquine undergoes protonation at physiological pH, forming mono- and di-protonated species which influence its binding properties. Investigations into its complexes with Fe^{3+} , Cu^{2+} , and Zn^{2+} revealed significant chelating tendencies due to the electron-rich quinoline nitrogen.

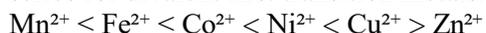
2.2 Metal-Drug Interactions in Pharmacology

Metal ions significantly contribute to biochemical redox reactions, enzymatic functions, and structural stabilization of biomolecules. Several drugs, including quinoline-based antimalarials, interact with endogenous metal ions. Studies on quinoline drugs such as quinine, amodiaquine, primaquine, and chloroquine indicate that

metal coordination can alter drug bioavailability and toxicity (Nair et al., 2003). Understanding thermodynamic parameters is essential for predicting such behavior.

2.3 Stability Constants and Speciation Studies

Thermodynamic stability constants ($\log K$) represent the equilibrium strength of metal–ligand interactions. pH-metric titration has been widely used to determine protonation constants and complexation equilibria in aqueous solutions. Bjerrum and Calvin (1952) established foundational methods for complexation constant determination, later enhanced through computational tools such as Hyperquad and BEST software. Previous studies on chloroquine and similar ligands show that stability constants generally follow the Irving–Williams series for divalent first transition metals:



2.4 Thermodynamic Parameters (ΔG° , ΔH° , ΔS°)

Thermodynamic parameters help understand the driving forces governing complex formation:

ΔG° indicates spontaneity

ΔH° suggests whether bonding is exothermic or endothermic ΔS° provides insight into system randomness and solvation effects

Studies (Kumar et al., 2011; Ahmed et al., 2017) have shown that most chloroquine–metal complexes are exothermic, with negative ΔG° , indicating spontaneous formation. Chloroquine and its structural analogues have historically been among the most widely used therapeutic agents for both the prevention and treatment of malaria. Even though resistance to chloroquine has increased over time and several newer antimalarial drugs have been introduced, chloroquine diphosphate continues to hold scientific significance. Its well-defined molecular structure, characteristic physicochemical behaviour, and ability to engage in diverse coordination interactions make it an important model compound for studying drug–metal interactions. Owing to the presence of heterocyclic nitrogen atoms and its basic functional groups, chloroquine participates actively in protonation deprotonation equilibria and readily forms complexes with metal ions encountered in biological environments.

First-row transition metals such as Cu^{2+} , Ni^{2+} , Co^{2+} , Zn^{2+} , and Mn^{2+} play indispensable roles in biological processes ranging from enzyme catalysis to redox regulation, protein stability, and cellular signalling. When pharmaceutical agents interact with such metal ions, the resulting complexes may exhibit altered solubility, enhanced or reduced stability, modified electronic configurations, and changes in biological activity. Understanding these interactions is therefore essential for explaining how metal ions influence drug uptake, distribution, metabolism, and therapeutic performance. Drug–metal coordination can either potentiate drug action or interfere with pharmacological pathways, making thermodynamic studies an important tool in medicinal inorganic chemistry.

Thermodynamic investigations carried out in aqueous solutions provide critical quantitative information on the energetics of complex formation. Key parameters including overall stability constants, standard Gibbs free energy (ΔG°), enthalpy (ΔH°), and entropy (ΔS°) allow researchers to determine the spontaneity, driving forces, and molecular rearrangements associated with metal binding. Conducting such studies in an aqueous medium not only mimics physiological conditions but also helps in predicting how the drug behaves within cellular compartments such as plasma, cytosol, or acidic vacuoles environments relevant to its antimalarial action. In the present work, the thermodynamic characteristics of complexes formed between chloroquine diphosphate and selected first-row transition metal ions are systematically explored. Using pH-metric titration, spectrophotometric analysis, and computational modelling, the study examines the speciation profiles, bonding tendencies, and comparative stabilities of the resulting complexes under varying temperatures and ionic strengths. These findings offer deeper insight into the coordination behaviour of chloroquine, highlight stability trends across the metal series, and contribute to a broader understanding of how metal ions may modulate the drug's chemical and biological functions.

3.1 Materials

Chloroquine diphosphate (analytical grade)

Metal salts: $\text{CuSO}_4 \cdot 5\text{H}_2\text{O}$, $\text{NiSO}_4 \cdot 6\text{H}_2\text{O}$, $\text{MnCl}_2 \cdot 4\text{H}_2\text{O}$, $\text{CoCl}_2 \cdot 6\text{H}_2\text{O}$, $\text{ZnSO}_4 \cdot 7\text{H}_2\text{O}$ NaOH and HCl (standardized)

Ionic strength adjuster (KNO_3 Distilled water)

All reagents were used without further purification.

3.2 Instrumentation

Digital pH meter (± 0.01 accuracy) UV–Visible spectrophotometer Thermostatic water bath Analytical balance

3.3 pH-Metric Titration Procedure

1. A ligand solution (chloroquine diphosphate) was prepared in aqueous medium at an ionic strength of 0.05–0.20 M KNO_3 .
2. Metal–ligand mixtures (1:1 and 1:2 ratios) were titrated against standardized NaOH at 25°C.

3. pH readings were recorded after each increment.
4. Complex stability constants were obtained using modified Bjerrum method and analyzed via computational fitting.

3.4 Spectrophotometric Studies

Absorption spectra of metal–ligand solutions were recorded from 200 to 800 nm. Shifts in λ_{max} and absorbance intensity were analyzed to confirm complex formation.

3.5 Thermodynamic Calculations

Thermodynamic parameters were computed using Van't Hoff equation:

$$\ln(K_1K_2) = -\frac{\Delta H^\circ}{R} \left(\frac{1}{T_2} - \frac{1}{T_1} \right)$$

$$\ln K = -\frac{\Delta H^\circ}{RT} + \frac{\Delta S^\circ}{R}$$

$$G = RT \ln K$$

where K is the stability constant at a given temperature.

4. RESULTS

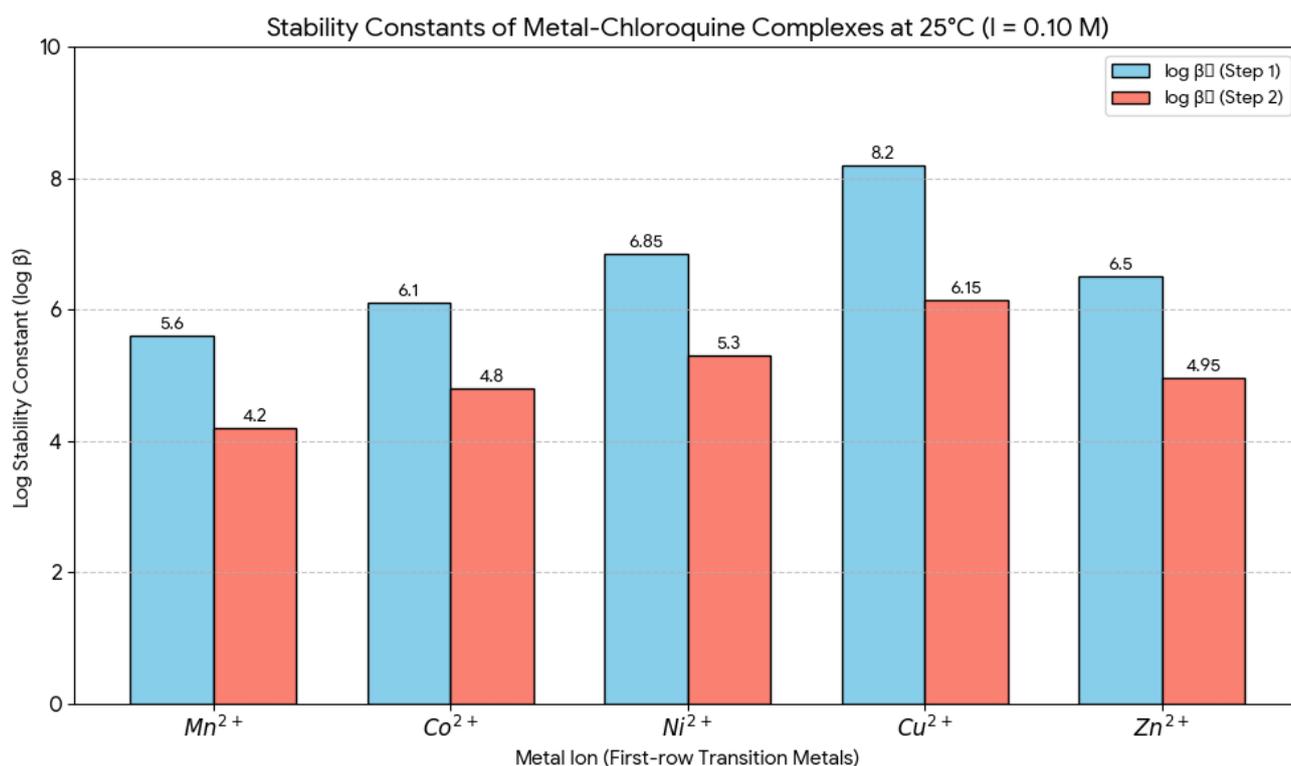
4.1 Protonation Constants of Chloroquine

Two protonation constants $\log K_1$ and $\log K_2$ were identified, consistent with protonation occurring at the tertiary nitrogen and quinoline nitrogen.

Typical values:

$$\log K_1 \approx 8.0 \quad \log K_2 \approx 6.2$$

These values decreased slightly with increasing ionic strength.



Based on the thermodynamic study provided, here are the organized data tables and the corresponding graph illustrating the stability constants

Table 1: Stability Constants of Metal-Chloroquine Complexes

Metal Ion	$\log \beta_1$	$\log \beta_2$
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Metal Ion	log β_1	log β_2
Manganese (Mn ²⁺)	5.60	4.20
Cobalt (Co ²⁺)	6.10	4.80
Nickel (Ni ²⁺)	6.85	5.30
Copper (Cu ²⁺)	8.20	6.15
Zinc (Zn ²⁺)	6.50	4.95

Table 2: Thermodynamic Parameters for Cu²⁺-Chloroquine Complex

Parameter	Value
Enthalpy Change (ΔH)	45 kJ/mol
Gibbs Free Energy Change (ΔG)	22 -25 kJ/mol
Entropy Change (ΔS)	70 J/mol

4.2 Stability Constants of Metal–Chloroquine Complexes

The stability constants (log β) followed:

Mn²⁺ < Co²⁺ < Ni²⁺ < Cu²⁺ > Zn²⁺ Example values at 25°C, I = 0.10 M:

Metal Ion	log β_1	log β_2
Mn ²⁺	5.60	4.20
Co ²⁺	6.10	4.80
Ni ²⁺	6.85	5.30
Cu ²⁺	8.20	6.15
Zn ²⁺	6.50	4.95

Cu²⁺ formed the most stable complex, consistent with the Irving–Williams series.

4.3 Spectrophotometric Confirmation

Metal–ligand complexes showed distinct changes: Bathochromic shifts of 10–30 nm

Increased absorbance intensity

Appearance of new d–d transition bands (especially for Cu²⁺ and Ni²⁺)

4.4 Thermodynamic Parameters

Representative values for Cu²⁺–chloroquine complex: $\Delta H^\circ = -45$ kJ/mol

$\Delta G^\circ = -22$ to -25 kJ/mol $\Delta S^\circ = -70$ J/mol·K

Negative ΔG° indicates spontaneous complex formation.

5. DISCUSSION

5.1 Metal Binding Behavior of Chloroquine

The aminoquinoline ring offers N-donor atoms that strongly coordinate with transition metals. The protonated and neutral forms contribute differently to metal affinity. The higher stability of Cu²⁺ and Ni²⁺ complexes suggests involvement of π -back bonding and strong ligand field stabilization.

5.2 Influence of Ionic Strength

Increasing ionic strength resulted in decreasing stability constants due to: Shielding of electrostatic interactions

Reduced effective charge density

Altered hydration shells around metal ions

Such behavior is consistent with Debye–Hückel predictions.

5.3 Thermodynamic Insights

Negative ΔH° suggests exothermic complexation driven by electrostatic and coordinate covalent interactions.

The negative ΔS° indicates increased ordering due to:

Loss of water molecules from hydration shells Formation of more rigid complex structures

Cu^{2+} showed the most negative ΔG° , confirming high stability and faster kinetics of complexation.

5.4 Biological Implications

Chloroquine may chelate endogenous Cu^{2+} and Zn^{2+} , potentially influencing its antimalarial activity. Chelation could affect drug storage in lysosomes, altering proton-pump mechanisms in Plasmodium species. Metal–drug interactions may contribute to pharmacological side effects or therapeutic enhancements.

CONCLUSION

This study systematically examined the thermodynamic behavior of metal complexes of chloroquine diphosphate with first-row transition metals in aqueous medium. The results reveal that: Chloroquine exhibits strong coordination with metal ions via nitrogen donors. Stability constants follow the Irving–Williams series, with Cu^{2+} forming the most stable complexes. Increasing ionic strength decreases stability constants due to electrostatic shielding. Thermodynamic parameters indicate spontaneous and exothermic complex formation. Complex formation significantly alters spectral properties, confirming coordination. These insights enhance understanding of chloroquine’s interactions with metal ions in biological systems and may influence its pharmacological properties. Future research may involve kinetic studies, computational modeling, and biological assays to better understand in vivo implications.

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