Formation Equilibria and Thermodynamic Stability of Cetirizine Complexes with Selected Transition and Lanthanide Metal Ions

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***Abstract*—The interaction of cetirizine dihydrochloride (CTZ) with transition and lanthanide metal ions was investigated potentiometrically in aqueous medium at 298.15 K and ionic strength $\mu = 0.10$ M ($NaNO_3$). Proton–ligand and metal–ligand stability constants were determined using the Irving–Rossotti pH-metric technique. The protonation constants of cetirizine were found to be $pK_1 = 4.40$ and $pK_2 = 7.83$, corresponding to the deprotonation of the carboxylic acid and piperazinium groups, respectively. Stepwise stability constants ($\log K_1$ and $\log K_2$) and overall stability constants ($\log\beta$) were evaluated for complexes formed with Cu(II), Co(II), Fe(III), Zn(II), Ni(II), Mn(II), Cr(III), Ce(III), Sm(III), and La(III). In all systems, $\log K_1$ values were higher than $\log K_2$ values, indicating reduced stability during the second ligand coordination step due to steric and electrostatic factors. The overall stability order was found to be Cu(II) > Co(II) > Fe(III) > Zn(II) > Ni(II) > Ce(III) > Sm(III) > Mn(II) > Cr(III) > La(III). Negative Gibbs free energy values confirmed the spontaneous nature of complex formation. The results indicate that cetirizine behaves as an effective chelating ligand and forms stable complexes with both transition and lanthanide metal ions. The study provides useful information regarding the coordination behaviour of cetirizine in biological and pharmaceutical environments.**

***Index Terms*—Cetirizine, Potentiometric Titration, Stability Constants, Metal Complexes, Irving–Rossotti Method, Gibbs Free Energy**

I. INTRODUCTION

The interaction of pharmaceutical compounds with metal ions has attracted considerable attention in bioinorganic and medicinal chemistry because metal complexation can significantly influence the physicochemical properties, bioavailability, pharmacokinetics, and biological activity of drugs. Many therapeutic agents contain functional groups capable of donating electron pairs to metal ions, resulting in the formation of coordination complexes with altered stability and reactivity. Understanding such metal–drug interactions is therefore important for evaluating the behaviour of pharmaceuticals in biological systems and formulation media.

Cetirizine dihydrochloride (CTZ) is a widely prescribed second-generation antihistamine used in the treatment of allergic rhinitis, chronic urticaria, and other allergic disorders. Structurally, cetirizine contains a carboxylic acid group and piperazine nitrogen atoms, providing potential coordination sites for metal-ion binding. The presence of both oxygen and nitrogen donor atoms enables cetirizine to act as a multidentate ligand capable of forming stable chelate complexes with a variety of metal ions. Such interactions may influence the transport, distribution, and therapeutic performance of the drug under physiological conditions.

Several studies have reported the synthesis, characterisation, and equilibrium behaviour of cetirizine complexes with transition metal ions. El-Sherif et al. demonstrated that cetirizine forms stable complexes with several divalent transition metals and highlighted the importance of nitrogen and oxygen donor atoms in metal coordination. Barakat and co-workers further investigated mixed-ligand systems involving cetirizine and amino acids, revealing the influence of ligand environment on complex stability. However, most reported studies have focused primarily on 1:1 (ML) complexes, while systematic investigations of 1:2 (ML_2) cetirizine complexes remain limited.

The formation of ML_2 species is of particular interest because the coordination of two ligand molecules around a metal centre can substantially modify the thermodynamic stability and solution speciation of the resulting complexes. The stability of such systems is influenced by factors including metal-ion charge density, ionic radius, hydration energy, ligand-field effects, and steric constraints associated with successive ligand coordination. Transition metal ions often exhibit characteristic stability trends described by the Irving–Williams series, whereas lanthanide ions show behaviour governed largely by electrostatic interactions and lanthanide contraction.

Potentiometric pH-metric titration remains one of the most reliable methods for investigating protonation equilibria and metal–ligand interactions in solution. The Irving–Rossotti method enables accurate determination of proton–ligand and metal–ligand stability constants and has been widely applied to biologically active ligands. Furthermore, the derived thermodynamic parameters provide valuable information regarding the spontaneity and driving forces of complex formation.

In the present study, the protonation behaviour of cetirizine and its complexation with selected transition metal ions [Cu(II), Co(II), Fe(III), Zn(II), Ni(II), Mn(II), and Cr(III)] and lanthanide ions [Ce(III), Sm(III), and La(III)] were investigated potentiometrically in aqueous solution at 298.15 K and an ionic strength of 0.10 mol dm^{-3} ($NaNO_3$). The stepwise stability constants ($\log K_1$ and $\log K_2$), overall stability constants ($\log\beta$), and Gibbs free energy changes (ΔG°) associated with the formation of 1:2 (ML_2) complexes were determined using the Irving–Rossotti approach. Particular attention was given to the influence of metal-ion characteristics on complex stability, the thermodynamic feasibility of ML_2 formation, and the comparative behaviour of transition and lanthanide metal ions under identical experimental conditions.

II. MATERIALS AND METHODS

2.1 Chemicals and Reagents

Cetirizine dihydrochloride (purity ≥ 99%) was used as the ligand without further purification. Analytical-grade nitrate salts of Cu(II), Co(II), Fe(III), Zn(II), Ni(II), Mn(II), Cr(III), Ce(III), Sm(III), and La(III) were employed for the preparation of metal-ion solutions. Sodium hydroxide solution was prepared in carbonate-free double-distilled water and standardised before use. Nitric acid (HNO_3) and sodium nitrate ($NaNO_3$) of analytical reagent grade were used throughout the study. All solutions were prepared using freshly distilled deionised water.

2.2 Potentiometric Measurements

Potentiometric pH-metric titrations were carried out at 298.15 ± 0.1 K using a calibrated digital pH meter fitted with a combined glass electrode. The ionic strength of all solutions was maintained at 0.10 mol dm^{-3} using sodium nitrate. Before each experiment, the electrode was calibrated with standard buffer solutions of pH 4.00, 7.00, and 9.18.

To minimise interference from atmospheric carbon dioxide, all titrations were performed under a nitrogen atmosphere. The temperature was maintained at a constant level using a thermostatically controlled water bath.

2.3 Titration Procedure

Three sets of solutions were prepared for potentiometric analysis:

(A) HNO_3 (1.0×10^{-2} mol dm^{-3}) + $NaNO_3$ (0.10 mol dm^{-3})

(A + L) HNO_3 (1.0×10^{-2} mol dm^{-3}) + cetirizine (1.0×10^{-3} mol dm^{-3}) + $NaNO_3$ (0.10 mol dm^{-3})

(A + L + M) HNO_3 (1.0×10^{-2} mol dm^{-3}) + cetirizine (1.0×10^{-3} mol dm^{-3}) + metal ion (1.0×10^{-3} mol dm^{-3}) + $NaNO_3$ (0.10 mol dm^{-3})

The metal-to-ligand ratio was maintained at 1:2 to facilitate the formation of ML_2 species. The total volume of each solution was adjusted to 50.0 mL and titrated against a standardised NaOH solution. Titration data were collected over the pH range 2.5–11.0.

2.4 Determination of Protonation and Stability Constants

The protonation constants of cetirizine and the stability constants of the metal complexes were determined using the Irving–Rossotti pH-metric method. The average number of protons associated with the ligand ($\bar{n}A$) and the average number of ligands coordinated per metal ion ($\bar{n}$) were calculated from the potentiometric data.

Protonation constants were evaluated by both the point-wise and half-integral methods. Stepwise stability constants ($\log K_1$ and $\log K_2$) were obtained from the corresponding $\bar{n}$ versus pL plots. The overall stability constants were calculated according to:

$$\log\beta = \log K_1 + \log K_2$$

All calculations were performed using Microsoft Excel.

2.5 Thermodynamic Calculations

The standard Gibbs free energy change associated with complex formation was calculated using the relation:

$$\Delta G^\circ = -2.303RT \log\beta$$

where R is the universal gas constant (8.314 J mol^{-1} K^{-1}) and T is the absolute temperature (298.15 K).

The calculated ΔG° values were used to evaluate the thermodynamic feasibility and spontaneity of complex formation.

III. RESULTS AND DISCUSSION

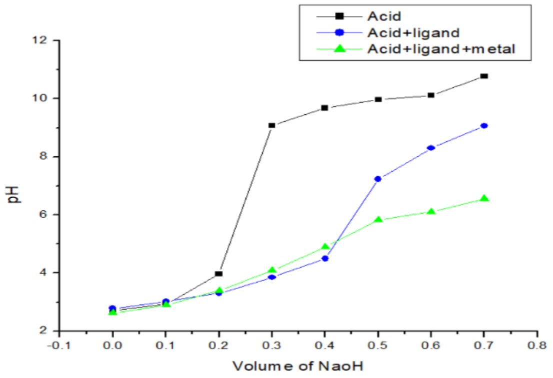


Figure 1. Potentiometric titration curves of acid, ligand and metal–ligand systems at 298.15 K and μ = 0.10 mol dm^{-3} $NaNO_3$.

Table 1. Protonation and Stability Constants of Cetirizine and Its ML_2 Complexes at 298.15 K and μ = 0.10 mol dm^{-3} $NaNO_3$

System / Metal Ion	$\log K_1$ (or pK_1)	$\log K_2$ (or pK_2)	Logβ
Cetirizine (Point-wise)	4.401622	7.827447	—
Cetirizine (Half-integral)	4.450880	7.827447	—
Cu(II)	6.776139	5.116519	11.892658
Co(II)	6.152910	4.823370	10.976280
Fe(III)	5.219222	5.044434	10.263656
Zn(II)	5.099991	4.912300	10.012291
Ni(II)	5.059365	4.863013	9.922378
Ce(III)	5.997754	3.813007	9.810761
Sm(III)	4.667114	3.951156	8.618270
Mn(II)	4.865471	3.617523	8.482994
Cr(III)	4.754835	3.716891	8.471726
La(III)	4.702743	3.749402	8.452145

3.1 Protonation Behaviour of Cetirizine

The protonation constants of cetirizine were determined potentiometrically using both the point-wise and half-integral methods. The obtained values are presented in Table 1. The ligand exhibited two protonation equilibria, indicating the presence of two ionisable functional groups within the studied pH range.

The first protonation constant ($pK_1 \approx 4.40$) is attributed to the deprotonation of the carboxylic acid group present in the ethoxyacetic acid moiety of cetirizine. The second protonation constant ($pK_2 \approx 7.83$) corresponds to the deprotonation of the protonated piperazine nitrogen atom. The agreement between the values obtained by the two computational methods confirms the reliability of the potentiometric measurements and the applicability of the Irving–Rossotti approach.

The observed protonation behaviour demonstrates that cetirizine can exist in different protonation states depending on the solution pH. Such behaviour is important for metal-ion coordination because deprotonation generates negatively charged donor sites capable of interacting with metal ions. The presence of both oxygen and nitrogen donor atoms enables cetirizine to function as an effective multidentate ligand in aqueous solution.

3.2 Formation of ML_2 Complexes

The potentiometric titration curves of the acid, ligand, and metal–ligand systems showed significant deviations after the addition of metal ions, indicating the formation of metal complexes. The displacement of the metal–ligand titration curves towards lower volumes of alkali consumption confirmed proton release during complexation.

Under the experimental conditions, the metal-to-ligand ratio was maintained at 1:2, favouring the formation of ML_2 species. The complexation process may be represented by the following equilibria:

$M + L \rightleftharpoons ML$

$ML + L \rightleftharpoons ML_2$

The corresponding stepwise stability constants, $\log K_1$ and $\log K_2$, were calculated using the Irving–Rossotti method. In all systems, the values of $\log K_1$ were higher than the corresponding $\log K_2$ values. This behaviour indicates that the first ligand molecule binds more strongly to the free metal ion than the second ligand molecule binds to the ML intermediate species.

The decrease in stability during the second coordination step can be attributed to steric hindrance around the coordination sphere, reduction of the positive charge density on the metal centre after the first coordination event, and competition between ligand molecules for the available coordination sites.

3.3 Stability Constants and Chelate Effect

The calculated stepwise and overall stability constants are presented in Table 1. The overall stability constants ($\log\beta$) varied significantly among the investigated metal ions, demonstrating the influence of electronic configuration, ionic radius, charge density, and hydration behaviour on complex stability.

The relatively high values of $\log\beta$ observed for most systems indicate that cetirizine forms stable chelate complexes in aqueous solution. The enhanced stability can be explained by the chelate effect, whereby simultaneous coordination through multiple donor atoms increases the thermodynamic stability of the complex compared with analogous monodentate ligands.

Based on the structure of cetirizine, coordination is expected to occur primarily through the deprotonated carboxylate oxygen atom and the piperazine nitrogen atom, resulting in the formation of stable chelate rings around the metal centre. Such chelation contributes significantly to the observed stability of the ML_2 species.

3.4 Stability Order of Metal Complexes

The overall stability constants followed the order:

Cu(II) > Co(II) > Fe(III) > Zn(II) > Ni(II) > Ce(III) > Sm(III) > Mn(II) > Cr(III) > La(III)

Among all investigated metal ions, Cu(II) exhibited the highest stability constant. The exceptional stability of the Cu(II) complex may be attributed to its strong affinity towards oxygen and nitrogen donor atoms and the additional stabilisation associated with Jahn–Teller distortion of the d^9 electronic configuration.

The transition-metal complexes generally exhibited higher stability than the lanthanide complexes. This behaviour reflects the greater contribution of covalent interactions and ligand-field effects in transition-metal coordination chemistry. Although the observed order does not strictly follow the classical Irving–Williams sequence, it shows a similar tendency for increasing stability toward Cu(II), which is characteristic of first-row transition-metal complexes.

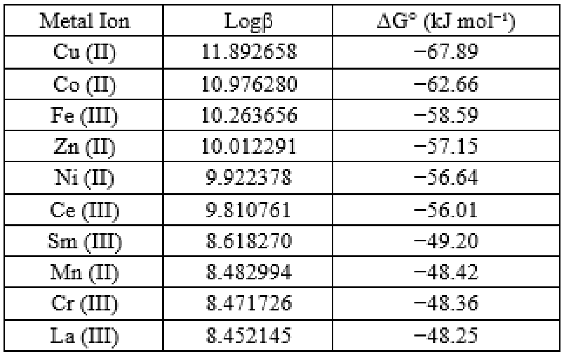
3.5 Lanthanide Complexes and Lanthanide Contraction

The lanthanide complexes showed the stability sequence: Ce(III) > Sm(III) > La(III)

The differences in stability may be explained by variations in ionic radius and hydration characteristics. Lanthanide ions generally form complexes through predominantly electrostatic interactions because the 4f orbitals participate only weakly in bonding.

As the ionic radius decreases across the lanthanide series, the charge density of the metal ion increases, enhancing metal–ligand interactions. This phenomenon, known as lanthanide contraction, contributes significantly to the stability of lanthanide complexes. The observed stability trend, therefore, reflects the combined influence of ionic size, hydration energy, and ligand accessibility

Table 2. Standard Gibbs Free Energy Changes (ΔG°) for the Formation of Cetirizine–Metal Complexes at 298.15 K



Metal Ion	Logβ	ΔG° (kJ mol⁻¹)
Cu (II)	11.892658	−67.89
Co (II)	10.976280	−62.66
Fe (III)	10.263656	−58.59
Zn (II)	10.012291	−57.15
Ni (II)	9.922378	−56.64
Ce (III)	9.810761	−56.01
Sm (III)	8.618270	−49.20
Mn (II)	8.482994	−48.42
Cr (III)	8.471726	−48.36
La (III)	8.452145	−48.25

3.6 Thermodynamic Evaluation

The thermodynamic feasibility of complex formation was evaluated from the calculated Gibbs free energy values. The ΔG° values obtained for all metal complexes were negative, confirming that the complexation reactions occur spontaneously under the experimental conditions.

The magnitude of ΔG° increased with increasing overall stability constant. Consequently, complexes possessing larger logβ values exhibited more negative Gibbs free energy values. The Cu(II) complex displayed the most negative ΔG° value, indicating the greatest thermodynamic driving force for complex formation, whereas the La(III) complex exhibited the least negative value, corresponding to comparatively weaker metal–ligand interactions.

The direct relationship between logβ and ΔG° confirms the consistency of the calculated thermodynamic parameters and supports the validity of the stability constants obtained from potentiometric measurements.

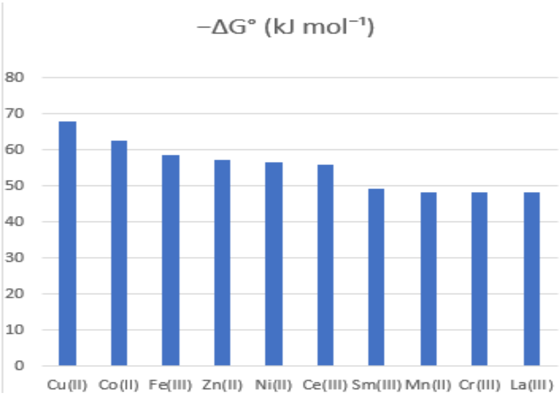


Figure 2. Standard Gibbs free energy changes (−ΔG°) for the formation of cetirizine–metal ML_2 complexes at 298.15K and ionic strength 0.10 mol dm^{-3} ($NaNO_3$).

Figure 2 shows the standard Gibbs free energy changes (ΔG°) for cetirizine–metal ML_2 complexes. All ΔG° values are negative, indicating spontaneous complex formation. The Cu(II) complex exhibits the most negative ΔG° value (−67.89 kJ mol^{-1}), reflecting the highest stability, whereas the La(III) complex shows the least negative value (−48.25 kJ mol^{-1}), indicating comparatively lower stability. The observed trend is consistent with the overall stability constants (logβ), confirming the thermodynamic favourability of complex formation.

3.7 Comparison with Reported Literature Values

The stability constants obtained in the present study are generally consistent with previously reported data for cetirizine and structurally related pharmaceutical ligands. El-Sherif et al. reported the formation of stable transition-metal complexes of cetirizine involving oxygen and nitrogen donor atoms, while Barakat et al. demonstrated the ability of cetirizine to form thermodynamically favourable mixed-ligand complexes.

Compared with previously reported 1:1 cetirizine complexes, the present ML_2 systems exhibited higher overall stability constants owing to the coordination of two ligand molecules. The enhanced stability highlights the importance of ligand stoichiometry in determining the thermodynamic properties of metal–drug complexes.

The lanthanide complexes showed stability values comparable to those reported for related oxygen-donor pharmaceutical ligands. However, the presence of both oxygen and nitrogen donor sites in cetirizine appears to provide additional stabilisation relative to simple monodentate carboxylate ligands.

Overall, the present investigation provides a systematic comparison of transition-metal and lanthanide complexes of cetirizine under identical experimental conditions and contributes valuable information regarding the solution chemistry of this important pharmaceutical ligand.

The stability constants obtained in the present investigation are in reasonable agreement with previously reported potentiometric studies of cetirizine–metal systems. El-Sherif et al. reported the formation of stable binary complexes between cetirizine and several first-row transition-metal ions, with the stability order Mn(II) < Co(II) < Ni(II) < Cu(II), consistent with the general Irving–Williams trend for divalent transition metals. The authors also demonstrated that cetirizine acts as an effective coordinating ligand through its ionizable functional groups and forms thermodynamically favourable complexes in aqueous solution.

Rayan et al. further investigated mixed-ligand systems containing cetirizine, alanine, and transition-metal ions. Their potentiometric studies confirmed the formation of stable metal–cetirizine species and highlighted the importance of ligand environment and metal-ion characteristics in determining overall stability. These findings support the present observation that cetirizine possesses significant metal-binding ability owing to the presence of both nitrogen and oxygen donor sites.

Unlike previous investigations that mainly focused on divalent transition-metal ions, the present work extends the study to include Fe(III), Cr(III), Ce(III), Sm(III), and La(III). The inclusion of trivalent transition and lanthanide ions provides a broader understanding of the coordination behaviour of cetirizine under identical experimental conditions. The results indicate that complex stability is influenced not only by ligand-field effects but also by ionic size, charge density, hydration energy, and lanthanide contraction.

The predominance of Cu(II) complex stability observed in the present work agrees with previous cetirizine studies and reflects the strong affinity of Cu(II) towards mixed nitrogen–oxygen donor ligands. However, the complete stability sequence obtained in this investigation differs from the classical Irving–Williams order because the studied metal-ion set includes both divalent and trivalent cations as well as lanthanides. Consequently, the observed trend represents the combined influence of electronic structure, ionic radius, hydration behaviour, and steric factors associated with successive ligand coordination.

Overall, the present study expands the available thermodynamic data for cetirizine complexes and provides a systematic comparison of transition-metal and lanthanide systems using a uniform potentiometric methodology.

IV. CONCLUSION

The present study investigated the protonation behaviour and complexation equilibria of cetirizine with selected transition and lanthanide metal ions using the Irving–Rossotti potentiometric method at 298.15 K and an ionic strength of 0.10 mol dm^{-3} ($NaNO_3$). Cetirizine exhibited two protonation constants ($pK_1 = 4.40$ and $pK_2 = 7.83$), confirming the presence of ionisable donor sites capable of coordinating metal ions.

The calculated stability constants demonstrated the formation of stable ML_2 complexes, with $\log K_1$ values consistently higher than $\log K_2$ values, indicating that the first coordination step is thermodynamically more favourable than the second. The overall stability order was found to be:

Cu(II) > Co(II) > Fe(III) > Zn(II) > Ni(II) > Ce(III) > Sm(III) > Mn(II) > Cr(III) > La(III).

Among the investigated metal ions, Cu(II) formed the most stable complex, whereas La(III) exhibited the lowest stability. The negative Gibbs free energy values obtained for all complexes confirmed the spontaneous and thermodynamically favourable nature of the complexation reactions. A close correlation between $\log\beta$ and $\Delta G°$ further supported the reliability of the potentiometric data.

Overall, the results demonstrate that cetirizine acts as an effective chelating ligand toward both transition and lanthanide metal ions. The study contributes to a better understanding of metal–drug interactions and provides useful thermodynamic information relevant to pharmaceutical speciation, bioinorganic chemistry, and the coordination behaviour of cetirizine in solution.

Declaration of Competing Interest

The author declares that there are no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data Availability Statement

The data supporting the findings of this study are available from the corresponding author upon reasonable request.

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