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Research Article

# Comparative pH-Metric Investigation of Stepwise Stability Constants of Phenylephrine Hydrochloride Complexes with Transition and Rare Earth Metal Ions

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**ABSTRACT**

A potentiometric investigation of the sympathomimetic drug phenylephrine hydrochloride (PEH) with selected transition and rare-earth metal ions was conducted using the Calvin–Bjerrum pH titration technique as modified by Irving and Rossotti. Proton–ligand dissociation constants and thermodynamic metal–ligand stability constants (log $K_1$ and log $K_2$) were determined at a constant temperature (298.15 K) and ionic strength ($\mu$ = 0.1 M $NaNO_3$). The ligand exhibits two distinct protonation constants corresponding to the sequential deprotonation of its secondary amino and phenolic hydroxyl groups, confirming its bidentate (O, N) coordination topology. Stepwise stability constants of coordination complexes formed with Ni(II), Co(II), Mn(II), Cu(II), Zn(II), Fe(III), Cr(III), La(III), Sm(III), and Ce(III) were evaluated concurrently using pointwise calculation and half-integral graphical methods.

Comparative equilibrium analysis revealed that the primary coordination step is uniformly more thermodynamically favourable than the secondary step (log $K_1$ > log $K_2$). Transition metal ions exhibited an exceptional affinity profile following the order:

Mn(II) < Co(II) < Ni(II) < Cu(II) > Zn(II) directly validates the Irving–Williams series, while Fe(III) displayed maximum stability governed by high charge density. Rare earth metal complexes exhibited moderate stabilities regulated by ionic radius contraction and electrostatic dominance. These findings map the solution coordination chemistry profiles of PEH, offering crucial structural parameters for prospective bioinorganic and pharmaceutical chemistry applications.

**Keywords:** Phenylephrine Hydrochloride, Potentiometric Titration, Irving–Rossotti Method, Stability Constants, Irving–Williams Series, Lanthanide Complexes.

## INTRODUCTION

The thermodynamic and coordination behaviour of biologically active pharmaceutical compounds with transition and rare-earth metal ions represents a major frontier in bioinorganic and medicinal chemistry. In vivo, drug molecules frequently encounter essential metal ions inside biological fluids. These interactions alter the baseline pharmacokinetics, metabolic pathways, systemic toxicity, and cell-membrane transport characteristics of parent drug molecules. Conversely, introducing specific metal centres into coordinate frameworks can optimise therapeutic efficiency or reveal novel metallodrug candidates.

Phenylephrine hydrochloride (PEH) is a potent sympathomimetic $\alpha_1$-adrenergic receptor agonist widely prescribed as a nasal decongestant, vasoconstrictor, and mydriatic agent.

### Structural Topography of PEH

Structurally, PEH features a chiral aromatic network equipped with a phenolic hydroxyl group and a secondary aliphatic amino group. This arrangement provides potential electron donor sites (O and N) suitable for forming stable chelate structures upon metal ion engagement. Among the available solution-state analytical methodologies, pH-metric potentiometry based on the Calvin–Bjerrum technique and modified by Irving and Rossotti remains a widely used and reliable approach for the determination of stability constants [1–3]. Quantifying the precise protonation equilibria and stability profiles of these metal complexes is necessary to map out their behaviour in solution. Several potentiometric investigations have demonstrated the coordination behaviour of biologically active ligands with transition metal ions and rare-earth metal ions under

controlled experimental conditions. Previous studies on triazoles, quinolone derivatives, substituted hydrazones, pharmaceutical ligands and related bioactive compounds have established the applicability of the Irving–Rossotti pH-metric technique for determining proton–ligand and metal–ligand stability constants [4–8].

This study details a comparative, systematic investigation of the stepwise stability constants (log $K_1$, log $K_2$) of PEH with biologically essential transition metal ions ($Mn^{2+}$, $Co^{2+}$, $Ni^{2+}$, $Cu^{2+}$, $Zn^{2+}$, $Cr^{3+}$, $Fe^{3+}$) and trivalent rare-earth metal ions ($La^{3+}$, $Ce^{3+}$, $Sm^{3+}$). The comparative balance between the d-block transitions and f-block elements is discussed in terms of ionic radii, Pearson's Hard–Soft Acid–Base theory, ligand-field stabilisation energy (LFSE), and steric constraints.

## MATERIALS AND METHODS

### Materials and Reagents

All chemicals utilised were of high-purity Analytical Reagent (AR) grade. Phenylephrine Hydrochloride (>99% purity) was procured and utilised as received without extra chemical treatment. Stock solutions of transition and rare-earth metal nitrates were prepared using freshly generated double-distilled water. These solutions were standardised volumetrically through complexometric titrations with standard disodium salt of EDTA using appropriate metallochromic indicators.

Carbonate-free sodium hydroxide (NaOH) titrant was prepared according to standard laboratory protocol and standardised regularly against primary standard potassium hydrogen phthalate (KHP). Dilute nitric acid ($HNO_3$) was utilised for initial solution acidification, and a constant ionic strength ($\mu$ = 0.1 M) was systematically maintained using sodium nitrate ($NaNO_3$) as an inert supporting electrolyte.

### Instrumentation and Standardisation

Potentiometric titrations were performed inside a double-walled glass vessel maintained at 25.0 ± 0.1°C using an automated circulating thermostatic water bath. The solution pH was monitored using a digital pH meter with a resolution of ±0.01 pH units, equipped with a sensitive combined glass-reference electrode loop. The instrument was calibrated daily prior to any experimental run utilising standard aqueous IUPAC buffers (pH 4.01, 7.00, and 10.01).

### Potentiometric Procedure

The structural modification developed by Irving and Rossotti was rigidly applied to track chemical shifts. Three distinct sequential fluid mixtures were titrated potentiometrically against the standard NaOH titrant (0.10 M):

*Acid Titration*

$HNO_3$ ($1.0 \times 10^{-2}$ M) + $NaNO_3$ (0.1 M)

*Ligand Titration*

$HNO_3$ ($1.0 \times 10^{-2}$ M) + $NaNO_3$ (0.1 M) + PEH ($2.0 \times 10^{-3}$ M)

*Metal–Complex Titration*

$HNO_3$ ($1.0 \times 10^{-2}$ M) + $NaNO_3$ (0.1 M) + PEH ($2.0 \times 10^{-3}$ M) + Metal Nitrate ($4.0 \times 10^{-4}$ M)

Total starting solution volumes were fixed at 50.0 mL. Small volumes of titrant (0.05 mL) were added sequentially, with the solution thoroughly stirred magnetically under an inert nitrogen blanket to avoid atmospheric carbon dioxide absorption. All titrations were performed in triplicate, and the calculated stability constants were reproducible within ±0.02 log units.

## RESULTS AND DISCUSSION

### Proton–Ligand Equilibrium Dynamics

From the volume–pH profiles obtained from the acid and ligand titration curves, the average number of protons associated with the ligand molecule ($\bar{n}A$) was calculated at chosen pH boundaries via Irving–Rossotti expressions.

The protonation steps correspond to the successive protonation–deprotonation equilibria involving the secondary amino group and the phenolic hydroxyl group:

$HL \rightleftharpoons L^- + H^+$ ($K_1^H$)
$H_2L^+ \rightleftharpoons HL + H^+$ ($K_2^H$)

The evaluated pKa values calculated using both half-integral and pointwise calculation techniques are summarised below:

The higher protonation constant ($pK_2 \approx 9.81$) is attributed to the protonated secondary amino group, whereas the lower protonation constant ($pK_1 \approx 8.47$) corresponds to the phenolic hydroxyl group. The obtained data confirm that, under physiological pH conditions (pH 7.4), Phenylephrine Hydrochloride remains substantially

**Table 1:** Protonation constants of phenylephrine hydrochloride

| *System* | *Method* | *pK1* | *pK2* |
|---|---|---|---|
| 1:2 | Pointwise | 8.04 | 9.26 |
| 1:2 | Half-Integral | 7.67 | 9.44 |
| 1:1 | Pointwise | 8.44 | 9.85 |
| 1:1 | Half-Integral | 8.49 | 9.77 |

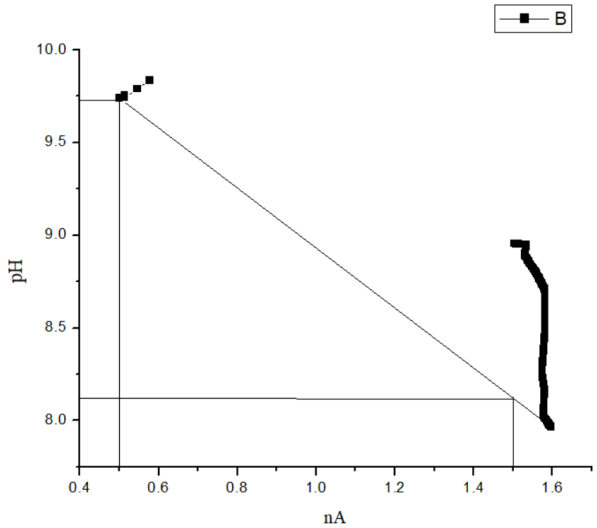


**Figure 1:** Proton–ligand formation curve of phenylephrine hydrochloride

protonated. It therefore behaves as a potential bidentate ligand capable of coordinating through oxygen and nitrogen donor atoms (Fig 1).

## Metal–Ligand Stability Constants Evaluation

By monitoring the lateral displacement between the ligand titration curve (2) and the metal–complex titration curve (3), the average number of ligand molecules coordinated per metal ion ($\bar{n}$) and the free ligand exponent (pL) were evaluated using the Irving–Rossotti computational approach. The calculated formation curves confirmed the progressive coordination of Phenylephrine Hydrochloride with both transition and rare-earth metal ions.

The stepwise metal–ligand stability constants ($\log K_1$ and $\log K_2$), together with the overall cumulative stability constants ($\log\beta$), were determined by pointwise and half-integral methods for all investigated systems. The obtained results revealed that the first coordination step is thermodynamically more favourable than the second coordination step ($\log K_1 > \log K_2$), indicating preferential formation of primary metal–ligand complexes before secondary ligand coordination.

The comparatively higher stability constants observed for Cu(II), Zn(II), and Fe(III) complexes suggest stronger interaction between the metal centres and the oxygen–nitrogen donor sites of Phenylephrine Hydrochloride. Rare-earth metal complexes exhibited relatively moderate stability because of their larger ionic radii and predominantly electrostatic mode of coordination.

## Comparative Chemical Behaviour

*Thermodynamic Stepwise Trend*

An examination of the stability parameters presented in Table 2 indicates that, for nearly all investigated systems, the first stepwise stability constant is significantly greater than the second stability constant ($\log K_1 > \log K_2$). This characteristic thermodynamic behaviour confirms that the primary coordination step is energetically more favourable than the secondary coordination step.

The comparatively lower values of $\log K_2$ may be attributed to steric hindrance generated after formation of the initial 1:1 metal–ligand complex. Coordination of the first Phenylephrine Hydrochloride molecule partially satisfies the coordination sphere of the central metal ion and simultaneously reduces its effective positive charge density. Consequently, the electrostatic attraction available for coordination of the second incoming ligand molecule decreases considerably, leading to lower secondary stability constants.

Furthermore, the bulky molecular framework of Phenylephrine Hydrochloride introduces additional steric crowding around the metal centre, thereby restricting the accommodation of the second ligand molecule within the coordination environment.

## Transition Metal Stability Analysis and Irving–Williams Validation

The experimentally determined stability constants for the divalent 3d transition metal ions were found to follow the classical Irving–Williams stability order:

Mn(II) < Co(II) < Ni(II) < Cu(II) > Zn(II)

The corresponding $\log K_1$ values obtained in the present investigation are:

Mn(II) (4.35) < Co(II) (4.00) < Ni(II) (5.23) < Cu(II) (6.61) > Zn(II) (5.26)

**Table 2:** Metal–ligand stability constants of 1:1 System

| *Metal Ion* | *log$K_1$* | *log$K_2$* | *Log$\beta$* |
|---|---|---|---|
| Ni(II) | 5.23 | 4.17 | 9.40 |
| Sm(III) | 5.16 | 3.75 | 8.91 |
| Zn(II) | 5.26 | 4.23 | 9.49 |
| Co(II) | 3.99 | 3.57 | 7.56 |
| Mn(II) | 4.35 | 4.05 | 8.41 |
| Fe(III) | 6.28 | 4.13 | 10.42 |
| La(III) | 5.07 | 3.30 | 8.37 |
| Cu(II) | 6.61 | 4.15 | 10.76 |
| Cr(III) | 4.73 | 4.67 | 9.40 |
| Ce(III) | 4.82 | 4.07 | 8.90 |

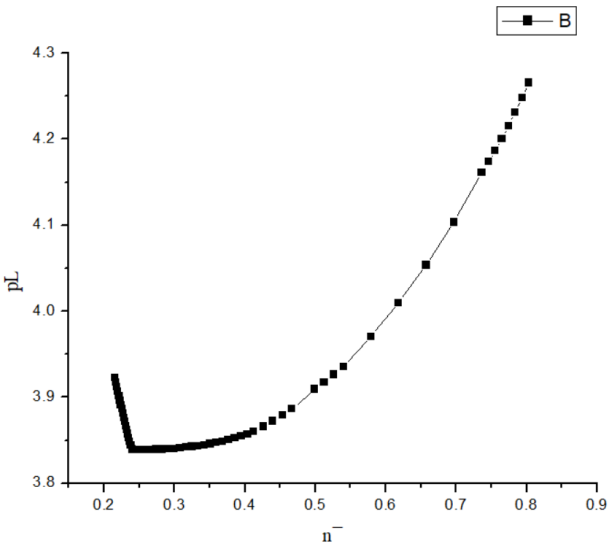


**Figure 2:** Metal–Ligand Formation Curve (pL vs $\bar{n}$) for 1:1 System

This trend strongly supports the applicability of the Irving–Williams series to Phenylephrine Hydrochloride metal complexes. The progressive increase in stability from Mn(II) to Cu(II) may be attributed to decreasing ionic radii, increasing ligand field stabilisation energy (LFSE), and stronger metal–ligand orbital overlap across the first-row transition series.

The exceptionally high stability of Cu(II) complexes may additionally arise from Jahn–Teller stabilisation effects and the strong affinity of Cu(II) ions toward oxygen and nitrogen donor atoms present within the ligand framework.

The slight deviation observed for Co(II) complexes may result from hydration effects, stereochemical preferences, or structural rearrangements occurring during the initial coordination process. Zn(II) complexes, although highly stable, exhibit comparatively lower stability than Cu(II) because Zn(II) possesses a filled $d^{10}$ electronic configuration and therefore lacks ligand field stabilisation energy contributions (Fig 2).

## Metal–Ligand Stability Constants of 1:2 System

The comparative analysis under high-ligand stoichiometric excess

**Table 3:** Stepwise stability constants of 1:2 metal–ligand system

| *Metal Ion* | *logK₁* | *logK₂* | *Logβ* |
|---|---|---|---|
| Ni(II) | 5.75 | 4.51 | 10.26 |
| Sm(III) | 5.35 | 4.07 | 9.43 |
| La(III) | 5.18 | 4.21 | 9.39 |
| Co(II) | 3.79 | 4.18 | 7.98 |
| Mn(II) | 4.19 | 3.86 | 8.06 |
| Fe(III) | 7.60 | 4.80 | 12.41 |
| Cu(II) | 6.70 | 4.68 | 11.38 |
| Zn(II) | 6.47 | 4.20 | 10.67 |
| Cr(III) | 4.91 | 3.89 | 8.81 |
| Ce(III) | 4.78 | 4.01 | 8.79 |

(System B) matches the parameters calculated in System A. The ligand maintains a strong coordination preference toward Cu(II), Fe(III), and Zn(II) ions. The values of Log $K_1$ remain greater than their corresponding log $K_2$ components, except Co(II), which shows an inversion, log $K_1$ = 3.79 < log $K_2$ = 4.18, under these specific concentration dynamics. This behaviour may arise from changes in coordination geometry, hydration effects, or experimental uncertainties under ligand-rich conditions of the cobalt centre, making the secondary binding event more thermodynamically favourable (Fig 3).

## Comparative Stability Behaviour of Transition and Rare Earth Metal Ions

Comparative analysis between transition and rare earth metal ions revealed stronger overall stability constants within the transition metal complexes. The enhanced stability of transition metal complexes is attributed to ligand field stabilisation effects, smaller covalent/ionic radii, and stronger d-orbital overlap with the O, N donor loops of the drug framework.

Rare-earth metal ions exhibited comparatively moderate stability because the 4f orbitals are effectively shielded by outer electrons, limiting significant covalent interaction with ligand donor atoms. Consequently, the bonding is predominantly ionic in nature (Figs 4 and 5).

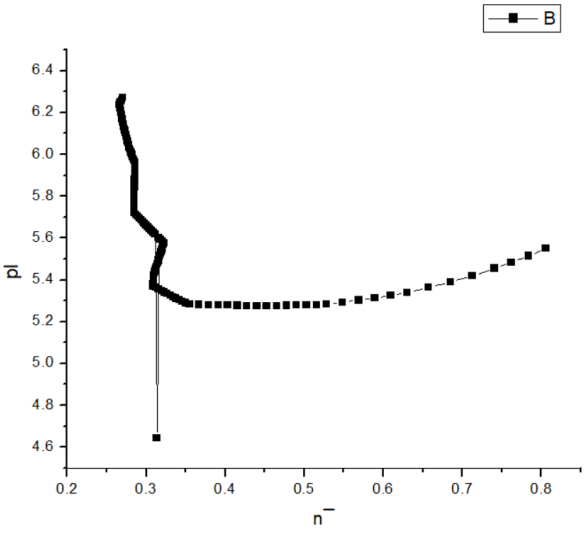


**Figure 3:** Metal–ligand formation curve (pL vs n̄) for 1:2 system

## Titration Curve Analysis

The pH-metric titration curves of the acid, acid–ligand, and acid–ligand–metal systems showed significant lateral displacement along the volume axis, confirming proton displacement and metal complex formation.

The ligand curve was displaced from the acid baseline curve due to the structural release of protons from ligand donor sites as the pH increased. The further pronounced lateral shifting observed across the metal-complex tracks confirms the coordination of metal ions with the active donor nodes of phenylephrine hydrochloride (Fig 6).

## Discussion of Stepwise Stability Constants

The higher values of log K1 compared to log K2 indicate that the first ligand coordination step is thermodynamically more favourable than the second coordination step. This behaviour is attributed to steric hindrance, electrostatic repulsion, and reduced availability of coordination sites after formation of the primary complex.

The observed stability order broadly follows the Irving–Williams sequence:

Mn(II) < Co(II)< Ni(II) < Cu(II) > Zn(II)

The stability pattern obtained in the present investigation is consistent with previously reported potentiometric studies on pharmaceutical

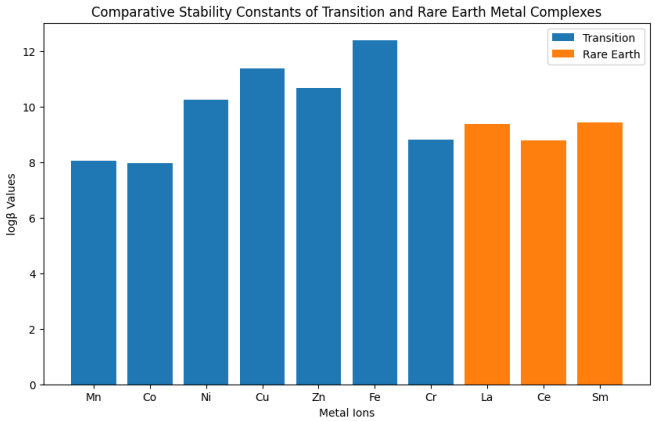


**Figure 4:** Comparative stability constants of transition and rare earth metal complexes

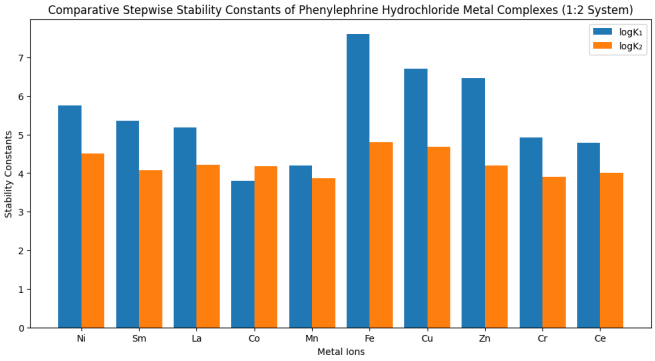


**Figure 5:** Comparative stepwise stability constants (logK1 and logK2) of 1:2 metal complexes

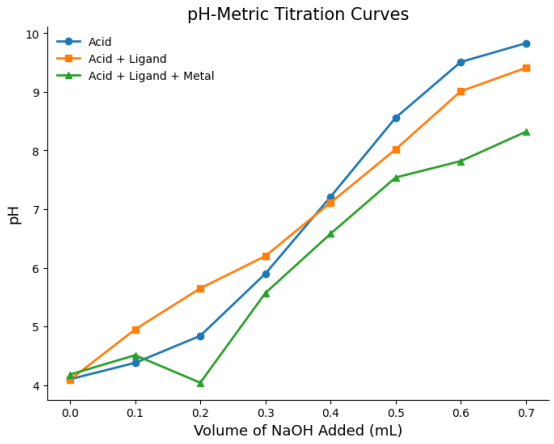


**Figure 6:** pH-metric titration curves of acid, acid–ligand, and acid–ligand–metal systems

ligands and biologically active coordination compounds. Similar observations regarding transition metal complex formation and solution equilibria have been reported in earlier investigations [9–12]. The enhanced stability of Cu(II) complexes is attributed to Jahn–Teller stabilisation and strong affinity toward oxygen and nitrogen donor atoms. Zn(II) complexes also exhibited considerable stability due to a favourable ionic radius and effective chelation with the ligand donor atoms.

### Fe(III)

complexes showed high stability constants because of their higher charge density and strong electrostatic interaction with ligand donor atoms, in accordance with Pearson's HSAB principle. Conversely, the lower stability of rare earth metal complexes is associated with their larger ionic radii and weaker ligand field stabilisation effects.

### Proposed Coordination Mode

Phenylephrine Hydrochloride behaves as a bidentate ligand coordinating through the amino nitrogen and phenolic oxygen donor atoms. The coordination leads to the formation of stable five-membered chelate rings. Both 1:1 and 1:2 complexes are proposed to form depending upon ligand concentration and the coordination environment.

## CONCLUSION

The present potentiometric investigation demonstrates that phenylephrine hydrochloride behaves as a bidentate ligand coordinating through amino nitrogen and phenolic oxygen donor atoms with transition and rare-earth metal ions. The proton–ligand and metal–ligand stability constants determined by pointwise and half-integral methods confirmed the formation of stable 1:1 and 1:2 complexes in solution.

In most cases, the first stepwise stability constant (log $K_1$) was greater than the second (log $K_2$), indicating that the initial coordination step is thermodynamically more favourable. The stability order of transition metal complexes broadly followed the Irving–Williams series:

Mn(II) < Co(II) < Ni(II) < Cu(II) > Zn(II)

Cu(II) and Fe(III) complexes exhibited comparatively higher stability due to stronger metal–ligand interactions and higher charge density effects. Rare-earth metal complexes showed moderate stability, mainly governed by electrostatic interactions and larger ionic radii.

The study provides valuable insight into the coordination behaviour of Phenylephrine Hydrochloride and may contribute to future investigations in medicinal, analytical, and bioinorganic chemistry.

## CONFLICT OF INTEREST

The authors declare no conflict of interest.

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