DETERMINATION OF METAL-LIGAND STABILITY CONSTANTS FOR LANTHANIDE (III) COMPLEXES WITH SUBSTITUTED DRUGS DERIVATIVES

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ABSTRACT

The interactions of Ce(III), Pr(III), Nd(III), Sm(III), Gd(III), Dy(III), Yb(III), and Lu(III) metal ions with Oxymetazoline (6-tert-butyl-3-(4,5-dihydro-1H-imidazol-2-ylmethyl)-2,4-dimethylphenol) Ligand-1 and Amikacin ((2S)-4-amino-N-[(1R,2S,3S,4R,5S)-5-amino-2-[(2S,3R,4S,5S,6R)-4-amino-3,5-dihydroxy-6-(hydroxymethyl)oxan-2-yl]oxy-4-[(2R,3R,4S,5S,6R)-6-(aminomethyl)-3,4,5-trihydroxyoxan-2-yl]oxy-3-hydroxycyclohexyl]-2-hydroxybutanamide) Ligand-2 were systematically investigated using pH-metric techniques under controlled conditions at an ionic strength of 0.1 M and

temperature ±0.1 °C in a 70% dioxane-water solvent system. The experimental data were utilised to determine the proton-ligand stability constants (pK) and the metal-ligand stability constants (log K). The findings reveal that the lanthanide metal ions - Ce(III), Pr(III), Nd(III), Sm(III), Gd(III), Dy(III), Yb(III), and Lu(III) - form both 1:1 and 1:2 complexes with the investigated ligands.
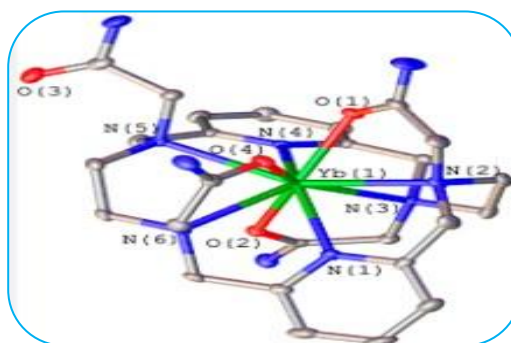
KEYWORDS: *Stability constant, Substituted drugs, Lanthanides (III), Metal-ligand stability, proton-ligand Stability.*

INTRODUCTION

Recent research in coordination chemistry has focused on studying the stability constants of metal-ligand complexes, particularly those involving trivalent metal ions and various organic compounds. Understanding these interactions is crucial for applications in medicine, catalysis, and environmental science. S Muthaiah et al. &T Patekar et al. [1] Organic molecules such as substituted sulphonic acids, isoxazolines, pyrazolines, aromatic ketones, alkyl monoamines, coumarins, and benzothiazoles have been widely investigated due to their ability to form stable complexes with metal ions. V Solov'ev, & J Sattar et al. [2,3]

This study focuses on the stability constants of complexes formed by two specific drugs: Oxymetazoline (Ligand-1), a widely used decongestant, and Amikacin (Ligand-2), an aminoglycoside antibiotic. These drugs were tested for their interactions with trivalent metal ions, including Ce(III), Pr(III), Nd(III), Sm(III), Gd(III), Dy(III), Yb(III), and Lu(III). The stability constants were determined using the pH-metric method, a reliable technique for studying metal-ligand complexes. A Sonar et al, A Vyas et al. & K Sonune et al. [4,5,6]

Experimental Work:

Two ligands were used in this study 1. Oxymetazoline (Ligand-1): 6-tert-butyl-3-(4,5-dihydro-1H-imidazol-2-ylmethyl)-2,4-dimethylphenol.2. Amikacin (Ligand-2): A complex aminoglycoside antibiotic with the formula [(2S)-4-amino-N-[(1R,2S,3S,4R,5S)-5-amino-2-[(2S,3R,4S,5S,6R)-4-amino-3,5-dihydroxy-6-(hydroxymethyl)oxan-2-yl]oxy-4-[(2R,3R,4S,5S,6R)-6-(aminomethyl)-3,4,5-trihydroxyoxan-2-yl]oxy-3-hydroxycyclohexyl]-2-hydroxybutanamide]. Both ligands were synthesised according to previously reported standard methods.[7,8]

Preparation of Solutions:

 Solvent - the ligands were dissolved in a solvent mixture of 70% dioxane and 30% water (v/v), used as the solvent for all experiments.[9] Metal Nitrate Solutions- Rare earth metal nitrates (from BDH Chemicals) were dissolved in perchloric acid. Their concentrations were determined using standard volumetric and spectrophotometric methods1.[10] The solutions were prepared with double-distilled water to ensure purity. Sodium Perchlorate Solution- A 0.1 M sodium perchlorate solution was prepared to maintain constant ionic strength during titration.[11]

Potentiometric Titration

Potentiometric titrations were performed using an Elico (L1-613) pH meter equipped with a combined glass and calomel electrode assembly, ensuring an accuracy of ±0.01 pH units.[12] The instrument was calibrated using 0.05 M potassium hydrogen phthalate (pH 4) and a standard buffer tablet (pH 9).[13]

All titrations were carried out at a constant temperature, maintaining an ionic strength of 0.1 M $NaClO_4$. The total volume of the solutions used was fixed at 50 mL. Metal ions involved in the study included Ce(III), Pr(III), Nd(III), Sm(III), Gd(III), Dy(III), Yb(III), and La(III). Each titration was repeated at least twice to ensure reproducibility.

Titration Protocol

The following solutions were titrated potentiometrically against 0.2 M sodium hydroxide (carbonate-free).
1. Free Acid Solution: 5 mL $NaClO_4$ solution + 5 mL $HClO_4$ solution + 15 mL dioxane solvent + 5 mL distilled water
2. Free Acid with Ligand: 5 mL $NaClO_4$ solution + 5 mL $HClO_4$ solution + 35 mL dioxane solvent + 3 mL distilled water + 2 mL ligand solution
3. Free Acid, Ligand, and Metal Ion: 5 mL $NaClO_4$ solution + 5 mL $HClO_4$ solution + 15 mL dioxane solvent + 1 mL distilled water + 2 mL ligand solution + 2 mL metal ion solution

The Irving and Rossotti method[14] was used to calculate the proton-ligand stability constant (pK) and the metal-ligand stability constant (log β) [1]. The solution's ionic strength was calculated using the formula $\mu = \frac{1}{2}\Sigma C_i Z_i$. The solution's ionic strength was maintained at 0.1 M, accounting for contributions from all ions, including Na^+ and ClO_4^-.

RESULTS AND DISCUSSION
Proton-Ligand Stability Constants

Substituted drugs can be categorized as monobasic acids due to their single replaceable proton originating from the hydroxyl (-OH) group. This group dissociates completely at pH values above 9, making these compounds chemically representable as HL, where H represents the dissociable proton and L represents the remaining molecular structure.

$$HL \leftrightarrow H^+ + L^-$$
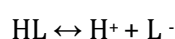
Titration experiments were conducted to study the dissociation and stability of these compounds. The titration data was used to create graphs plotting the volume of sodium hydroxide

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(NaOH) added against pH. These graphs were generated for the acid-ligand system and the acid-ligand-metal system.

From the titration curves, it was observed that ligand curves start deviating from the free acid (HClO4) curves at approximately pH 7, and this deviation continues steadily up to pH 12. This indicates the dissociation of the -OH group in substituted drugs, a key factor in their proton-ligand interaction.

To quantify this dissociation, the degree of protonation, denoted as nA, was calculated at different pH levels using the acid titration curves (curve A) and ligand titration curves (curve B). These calculations were performed using the formula proposed by Irving and Rossotti[14], which is a widely accepted method for such studies.

The proton-ligand stability constants (pK values) were determined by plotting nA against pH. The pK values were specifically calculated using two methods:
1. Half-integral method: In this approach, the pK is determined by identifying the pH at which nA = 0.5.
2. Pointwise calculation method: This involves calculating pK values for each data point, ensuring a more precise result.

The calculated pK values for the studied ligands are summarized in Table 1.

Table 1: Proton-Ligand Stability Constants (pK) at 0.1 M Ionic Strength

Systems	Constant pK	
	Half integral	**Point wise calculation**
Oxymetazoline Ligand-1	11.60	11.63 ± 0.05
Amikacin Ligand-2	11.80	11.82 ± 0.03

The results indicate that Ligand-2 has a higher stability constant compared to Ligand-1. This can be attributed to the presence of a strong electron-withdrawing chlorine (Cl) group in Ligand-2. The Cl group stabilizes the conjugate base, thereby increasing the acidity of Ligand-2. Consequently, Ligand-2 dissociates more readily than Ligand-1. The observed order of dissociation is: Ligand-2 > Ligand-1.

Metal-Ligand Stability Constants

The stability constants of metal-ligand complexes involving Ce(III), Pr(III), Nd(III), Sm(III), Gd(III), Dy(III), Yb(III), and Lu(III) with substituted drugs were determined using the Bjerrum-Calvin pH titration technique, as adapted by Irving and Rossotti. This technique allows for precisely determining stability constants by analyzing the behaviour of metal-ligand interactions in solution.

Evidence of Complex Formation
The formation of metal-ligand complexes was confirmed by the following observations:
1. Titration Curve Deviations:
For Ce(III), Gd(III), and Pr(III), significant deviations in the metal-ligand titration curves from the ligand-only curves were observed starting at pH 3.
For Nd(III), Yb(III), Sm(III), and Lu(III), deviations began at pH 4.5.
For Dy(III), the deviation occurred at pH 5.

2. Color Changes:
The solutions displayed distinct colour changes, transitioning from yellowish-white to light brown and eventually to dark brown as the pH increased from 2.5 to 8.5.

These deviations and colour changes indicate the release of protons during chelation, confirming the formation of stable metal-ligand complexes.

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CALCULATION OF STABILITY CONSTANTS

The primary stability constant (log K1) and secondary stability constant (log K2) were calculated from the formation curves. These constants correspond to specific values of n, with n = 0.5 for log K1 and n = 1.5 for log K2. The calculated stability constants are shown in Table 2.

Table 2: Metal-Ligand Stability Constants (log K) at 0.1 M Ionic Strength

System	Constant	
	$logK_1$ i.e. pL_1	$logK_2$ i.e. pL_2
Ce (III) Ligand-1	07.65	09.75
Pr (III) Ligand-1	08.50	10.15
Nd (III) Ligand-1	08.90	09.95
Sm (III) Ligand-1	07.60	10.25
Gd(III) Ligand-1	09.95	10.98
Dy (III) Ligand-1	08.15	10.35
Yb (III) Ligand-1	07.15	09.97
Lu (III) Ligand-1	08.05	10.55
Ce (III) Ligand-2	07.95	10.21
Pr (III) Ligand-2	0734	10.84
Nd (III) Ligand-2	09.04	10.34
Sm (III) Ligand-2	07.23	09.78
Gd(III) Ligand-2	09.74	11.74
Dy (III) Ligand-2	07.37	09.97
Yb (III) Ligand-2	08.57	10.27
Lu (III) Ligand-2	09.26	10.66

The data shows that the difference between log K1 and log K2 is relatively small, suggesting a trans-structure for the complexes. This structure facilitates the addition of secondary ligands without steric hindrance, as indicated by the positive ratio of log K1/log K2 for all systems.

Stability Trends

The order of stability for metal-ligand complexes based on log K1 is as follows:
1. Ligand-1:
Gd > Nd > Pr > Dy > Lu > Ce > Sm > Yb
2. Ligand-2:
Gd > Lu > Nd > Yb > Ce > Dy > Pr > Sm

These results align with prior research by Tambatkar et al[15]. and Y.K. Meshram et al[6]., further validating the observed trends.

Table 3: Differences in Stability Constants

System	$logK_2 - logK_1$	$logK_2 / logK_1$
Ce (III) Ligand-1	02.10	01.27
Ce (III) Ligand-2	02.26	01.28
Pr (III) Ligand-1	01.65	01.19
Pr (III) Ligand-2	03.50	01.47
Nd (III) Ligand-1	01.05	01.11
Nd (III) Ligand-2	01.30	01.14
Sm (III) Ligand-1	02.65	01.35
Sm (III) Ligand-2	02.55	01.35
Gd(III) Ligand-1	01.43	01.15
Gd(III) Ligand-2	02.00	01.21

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Dy (III) Ligand-1	02.20	01.27
Dy (III) Ligand-2	02.60	01.35
Yb (III) Ligand-1	02.82	01.39
Yb (III) Ligand-2	01.70	01.20
Lu (III) Ligand-1	02.50	01.31
Lu (III) Ligand-2	01.40	01.15

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