



# SYNTHESIS OF TERNARY COMPLEXES OF RARE EARTH WITH SCHIFF BASE FROM 4-AMINOANTIPYRINE AND SOME AMINO ACIDS

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## ABSTRACT

The mixed ligand metal complexes of lanthanum (III) and cerium (III) with Schiff base derived from 4-aminoantipyrine and some amino acids, viz. L-tyrosine, L-cysteine, L-alanine and L-histidine have been synthesized and studied. These complexes have been characterized on the basis of elemental analysis, conductivity data, magnetic susceptibility measurements, spectral methods and thermal analysis data. The Schiff base 2, 3-dimethyl-1-phenyl-4-salicylidene-3-pyrazolin-5-one (HL) acts as a primary ligand and amino acids act as a secondary ligand which coordinates through the carboxylate oxygen and the amino nitrogen. The rare earth complexes were screened for their antimicrobial activities and exhibited the potent biological activities.

**Keywords:** Ternary Complexes, Rare Earth, Schiff base, Amino acids, Biological Activity

## INTRODUCTION

The study of rare earth complexes with organic ligands is gaining significant importance in recent years<sup>1-3</sup>. Rare earth ions possess the properties of antibacterial<sup>4</sup>, antitumor<sup>5</sup> and antiviral<sup>6</sup> agents when co-ordinated with organic ligands and participate effectively in many important life processes. Many researchers have studied preparation, characterization, antimicrobial, and toxicological activity of mixed ligand complexes of transition metal, lanthanide metal and actinide metal ions<sup>7-10</sup>. The ternary complexes of the Schiff bases and amino acids with metal ions bear the importance in recent years. The literature survey revealed that mixed ligand complexes of some

transition metals with amino acids have been studied for their preparation, characterization and biological importance<sup>11-12</sup>.

Lanthanide complexes have been studied for their interesting and important properties like their reversibly ability to bind oxygen, catalytic activity in hydrogenation of olefins, structural probes in biological systems<sup>13</sup>. Lanthanides (III) with ionic radii of 1.06-0.85 Å and +3 charge fulfill the optimum conditions for higher coordination<sup>14</sup>. However, there is a continuing interest in mixed ligand metal complexes of Schiff bases and some nitrogen and / or oxygen donor ligands due to their unusual magnetic properties, novel structural features and relevance to the biological system.

In recent years, there has been a considerable interest in the chemistry of antipyrine and its derivatives. Antipyrine derivatives are reported to exhibit analgesic, anti-inflammatory, antiviral, antibacterial effect and also have been used as hair colour additives<sup>15-17</sup>. These compounds have been widely used in spectrophotometric determination of metal ions. Antipyrine Schiff base derivative can serve as antiparasitic agents and their complexes with platinum (II) and cobalt (II) ions have been shown to act antitumor substances<sup>18</sup>. This prompted us to synthesis the Schiff base ligand from 4-aminoantipyrine.

We report herein the synthesis, characterization and antibacterial studies of the ternary complexes of lanthanum (III) and cerium (III) with 2, 3-dimethyl-1-phenyl-4-salicylidene-3-pyrazolin-5-one (HL) and amino acids. The amino acids used were L-tyrosine, L-cysteine, L-alanine and L- histidine. The complexes were characterized based on elemental analysis, molar conductivity, spectroscopic methods, and thermal studies. The complexes were screened for their *in-vitro* antibacterial activity.

## 1 EXPERIMENTAL:

### 1.1 Materials

Lanthanum nitrate hexahydrate, cerium nitrate hexahydrate, L-tyrosine, L-cysteine, L-alanine, L-histidine, 4-aminoantipyrine and salicylaldehyde were obtained from S.D. Fine Chemicals, Mumbai and used as supplied. Solvents like methanol, ethanol, dimethylformamide and dimethylsulphoxide whenever used were distilled and purified according to standard procedures<sup>19</sup>.

### 1.2 Measurement Techniques

The content of elements (C, H, N, S) were obtained on ThermoFinnigan, Elemental Analyzer, Model No. FLASH EA 1112 at Sophisticated Analytical Instrumentation facility (SAIF), IIT, Bombay. The metal content was estimated gravimetrically<sup>20, 21</sup>. The conductance measurements were carried out on an Equiptronics Auto ranging Conductivity Meter. Magnetic susceptibility measurements for all the complexes reported in the present study were recorded at room temperature by the Gouy's method using Hg [Co (SCN)<sub>4</sub>] as a calibrant. The electronic spectra of the complexes were recorded in DMSO solution (10<sup>-3</sup> M) on a Shimadzu UV/VIS-160 Spectrophotometer. Infrared spectra of the ligand and all metal complexes were recorded in KBr disc on a Perkin-Elmer FTIR Spectrophotometer in the region 4000-400 cm<sup>-1</sup>. The thermal analysis of the complexes were carried out in controlled nitrogen atmosphere on a Perkin-Elmer Diamond TG-DTA instrument at Sophisticated

Analytical Instrumentation facility (SAIF), IIT, Bombay by recording the change in weight of the complexes on increasing temperature up to 900°C at the heating rate of 10°C per minute.

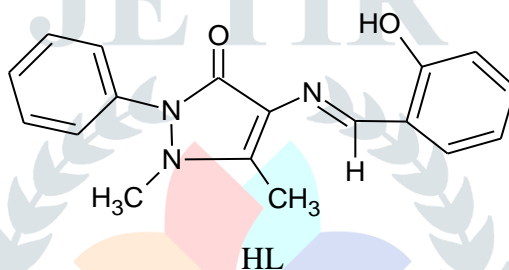
The antibacterial activity of the ligands and complexes was evaluated by agar cup and tube dilution methods using Muller-Hinton agar medium<sup>22</sup>. The antibacterial effect was studied after 24 h incubation at 37°C. The MIC of the complexes was studied in liquid Muller-Hinton medium. Test compounds were dissolved to different concentrations in nutrient broth. The MIC was determined after 24 h incubation at 37°C.

### 1.3 Synthesis of Schiff Base (HL)

The Schiff base ligand was prepared from condensation between 4-aminoantipyrine and salicylaldehyde yields 2, 3-dimethyl-1-phenyl-4-salicylidene-3-pyrazolin-5-one (HL).

Equimolecular amounts of salicylaldehyde and 4-aminoantipyrine were mixed in ethanol and refluxed for 3 h, then cooled. The Schiff base obtained was filtered, washed with ethanol and dried under vacuum.

The Schiff base was purified by re-crystallization from ethanol and washed thoroughly with diethyl ether.



### 1.4 Synthesis of Ternary Complexes

All the complexes were prepared by the following general procedure:

To a hot methanol solution (25 cm<sup>3</sup>) of 2, 3-dimethyl-1-phenyl-4-salicylidene-3-pyrazolin-5-one (HL) (1mmol), an aqueous solution (10 cm<sup>3</sup>) of metal salt (1mmol) was added. To this hot solution, an aqueous/alcoholic solution (10 cm<sup>3</sup>) of amino acids (1 mmol) was added with constant stirring. The mixture (1:1:1 molar proportion) was again heated till it reaches to boiling. The complexes were obtained by raising pH of the reaction mixture by adding dilute ammonia solution. The mixture was cooled and solid complexes obtained were filtered, washed with water, methanol and then with diethyl ether. The complexes thus prepared were dried under vacuum.

Ternary complexes of La (III) were prepared from lanthanum (III) nitrate hexahydrate with 2, 3-dimethyl-1-phenyl-4-salicylidene-3-pyrazolin-5-one(HL) as a primary ligand and amino acids (AA) such as L-tyrosine and L-cysteine as secondary ligands. Similarly ternary complexes of Ce (III) were prepared from cerium (III) nitrate hexahydrate with 2, 3-dimethyl-1-phenyl-4-salicylidene-3-pyrazolin-5-one(HL) as a primary ligand and amino acids (AA) such as L-alanine and L-histidine as secondary ligands.

L is deprotonated primary ligand whereas secondary ligand Tyr, Cys, Ala and His represents deprotonated L-Tyrosine, L-Cysteine, L-Alanine and L-Histidine respectively.

**Table 1 :Molecular Weight, Colour and Decomposition Temperature of La (III) and Ce (III) Complexes**

Complex	Empirical Formula	Molecular Weight	Colour	Decomposition Temperature (° C)
[La (L) (Tyr) NO <sub>3</sub> ] · 2H <sub>2</sub> O	C <sub>27</sub> H <sub>30</sub> LaN <sub>5</sub> O <sub>10</sub>	723.46	Yellow	180
[La (L) (Cys) NO <sub>3</sub> ] · 2H <sub>2</sub> O	C <sub>21</sub> H <sub>26</sub> LaN <sub>5</sub> O <sub>9</sub> S	663.43	Light Yellow	180
[Ce (L) (Ala) NO <sub>3</sub> ] · 2H <sub>2</sub> O	C <sub>21</sub> H <sub>26</sub> CeN <sub>5</sub> O <sub>9</sub>	632.57	Light Brown	220
[Ce (L) (His) NO <sub>3</sub> ] · 2H <sub>2</sub> O	C <sub>24</sub> H <sub>28</sub> CeN <sub>7</sub> O <sub>9</sub>	698.63	Dark Brown	180

## 2 RESULT AND DISCUSSION

The reaction of Schiff base ligand (HL) as primary ligand and different amino acids as secondary ligands with rare earth salts yielded different ternary complexes.

All the complexes are non-hygroscopic, stable solids, insoluble in water and in common organic solvents such as ethyl alcohol, acetone, chloroform, etc., but moderately soluble in DMF and DMSO

### 2.1 Elemental Analysis and Conductance Measurement

Elemental analysis data shows that, rare earth metal salts react with a primary ligand Schiff base (HL) and secondary the participation of the nitrogen atom of the azomethine group in coordination<sup>11</sup>. A broad vibration band at 3284 cm<sup>-1</sup> in the free ligand is assigned to the phenolic OH group. The disappearance of this peak in the spectra of all the complexes indicates the deprotonation of phenol proton prior to coordination. The stretching frequency due to N-N in free ligand was observed at 1034 cm<sup>-1</sup> is slightly affected in all metal complexes. This indicates the non-involvement of this linkage in coordination to the central metal ion. An important feature of infrared spectra of the metal complexes is the absence of band due to O-H stretching vibrations of either the free -OH group of 2, 3-dimethyl-1-phenyl-4-salicylidene-3-pyrazolin-5-one (HL) or of the -COOH group of the amino acid. This observation leads to the conclusion that the complex formation takes place by deprotonation of hydroxyl group of HL and carboxylic group of the amino acid moiety<sup>11</sup>.

Broad band observed in the region between 3376-3284 cm<sup>-1</sup> due to asymmetric and symmetric O-H stretching modes and a weak band in the range 1579-1574 cm<sup>-1</sup> due to H-O-H bending vibrations indicating presence of water molecules, further confirmed by thermal studies.

Broad band observed at 3040cm<sup>-1</sup> and 2960cm<sup>-1</sup> due to N-H (asymmetric) and N-H (symmetric) vibrations of free amino acid moiety are shifted to higher wave numbers in the range 3165-3130 cm<sup>-1</sup> and 3060-3050 cm<sup>-1</sup> respectively in the spectra of metal complexes, suggesting coordination of the amino group through nitrogen with the metal ion.

The vsymmetric (COO-) mode observed at ~1400 cm<sup>-1</sup> in the spectra of free amino acids is found to be shifted to lower wave number in the range of 1393-1303 cm<sup>-1</sup>, in the spectra of complexes indicating the coordination of carboxylic acid group via oxygen with the metal ion.

The C-N symmetrical stretching frequency observed at  $\sim 950\text{ cm}^{-1}$  in the spectra of amino acids is found to be shifted to lower wave numbers in the range of  $917\text{-}898\text{ cm}^{-1}$  in the spectra of the complexes, confirming coordination through the amino group of the amino acids. The presence of hydroxyl group in the molecule of carboxylic acid is readily established by the observation of intense band due to O-H stretching vibrations in the region  $3650\text{-}3200\text{ cm}^{-1}$ . The absence of bands due to O-H stretching vibrations in the metal complexes can be used as evidence for replacement of proton of hydroxyl group and bonding via oxygen atom to the metal ion. Some new bands of weak intensity observed in the regions of  $768\text{-}763\text{ cm}^{-1}$  and  $550\text{-}470\text{ cm}^{-1}$  may be ascribed to the M-O and M-N vibrations respectively. The M-O bond has much less covalent character than the M-N bond so the stretching bands of the former appear in high frequency region.

## 2.2 Thermal Analysis

The thermal behavior of the studied rare earth complexes was investigated by TG and DTA techniques. The thermogram indicates that the complexes are pretty stable to varying temperature. All the complexes show the gradual loss in weight due to decomposition with increasing temperature.

**Table 4: Characteristic Infrared Spectral Bands ( $\text{cm}^{-1}$ ) of La (III) and Ce (III) Complexes**

Comp lex	$\nu$ (O- H) H <sub>2</sub> O	$\nu$ (N- H) Asy m (A. a.)	$\nu$ (N- H) Sym . (A. a.)	$\nu$ (C= O) (HL ) (A. a.)	$\nu$ (C= N) (HL )	$\nu$ (C- O) (A. a.)	$\nu$ (C- O) (H L)	$\nu$ (N- N) (H L)	$\nu$ (C- N) (M- O)	$\nu$ (M- N)	$\nu$ (NO <sub>3</sub> )	
[La (L) (Tyr) NO <sub>3</sub> ] ·2H <sub>2</sub> O	3320 (b)	3130 (w)	3060 (w)	1594 (s)	1445 (m)	1393 (w)	115 2 (m)	106 0 (w)	917 (w)	766 (m)	470 (w)	1267( w) 963(w )
[La (L) (Cys) NO <sub>3</sub> ] ·2H <sub>2</sub> O	3376 (b)	3140 (w)	3050 (w)	1592 (s)	1451 (s)	1328 (m)	115 0 (m)	103 7 (m)	898 (w)	763 (m)	480 (w)	1297( m) 898 (m)
[Ce (L)	3284 (b)	3165 (w)	3054 (w)	1609 (s)	1491 (m)	1307 (m)	113 9	106 8	916 (w)	768 (m)	550 (w)	1269( m)

(Ala) NO <sub>3</sub> ·2H <sub>2</sub> O							(m)	(m)				935(m)
[Ce (L) (His) NO <sub>3</sub> ·2H <sub>2</sub> O	3331 (b)	3130 (w)	3050 (w)	1593 (s)	1451 (m)	1303 (m)	114 1 (m)	107 5 (m)	902 (w)	768 (m)	473 (w)	1253(m) 902(w)

Where, s: strong, m: medium, b: broad, w: weak

The decomposition products have been identified on the basis of percentage weight loss observed. The thermograms of complexes shows the first decomposition at initial stage in the temperature range of 25-180 °C corresponding to loss of two molecules of lattice water. This followed by decomposition of organic ligand and amino acid moiety in the range of 270-900 °C. The final stage of decomposition observed corresponding to the weight loss of NO<sub>3</sub>, CO<sub>2</sub>, etc. The weight loss of these prepared complexes exhibited a good agreement with proposed stoichiometry of metal and ligands. The DTA of the complexes shows a small endothermic peak in the range of 170-200 °C indicates the presence of water molecule.

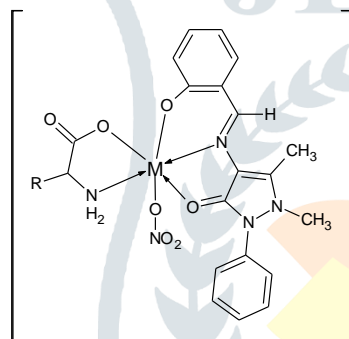
A broad exothermic peak at increased temperature attributed to the decomposition of Schiff base Ligand (HL) moiety, nitrate group and amino acid moiety present in the complexes. The probable assignment to the expelled groups due to decomposition of the complexes is proposed on the basis careful examination of TG and DTA and summarized in table 5.

**Table 5: Thermal Data of La (III) and Ce (III) Complexes**

Complex	Temperature Range (° C)	% Weight Loss		Assignment of the expelled group
		Found	Calculated	
[La (L) (Tyr) NO <sub>3</sub> ] · 2H <sub>2</sub> O	25-180	7.03	7.46	Two molecules of lattice water and one molecule of water from amino acid
	180-310	24.66	24.88	C <sub>7</sub> H <sub>4</sub> NO from ligand and one molecule of NO <sub>3</sub>
	310-500	28.7	25.85	C <sub>11</sub> H <sub>11</sub> N <sub>2</sub> O from ligand
	500-900	5.72	6.08	CO <sub>2</sub> from amino acid
[La (L) (Cys) NO <sub>3</sub> ] · 2H <sub>2</sub> O	25-180	8.99	7.69	Two molecules of lattice water and CH <sub>3</sub> from ligand
	180-900	43.02	43.86	C <sub>17</sub> H <sub>13</sub> N <sub>3</sub> O <sub>2</sub> from ligand

[Ce (L) (Ala) NO <sub>3</sub> ] · 2H <sub>2</sub> O	30-280	18.71	17.71	Two molecules of lattice water and C <sub>6</sub> H <sub>4</sub> from ligand
	280-905	28.63	31.3	C <sub>12</sub> H <sub>12</sub> N <sub>3</sub> from ligand
	905-1040	27.37	23.71	C <sub>3</sub> H <sub>6</sub> NO <sub>2</sub> of amino acid and one molecule of NO <sub>3</sub>
[Ce (L) (His) NO <sub>3</sub> ] · 2H <sub>2</sub> O	25-180	6.00	5.15	Two molecules of lattice water
	180-900	46.45	47.81	C <sub>18</sub> H <sub>16</sub> N <sub>3</sub> O from ligand and CO <sub>2</sub> from amino acid

On the basis of elemental analysis data and various physico-chemical studies, coordination number six is proposed for Cerium (III) complexes. The bonding and structure for the Cerium (III) complexes may be represented as shown in figure 1



M= La, Ce and R= -CH<sub>2</sub>-C<sub>6</sub>H<sub>4</sub>OH (Tyr), -CH<sub>2</sub>SH (Cys), -CH<sub>3</sub> (Ala), -CH<sub>2</sub>C<sub>3</sub>H<sub>3</sub>N<sub>2</sub>(His)

Figure 1 Proposed General Structure of M L-AA complexes

### 2.3 Antibacterial Study

The antibacterial activities of the complexes were evaluated by the agar cup method using tetracycline as a standard against the bacteria *Staphylococcus aureus*, *Corynebacterium diphtheriae*, *Pseudomonas aeruginosa* and *Escherichia coli*. The results, expressed as the diameter of growth inhibition area in millimeters, are given in Table 6. The minimum inhibitory concentration (MIC) of the test sample which is expressed in µg /cm<sup>3</sup> was determined by using Mueller-Hinton culture medium, are given in Table 7.

**Table 6: Antibacterial Activity of La (III) and Ce (III) Complexes by agar cup method**

Complex	Antibacterial Activity (mm)			
	<i>S. aureus</i>	<i>C. diphtheriae</i>	<i>P. aeruginosa</i>	<i>E. coli</i>
[La (L) (Tyr) NO <sub>3</sub> ] · 2H <sub>2</sub> O	14	11	11	16
[La (L) (Cys) NO <sub>3</sub> ] · 2H <sub>2</sub> O	13	13	12	14
[Ce (L) (Ala) NO <sub>3</sub> ] · 2H <sub>2</sub> O	13	12	12	14

[Ce (L) (His) NO <sub>3</sub> ] · 2H <sub>2</sub> O	14	13	12	15
Tetracycline	30	25	26	18

**Table 7: Antibacterial Activity of La (III) and Ce (III) Complexes by tube dilution method**

Complex	MIC (µg/cm <sup>3</sup> )			
	<i>S. aureus</i>	<i>C. diphtheriae</i>	<i>P. aeruginosa</i>	<i>E. coli</i>
[La (L) (Tyr) NO <sub>3</sub> ] · 2H <sub>2</sub> O	300	400	400	300
[La (L) (Cys) NO <sub>3</sub> ] · 2H <sub>2</sub> O	300	450	400	300
[Ce (L) (Ala) NO <sub>3</sub> ] · 2H <sub>2</sub> O	350	450	450	250
[Ce (L) (His) NO <sub>3</sub> ] · 2H <sub>2</sub> O	350	450	400	300
HL	450	500	450	400

The antimicrobial activity results indicate that lanthanum (III) and cerium(III) complexes exhibit good antimicrobial activity against *S. aureus*, *C. diphtheriae*, *P. aeruginosa* and *E. coli*, especially against *E. coli*. The complexes have better antibacterial activity than that of each ligand.

The enhancement in the activity is rationalized on the basis of the structures of the ligands by possessing an additional azomethine (C=N) linkage which is significant in determining the mechanism of transamination and resamination reaction in biological system<sup>24, 25</sup>. The ligand with nitrogen and oxygen donor system might inhibit enzyme production, since the enzymes which requires these groups for their activity appear to be more liable to deactivation by metal ions upon chelation.

## CONCLUSIONS:

In conclusion, we have reported the synthesis of ternary complexes of rare earth metals with Schiff base derived from 4-aminoantipyrine and some amino acids. All the complexes were characterized and it is found that the Schiff base participated in the bonding to metal as monobasic tridentate ONO ligand and the amino acids as monobasic bidentate ligand by deprotonation of the Schiff base phenolic OH and the amino acid COOH. The correlation of the elemental analysis data and various physico-chemical studies, coordination number six is proposed for the complexes. These complexes exhibit excellent antibacterial ability against *S. aureus*, *C. diphtheriae*, *P. aeruginosa* and *E. coli*. Thus the rare earth complexes can hopefully become a novel kind of drugs.



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