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Synthesis, characterization and antibacterial properties of the ternary complexes of cerium with Schiff base derived from 4-aminoantipyrine and some amino acids

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ABSTRACT

The ternary complexes of cerium (III) with 2, 3-dimethyl-1-phenyl-4-salicylidene-3-pyrazolin-5-one and some amino acids, viz. L-tryptophan, L-tyrosine, L-cysteine, L-leucine and L-serine have been synthesized. 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 acts as secondary ligand which coordinates through the carboxylate oxygen and the amino nitrogen. These complexes were screened for their antimicrobial activities and show the potent biological activities against Staphylococcus aureus, Corynebacterium diphtheriae, Pseudomonas aeruginosa and Escherichia coli.

Keywords: Ternary complexes, Cerium, Schiff base, Amino acids, Antimicrobial activity

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INTRODUCTION

Metal complexes are gaining importance in recent years particularly in the design of repository, slow release or long acting drug in nutrition and in the study of metabolism [1]. Metal ions are known to accelerate the drug action [2]. Mixed ligand complexes are well known to play an important role in biological processes [3-5]. Many researchers have extensively investigated metal complexes of biologically active ligands [6, 7]. The literature survey revealed that mixed ligand complexes of some transition metals with amino acids have been studied for their synthesis, characterization and biological importance [8, 9]. Ternary complexes containing an amino acid as a secondary ligand have significance as they are potential models for enzyme metal ion substrate complexes [10].

Rare earth ions possess the properties of antibacterial [11], antitumor [12] and antivirus [13] agents when co-ordinate 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 [14-17]. 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 [18]. Lanthanides (III) with ionic radii of 1.06-0.85 Å and +3 charge fulfill the optimum conditions for higher coordination [19]. Lanthanide (III) salts have been reported to exert moderate effects against proliferation in vitro and in vivo. 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. Hence it is required to develop new series of mixed ligand complexes with various metals and understand their role in biological processes.

Antipyrine derivatives are reported to exhibit analgesic, anti-inflammatory, antiviral, antibacterial effect and also have been used as hair colour additives [20-22]. These compounds have been widely used in spectrophotometric determination of metal ions. Antipyrine Schiff base derivative can serve as anti-parasitic agents and their complexes with platinum (II) and cobalt (II) ions have been shown to act antitumor substances [23]. This encouraged us to synthesis the Schiff base ligand from 4-aminoantipyrine.

Herein we report the synthesis, characterization and biological studies of the ternary complexes of cerium (III) with 2, 3-dimethyl-1-phenyl-4-salicylidene-3-pyrazolin-5-one (HL) and amino acids. The amino acids used were L-tryptophan, L-tyrosine, L-cysteine, L-leucine and L-serine. The complexes were characterized based on elemental analysis, molar conductivity, spectroscopic methods and thermal studies. The complexes were screened for their biological activities.

MATERIALS AND METHODS

2.1. Materials

The chemicals used were of analytical grade and used without further purification. Ce (III) as cerium nitrate hexahydrate salt, L-tryptophan, L-tyrosine, L-serine, L-cysteine, L-leucine, 4-aminoantipyrine and salicylaldehyde were obtained from S.D. Fine Chemicals, Mumbai. The organic solvents whenever used were distilled and purified according to standard procedures [24].

2.2. Measurement Techniques

The content of elements (C, H, N, S) were obtained on Thermo Finnigan, Elemental Analyzer, Model No. FLASH EA 1112 at Sophisticated Analytical Instrumentation Facility (SAIF), IIT, Bombay. The metal content was estimated gravimetrically [25, 26]. 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) $_4$] as a calibrant. The electronic spectra of the complexes were recorded in DMSO solution (10^{-3} 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^{-1}. 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^{o}C at the heating rate of 10^{o}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 [27]. The antibacterial effect was studied after 24 h incubation at 37 ^{o}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 ^{o}C.

2.3. Synthesis of 2, 3-dimethyl-1-phenyl-4-salicylidene-3-pyrazolin-5-one (HL)

The organic Schiff base ligand (HL) was prepared from condensation between salicylaldehyde and 4-aminoantipyrine.

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.

2.4. Synthesis of Ternary Complexes

The 1:1:1 [M:HL:AA] complexes were prepared from cerium (III) nitrate hexahydrate, 2,3-dimethyl-1-phenyl-4-salicylidene-3-pyrazolin-5-one (HL) as a primary ligand and some amino acids (AA) such as L-tryptophan, L-tyrosine, L-cysteine, L-leucine and L-serine as secondary ligands.

The cerium (III) complexes were prepared by the following general procedure:

To a solution of 2, 3-dimethyl-1-phenyl-4-salicylidene-3-pyrazolin-5-one (HL) (1mmol) in hot methanol (25 cm^3), an aqueous solution (10 cm^3) of cerium (III) nitrate hexahydrate (1mmol) was added. To this solution, an aqueous/alcoholic solution (10 cm^3) of amino acids (1mmol) was added with constant stirring. The mixture (1:1:1 molar proportion) was again heated for about 10 minutes 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.

RESULTS AND DISCUSSION

The reactions of Schiff base ligand (HL) as a primary ligand and some amino acids as secondary ligands with cerium (III) nitrate hexahydrate salt yielded different ternary complexes. The following representative equation illustrates the formation of ternary complexes:

$$Ce(NO_3)_3 \cdot 6H_2O + HL + AA \longrightarrow [Ce(L)(AA)NO_3] \cdot 2H_2O + 2HNO_3 + 4H_2O$$

Where, L is deprotonated 2, 3-dimethyl-1-phenyl-4-salicylidene-3-pyrazolin-5-one as ONO donor primary ligand, and AA is different amino acids as deprotonated N and / or O donor secondary ligands.

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.

Table 1 Molecular Weight, Colour and Decomposition Temperature of Cerium (III) Complexes

Complex	Empirical Formula	Molecular Weight	Colour	Decomposition Temperature (^oC)
[Ce (L) (Trp) NO_3] ·$2H_2O$	$C_{29}H_{31}CeN_6O_9$	747.7	Light Brown	240
[Ce (L) (Tyr) NO_3] ·$2H_2O$	$C_{27}H_{30}CeN_5O_{10}$	724.67	Brown	230
[Ce (L) (Cys) NO_3] ·$2H_2O$	$C_{21}H_{26}CeN_5O_9S$	664.64	Light Brown	245
[Ce (L) (Leu) NO_3] ·$2H_2O$	$C_{24}H_{32}CeN_5O_9$	674.65	Light Brown	233
[Ce (L) (Ser) NO_3] ·$2H_2O$	$C_{21}H_{26}CeN_5O_{10}$	648.57	Brown	175

Where Trp, Tyr, Cys, Leu and Ser represents L-tryptophan, L-tyrosine, L-cysteine, L-leucine and L-serine respectively

3.1 Elemental analysis and conductance measurement

The results of elemental analysis data shows that, cerium (III) nitrate hexahydrate reacts with a primary ligand 2,3-dimethyl-1-phenyl-4-salicylidene-3-pyrazolin-5-one and secondary ligands L-tryptophan, L-tyrosine, L-cysteine, L-leucine and L-serine in the proportion 1:1:1 to form complexes of the type [Ce (L) (AA) NO_3]·$2H_2O$. The molar conductance values of these complexes in DMSO fall in the range of 9 to 16 Mhos cm^2 mol^{-1}, indicating their non-electrolytic nature. According to the configuration of cerium atom, the compounds are expected to be paramagnetic as it has unpaired electron. The magnetic moments of the cerium (III) complexes were calculated from the measured magnetic susceptibilities after employing diamagnetic corrections which revealed their paramagnetic nature. The observed values for effective magnetic moment (μ_{eff}) are found to be in the range of 1.81 to 1.87 B.M.

Table 2 Elemental Analysis Data, Molar Conductance and Magnetic Moments of Cerium (III) Complexes

Complex	Elemental Analysis Found (Calculated)					Molar Conductance (Mhos cm^2 mol^{-1})	μ_{eff} (B.M.)
	% C	% H	% N	% S	% M		
[Ce (L) (Trp) NO_3] ·$2H_2O$	46.89 (46.57)	4.23 (4.18)	11.93 (11.24)	---	18.45 (18.75)	9	1.85
[Ce (L) (Tyr) NO_3] ·$2H_2O$	44.29 (44.73)	4.35 (4.18)	9.18 (9.67)	---	19.25 (19.34)	13	1.84
[Ce (L) (Cys) NO_3] ·$2H_2O$	37.92 (37.94)	3.89 (3.94)	10.13 (10.54)	4.23 (4.81)	21.55 (21.09)	16	1.87
[Ce (L) (Leu) NO_3] ·$2H_2O$	41.75 (42.71)	4.20 (4.78)	10.19 (10.38)	---	20.65 (20.78)	13	1.81
[Ce (L) (Ser) NO_3] ·$2H_2O$	38.83 (38.87)	4.13 (4.04)	10.63 (10.80)	---	21.45 (21.62)	10	1.86

3.2 Infrared spectra and mode of bonding

The IR spectra of the complexes are compared with that of the free ligand to determine the changes that might have taken place during the complexation. The band at 1655 cm^{-1} is characteristic of the carbonyl group present in the Schiff base ligand. This group was shifted to lower frequency (50-59 cm^{-1}) in all complexes indicating the involvement of the carbonyl oxygen in coordination [28]. The band assigned to azomethine group in the free Schiff base ligand was observed at 1503 cm^{-1} and shifted to lower frequency in all metal complexes (43-58 cm^{-1}). This indicates the participation of the nitrogen atom of the azomethine group in coordination [29]. A broad vibration band at 3284 cm^{-1} 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^{-1} 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-5one (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 [8]. Broad band observed in the region between 3329-3280 cm^{-1} due to asymmetric and symmetric O–H stretching modes and a weak band in the range 1579-1574 cm^{-1} due to H–O–H bending vibrations indicating presence of water molecules, further confirmed by thermal studies.

Broad band observed at 3040 cm^{-1} and 2960 cm^{-1} due to N-H (asymmetric) and N-H (symmetric) vibrations of free amino acid moiety are shifted to higher wave numbers in the range 3150-3135 cm^{-1} and 3055-2967 cm^{-1} respectively in the spectra of metal complexes, suggesting coordination of the amino group through nitrogen with the metal ion.
The νasymmetric (COO^-) band of free amino acids i.e. 1610-1590 cm^{-1} is shifted in the range 1605-1596 cm^{-1} and the νsymmetric (COO^-) mode observed at ~1400 cm^{-1} in the spectra of free amino acids is found to be shifted to lower wave number in the range of 1385-1303 cm^{-1}, 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 ~950 cm^{-1} in the spectra of amino acids is found to be shifted to lower wave numbers in the range of 917-899 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 3650-3200 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 768-748 cm^{-1} and 535-470 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.

Table 3 Characteristic Infrared Spectral Bands (cm^{-1}) of Cerium (III) Complexes

Complex	ν (O-H) H_2O	ν (N-H) Asym (A. a.)	ν (N-H) Sym. (A. a.)	ν (C=O) (HL) (A. a)	ν (C=N) (HL)	ν (C-O) (A. a.)	ν (C-O) (HL)	ν (N-N) (HL)	ν (C-N)	ν (M-O)	ν (M-N)	ν (NO_3)
[Ce (L) (Trp) NO_3] ·$2H_2O$	3280 (b)	3150 (w)	3055 (w)	1605 (s)	1445 (m)	1382 (w)	1151 (m)	1043 (w)	912 (w)	748 (m)	535 (w)	1231(m) 920(w)
[Ce (L) (Tyr) NO_3] ·$2H_2O$	3320 (b)	3135 (w)	3055 (w)	1596 (s)	1445 (m)	1385 (w)	1152 (s)	1060 (m)	905 (w)	760 (m)	480 (m)	1240(w) 930 (w)
[Ce (L) (Cys) NO_3] ·$2H_2O$	3286 (b)	3140 (w)	3050 (w)	1599 (s)	1451 (s)	1303 (m)	1151 (m)	1038 (m)	899 (w)	755 (m)	470 (w)	1290(m) 899(w)
[Ce (L) (Leu) NO_3] ·$2H_2O$	3329 (b)	3140 (w)	2967 (w)	1603 (s)	1460 (m)	1384 (m)	1147 (s)	1034 (m)	903 (w)	755 (m)	480 (w)	1201(m) 903(w)
[Ce (L) (Ser) NO_3] ·$2H_2O$	3295 (b)	3135 (w)	3055 (w)	1598 (s)	1445 (m)	1308 (m)	1141 (m)	1052 (m)	917 (w)	768 (m)	470 (w)	1257(w) 893(m)

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

3.3 Thermal analysis

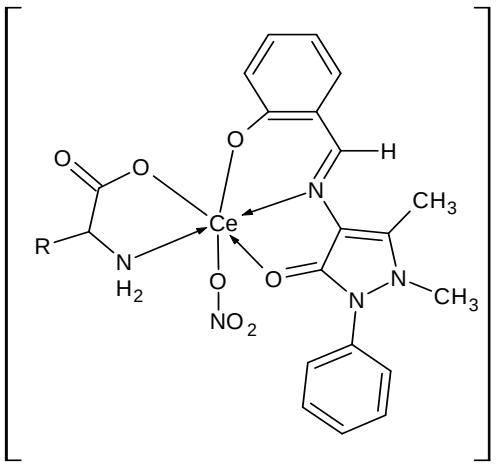
The thermal behavior of the cerium (III) complexes was investigated by TG and DTA techniques. The thermogram indicates that the complexes are pretty stable to varying temperature. All the complexes show the gradual loss in weight due to decomposition with increasing temperature. The decomposition products have been identified on the basis of percentage weight loss observed. The thermograms of cerium (III) complexes shows the first decomposition at initial stage in the temperature range of 25-275 ^{0}C corresponding to loss of two molecules of lattice water and decomposition of the ligand. This loss in weight followed by decomposition of organic ligand and amino acid moiety in the range of 250-900 ^{0}C.The final stage of decomposition observed corresponding to the weight loss of NO_3, CO_2, etc. The weight loss of these prepared complexes exhibited a good agreement with proposed stiochiometry of metal and ligands.

Table 4 Thermal Data of Cerium (III) Complexes

Complex	Temperature Range (º C)	% Weight Loss		Assignment of the expelled group
		Found	Calculated	
[Ce (L) (Trp) NO_3] ·2H_2O	25-250	9.32	8.83	Two molecules of lattice water & Two molecules of CH_3 from ligand
	250-905	37.36	36.91	$C_{10}H_{10}N_3O_2$ from ligand
	905-1040	3.53	3.74	CO molecule from amino acid
[Ce (L) (Tyr) NO_3] ·2H_2O	40-270	16.50	17.25	Two molecules of lattice water & C_7H_5 from ligand
	270-905	27.27	27.74	$C_{11}H_{11}N_3O$ from ligand
	905-1040	3.04	3.86	CO molecule from amino acid
[Ce (L) (Cys) NO_3] ·2H_2O	25-270	14.74	16.85	Two molecules of lattice water & C_6H_4 from ligand
	270-900	33.41	32.20	$C_{12}H_{12}N_3O$ from ligand
	900-1040	15.40	15.95	CO_2 from amino acid & one molecule of NO_3
[Ce (L) (Leu) NO_3] ·2H_2O	25-275	14.32	16.60	Two molecules of lattice water & C_6H_4 from ligand
	275-902	28.83	29.35	$C_{12}H_{12}N_3$ from ligand
	902-1040	7.45	6.52	CO_2 from amino acid
[Ce (L) (Ser) NO_3] ·2H_2O	25-165	6.03	5.55	Two molecules of lattice water
	165-900	42.01	42.25	$C_{18}H_{16}N_3$ from ligand

**Ligand- 2, 3-dimethyl-1-phenyl-4-salicylidene-3-pyrazolin-5-one (HL)*

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 complexes may be represented as shown in figure 1.



R= -CH_2-C_8H_6N (Trp),
-CH_2-C_6H_4OH (Tyr),
-CH_2SH (Cys),
-CH_2-CH (CH_3)$_2$ (Leu),
-CH_2OH (Ser)

Figure 1 Proposed General Structure of Ce-L-AA complexes

3.4 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

5. The minimum inhibitory concentration (MIC) of the test sample which is expressed in µg /cm^3 was determined by using Mueller-Hinton culture medium, are given in Table 6.

Table 5 Antibacterial Activity of Cerium (III) Complexes by agar cup method

Complex	Antibacterial Activity (mm)			
	S. aureus	***C. diphtheriae***	***P. aeruginosa***	***E. coli***
[Ce (L) (Trp) NO_3] ·$2H_2O$	14	13	12	16
[Ce (L) (Tyr) NO_3] ·$2H_2O$	13	13	12	15
[Ce (L) (Cys) NO_3] ·$2H_2O$	13	11	12	15
[Ce (L) (Leu) NO_3] ·$2H_2O$	14	12	13	16
[Ce (L) (Ser) NO_3] ·$2H_2O$	13	12	13	16
Tetracycline	30	25	26	18

Table 6 Antibacterial Activity of Cerium (III) Complexes by tube dilution method

Complex	MIC (µg/cm^3)			
	S. aureus	***C. diphtheriae***	***P. aeruginosa***	***E. coli***
[Ce (L) (Trp) NO_3] ·$2H_2O$	350	500	400	250
[Ce (L) (Tyr) NO_3] ·$2H_2O$	300	400	450	300
[Ce (L) (Cys) NO_3] ·$2H_2O$	350	500	500	250
[Ce (L) (Leu) NO_3] ·$2H_2O$	350	400	450	250
[Ce (L) (Ser) NO_3] ·$2H_2O$	300	450	400	300
Tetracycline	1.5	2.0	1.5	2.5

The antimicrobial activity results indicate that 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 [30, 31]. 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.

CONCLUSION

In conclusion, we have reported the synthesis of ternary complexes of cerium (III) metal with 2, 3-dimethyl-1-phenyl-4-salicylidene-3-pyrazolin-5-one (HL) and various amino acids. All the complexes were characterized and it is found that the Schiff base participated in the bonding to cerium 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 cerium (III) complexes. These complexes exhibit excellent antibacterial ability against *S. aureus, C. diphtheriae, P. aeruginosa* and *E. coli*. Thus the series of cerium complexes can hopefully become a novel kind of drugs.

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