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Synthesis, IR Spectral Studies and Biological Activities of some Rare Earth Metal Complexes with Biochemically relevant Ligand

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ABSTRACT

Biologically active La (III), Sm (III), Gd (III) and Dy (III) complexes were synthesized by using Furan-2-carboxylic acid (FCA) as ligand and were characterized by elemental analysis and spectral measurements. Coordination of the ligand atoms to the metal ion was deduced by IR spectral data. The in vitro antibacterial screening of the free acid and its metal complexes has been carried out against Escherichia coli, Staphylococcus aureus. Antifungal activities of all the synthesized compounds were screened for in vitro growth inhibitory activity against Aspergillus fumigatus and Aspergillus niger, Aspergillus flavus by using the cup plate method. Antimicrobial activities of the ligand increase on coordination with the metal ion and show more promising activity than the corresponding free acid, and the standard control antibiotics. Such increased activity of the metal chelates can be explained on the basis of Overtone's concept and chelation theory.

Keywords: Furan-2-carboxylic acid (FCA), antibacterial and antifungal, antibiotic, chelation

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INTRODUCTION

Rare earth complexes is a subject of increasing interest in bioinorganic and coordination chemistry [1-6], because of their application in biomedical analysis as MRI contrast agents [7,8] and as effective catalysts for the hydrolytic cleavage of phosphate ester bonds [9]. Lanthanide complexes have also been found to exhibit anticancer and fungicidal properties [10]. Furan-2-carboxylic acid (FCA) is a heterocyclic aromatic compound with five-membered ring structure consisting of four CH₂ groups, one oxygen atom and a carboxylic group. There are two isomers at 2 or 3 positions. 2-Furoic acid is called pyromucic acid. It is a volatile and mildly toxic liquid, can be obtained from wood oils. It is used as a solvent as well as in the synthesis of furfural and other organic compounds. It is also used as a preservative and bactericide and as a starting material of numerous furoate esters. Its sulfur-substituted derivatives are widely used as flavouring agents and nitro-substituted derivatives in medicinal preparations and in biological research. [11-14] Furan-2-Carboxylic acid derivatives are capable of activating AMP-activated protein kinase (AMPK) which is useful for the prevention and treatment of metabolic syndromes including diabetes, obesity, hyperlipidemia, hypercholestromia, fatty liver and steatohepatitis factors. 4-amino-furan-2-carboxylic acid (proximicin) is an antibiotic which shows a weak antibacterial activity but a strong cytostatic effect to various human tumor cell lines.[15-17] Naphtho [2,1- b] furan derivatives have antioxidant activities and can be used as a powerful source used for suppression of pimples [18]. Prompted by these facts it was contemplated to synthesize various rare earth complexes with FCA and to screen them for their antimicrobial activities.

Experimental

Preparation of binary complex

The solid complexes of La (III), Sm (III), Gd (III) and Dy (III) with FCA were isolated from the mixture of equimolar solutions of metal nitrates and ligands. The pH of the mixture was adjusted to 7 by adding dilute solution of KOH. The mixture was refluxed in ethanol (15-20 ml) for 3-4 hours on a steam bath. The clear solution gave a solid mass on cooling, which was filtered through G-4 glass crucible and washed several times with the mixture of doubly distilled water and alcohol. It was recrystallised to give pure crystal and then dried at 60^o-70^oC.

The solid complexes were subjected to elemental analysis for metal, carbon and hydrogen. The Perkin-Elmer model-RX100 automatic recording spectrophotometer was used for the recording of IR spectra of the complexes in solid state. The complexes were run as pressed KBr disks medium. Approximately 3-5 mg of the complex compounds was mixed with 100 mg of KBr for each disk. The chart speed maintained was 5 to 12 minutes and were recorded at room temperature.

Antibacterial activity

The antibacterial activity of the ligand, and the corresponding complexes were assayed simultaneously against (gram negative) *Escherichia coli* and (gram positive) *Staphylococcus aureus*, by cup-plate method. Nutrient broth was prepared by dissolving peptone (0.5%), yeast extract (0.15%), beef extract (0.15%), sodium chloride (0.36%), and monopotassium phosphate (0.13%) in distilled water (100 mL). The pH of the solution was adjusted to 7.2 by adding sodium hydroxide solution (4%) and the resulting solution was autoclaved for 20 minutes at 15 psi. One day prior to the experiment, the cultures of *Escherichia coli* and *Staphylococcus aureus* were inoculated in nutrient broth (inoculation medium) and incubated overnight at 37°C. Nutrient agar medium was prepared by dissolving peptone (1%), yeast extract (0.6%), beef extract (0.5%), and sodium chloride (0.5%) in distilled water. The pH of the solution was adjusted to 7.2 by adding 4% aqueous sodium hydroxide solution. Agar (2.4%) was then added and the whole solution was autoclaved for 20 minutes at 15 psi. A known weight of the test sample was dissolved in DMSO in suitably sterile test tube to get final concentration of 0.1%, 0.2% and 0.3% and 0.1 mL of this solution (10 µg) was used for testing. Inoculation medium containing 24-hours grown culture was added aseptically to the nutrient medium and mixed thoroughly to get the uniform distribution. This solution was poured (25 mL in each dish) into Petri dishes and then allowed to attain room temperature. Thereafter, punching the set of agar with a sterile cork borer and scooping out the punched part made the cups. The diameter of each cup was 5 mm. Norfloxacin was used as the standard and DMSO as the solvent control. The test samples and the standard were tested at a concentration of 10 µg. The plates were allowed to stand for an hour in order to facilitate the diffusion of the drug solution. Then the plates were incubated at 37°C for 48 hours. The zones of inhibition against all the microorganisms were measured in millimeters. The results are given in tables 2.

Table 2– The antibacterial activity of FCA and its lanthanide metal complexes, Percentage growth inhibition (in mm) after 72 hours at 30°C

S. No	Compound	E. coli	S. aureus
1	FCA	5.2	4.8
2	La- FCA	8.7	8.9
3	Sm- FCA	8.9	9.4
4	Gd- FCA	9.6	8.6
5	Dy- FCA	9.3	9.0

Antifungal activity

The antifungal activity of the ligand and the corresponding metal complexes were tested against the pathogenic fungi *Aspergillus niger*, *Aspergillus fumigatus* and *Aspergillus flavus* by cup-plate method. Nutrient agar medium was prepared by the same method as explained under evaluation of antibacterial activity. One and half day prior to the experiment, the fungal cultures of *Aspergillus niger*, *Aspergillus fumigatus* and *Aspergillus flavus* prepared in the inoculation medium were incubated at 37°C for 36 hours. The fungal medium was prepared by dissolving peptone (0.5%), sodium chloride (0.36%), monopotassium phosphate (0.13%), and glucose (2%) in distilled water (100 mL). The pH of the solution was adjusted to 7.2 by adding sodium hydroxide solution (4%) and the resulting solution was autoclaved for 20 minutes at 15

psi. This was cooled to 45–50°C with gentle shaking. One and half day, grown cultures were added aseptically to this medium and mixed thoroughly to get uniform distribution. The solutions of the test samples and standard were evaluated for antifungal activity by cup-plate method at a concentration of 10 µg. The zone of inhibition was measured in millimeter for the particular test sample with each organism at 48 hours interval. Griseofulvin was used as the standard. The radial growth of colony after 72 hours of incubation and then percentage inhibition was calculated with the help of following formula.

$$I = \frac{(C - T) * 100}{C}$$

Where, I = Percentage inhibition

C= Average diameter of fungal growth on the control plate

T = Average diameter of fungal growth on the tested plate

The results are given in tables 3.

Table 3– The antifungal activity of Furan-2-carboxylic acid (FCA) and its lanthanide metal complexes, Percentage growth inhibition (in mm) after 72 hours at 30°C

S.No.	Compound	A. flavus			A.fumigatus			A.niger		
		0.1 %	0.2%	0.3%	0.1 %	0.2 %	0.3 %	0.1 %	0.2 %	0.3 %
1	FCA	11.5	16.1	22.7	15.8	16.8	26.3	20	25	35
2	La- FCA	33.8	38.8	44.4	36.6	47.4	52.8	40	50	55
3	Sm- FCA	33.7	43.3	50	36.6	47.4	52.8	45	50	60
4	Gd- FCA	27.3	33.2	38.8	31.1	36.6	47.4	40	45	55
5	Dy- FCA	38.1	44.4	50	42.1	32.4	57.9	50	55	60

RESULTS AND DISCUSSION

All the Co-ordination compounds were found to be stable and can be stored without any appreciable change. The analytical data given in Table 1 correspond with the calculated ones; it gives evidence for the purity of the complex synthesized.

Table1. The Physical and analytical data of Ligand and its Complexes

Compound	Mol.Wt	Colour	Elemental analysis Found and (Calcd) (%)		
			C	H	M
FCA	112.08	White	53.57 (53.17)	3.56 (3.19)	-
La- FCA Complex	250.98	White	23.92 (23.86)	1.59 (1.52)	55.34 (55.27)
Sm- FCA Complex	262.44	Light pink	22.88 (22.34)	1.52 (1.43)	57.29 (57.18)
Gd- FCA Complex	269.33	Light green	22.29 (22.03)	1.48 (1.14)	58.38 (58.03)
Dy- FCA Complex	274.58	Whitish cream	21.86 (21.33)	1.45 (1.23)	59.18 (58.96)

Inspection of IR spectra of binary complexes reveals that all the spectra are identical in all respects indicating that the bonding pattern must be the same in all the complexes. The comparison of IR spectrum of the parent ligand with that of its each metal complex has revealed certain characteristic differences as in fig.1.

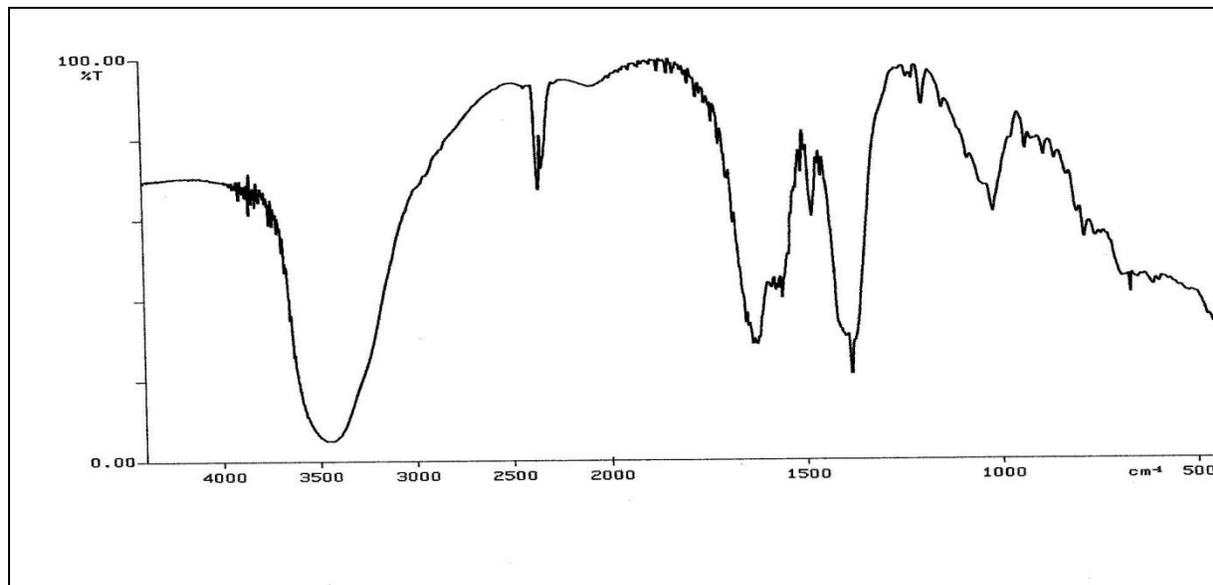


Fig. 1 The infrared spectrum of binary complex of Sm(III) and Furan-2-carboxylic acid (FCA)

The presence of water molecules outside the coordination sphere is indicated by a broad band in the region of $3500\text{--}3550\text{ cm}^{-1}$. This is further confirmed by the appearance of rocking vibrational mode of water molecules [19]. On coordination, the position of some of the bands is expected to alter.

One of the significant differences to be expected between the IR spectrum of the parent ligand and its metal complex is the presence of more broadened bands in the region of $3200\text{--}3600\text{ cm}^{-1}$ for the metal complex as the oxygen of the O-H group of the ligands forms a coordinate bond with the metal ions [20-22]. This is explained by the fact that water molecules might have strongly absorbed to the metal chelate sample during their formation.

Another noticeable difference is that the infra red spectra of binary complexes do not display the band due to free carboxylic group indicating the coordination through carboxylic group. It is a simple rule that unionized and uncoordinated COO^- stretching band occurs at $1750\text{--}1700\text{ cm}^{-1}$, whereas the ionized and coordinated COO^- stretching band occurs at $1610\text{--}1550\text{ cm}^{-1}$ and $1400\text{--}1300\text{ cm}^{-1}$ which correspond to antisymmetrical and symmetrical vibrations of the carboxyl group. The later frequencies depend upon the nature of the metals. [23]

The results of the antibacterial and antifungal studies are given in Table 2 & 3. It is observed that, all synthesized metal complexes show more inhibitory activity against bacteria

and fungi as compared to the parental ligands. Similar correlation and increase in antifungal and antibacterial activity of ligands on complexation with reference to parent ligands has been well cited. [24] Such increased activity of the metal chelates can be explained on the basis of Overtone's concept and chelation theory. According to Overtone's concept of cell permeability the lipid membrane that surrounds the cell favors the passage of only lipid soluble materials due to which liposolubility is an important factor that controls antimicrobial activity. On chelation, the polarity of metal ion is reduced to a greater extent due to the overlap of the ligand orbital and partial sharing of the positive charge of the metal ion with donor groups. Further, it increases the delocalization of π -electrons over the whole chelate ring and enhances the lipophilicity of the complex. The increased lipophilicities of complexes permit easy penetration into lipid membranes of organisms and facilitates as blockage of metal binding sites in enzymes.[25]

CONCLUSION

Binary complexes of La (III), Sm (III), Gd (III) and Dy (III) with Furan-2-carboxylic acid (FCA) were synthesized and characterized. All the complexes exhibited considerable antifungal activity against *Aspergillus niger*, *Aspergillus fumigatus* and *Aspergillus flavus* and antibacterial properties against (gram negative) *Escherichia coli* and (gram positive) *Staphylococcus aureus*. Preliminary results indicate that newly synthesized rare earth complexes with FCA exhibited promising antibacterial and antifungal activities and they warrant more consideration as prospective antimicrobials.

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