ANTIBACTERIAL STUDIES OF NEWLY SYNTHESIZED 3d MACROCYCLES

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ABSTRACT

Macrocyclic complexes of Cr³⁺, Fe³⁺ and Co³⁺ with Hexane-1, 6-diamine and ninhydrin as chlorides and bromides were prepared, characterized and their antibacterial studies were carried out. For structural determination of the complexes, data obtained from spectral studies such as analyses of elements, infrared spectra, conductivity measurements, C¹³ Nuclear Magnetic Resonance, Electron Spin Resonance, electronic spectra, mass spectral has been used. Crystal Structure was determined by powder X-ray diffraction method. All of the trivalent metal complexes show five-coordinate square-pyramidal geometry. The antibacterial study of newly prepared macrocyclic complexes was mainly focused on *Bacillus subtilis*, *Bacillus thermophilus*; the gram-positive strains and *Escherichia coli*, *Pseudomonas putida*; the gram-negative strains. The method used was Disc Diffusion Assay technique using Agar media. Streptomycin and Chloramphenicol were used as a reference for comparison as they are highly effective, broad-spectrum antibiotic drugs used both in humans and animals. Some of the complexes show antibacterial properties.

Keywords- Hexane-1, 6-diamine, Metal Halide, 2, 2-Dihydroxyindane-1, 3-dione, Physico-chemical Techniques, Antibacterial Screening.

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INTRODUCTION

Peeping into the history of macrocyclic complexes, they are the compounds with versatility in their application. We find their wide and effective use as a therapeutic agent. Most of them have been recognized as good diagnostic agents. Transition metal complexes find resourcefulness in their behaviour due to small ionic size, high nuclear charge and empty d-orbitals present in metal and locked stable macrocyclic chelated rings^{1, 2, 3}. The host-guest behaviour of the macrocyclic complexes has been shown due to different sizes of the cavities present in them which cause macrocyclic effect and significant molecular recognition properties. Naturally occurring macrocyclic complexes such as Haemoglobin, Chlorophyll, Vitamin B₁₂ and Pthalocyanine, play an ideal role in biological systems. Macrocyclic complexes are of significant importance in medicines such as Cisplatin, Carboplatin and Oxaliplatin which are metal-based drugs used for chemotherapy. Gadolinium complexes are used in MRI⁴⁻⁸ (Magnetic Resonance Imaging). These features show a correlation between chemistry and biology.

To synthesize new effective antibacterial drugs, our present work involves the synthesis of a new family of trivalent metal-based macrocyclic complexes using 2, 2-Dihydroxyindane-1, 3-dione and Hexane-1, 6-diamine. Out of the two methods of synthesis, the high yielding template method was preferred over low yielding non- template one. The characterization of synthesized macrocyclic complexes was done via spectroscopic techniques like UV-VIS, IR, ESR, MASS, ¹³C NMR etc. The gram-positive strains of the bacteria *Bacillus subtilis* and *Bacillus thermophilus* were picked up for testing. The antibacterial activity was repeated for gram-negative bacteria, *Escherichia coli* and *Pseudomonas putida*.

EXPERIMENTAL

Material and Methods

The chemicals used in the synthesis were purchased from the standard brands Merck, Fischer scientific and NICE chemicals. 2, 2-Dihydroxyindane-1, 3-dione(Ninhydrin) was purchased from Pierce Protein Research Products. Both the template and non-template methods of synthesis were tried and the template synthesis was preferred as the yields obtained were better in it.

General Procedure

The salt of trivalent chromium, iron, cobalt (5mmol) dissolved in the least amount quantity of methanol was mixed with a hot solution (~50cm³) of 2, 2-Dihydroxyindane-1, 3-dione (10mmol) made in methanol in a round bottom flask. This mixture was refluxed for half an hour. Later, Hexane-1, 6-diamine (10mmol) was added to the refluxing mixture and further refluxing was continued for 8-10 hrs. The mixture was reduced to half of its original volume. It was then stored in a desiccator for 2 days for precipitation of the complexes. The coloured crystals of the complexes were obtained which were found soluble only in Dimethylformamide or Dimethylsulphoxide Table-4. The synthesized complexes were filtered and dried. TLC was used to check the purity of the complex obtained.

Scheme-1

RESULTS AND DISCUSSION

Molar Conductance of the complexes was determined by Dip type Conductivity Bridge (HPG System, G3001) and it was found to be in the range 95-120 mho cm² mol⁻¹. These results suggest the number of cations and anions which are released in the solution through ionization. The molar conductance measurements in DMF indicated the ratio of cation to anion as 1:2⁹. The analytical data obtained from SAIF, CFL, Panjab University, Chandigarh and molar conductance data suggest the formula of the complexes as [M(C₃₀H₂₄N₄O₂X)] X₂ Where M= Cr³⁺, Fe³⁺ and Co³⁺ and X is either bromine or chlorine. Table-1 and 2 represent the obtained analytical analysis.

Table-1: Elemental Analysis of Cr³⁺, Fe³⁺ and Co³⁺ Complexes obtained from Hexane-1, 6-diamine and 2,2-Dihydroxyindane-1,3-dione

S.No.	Complexes	Found (cal %)				Mol wt
		M	C	H	N	
1	[Cr(C ₃₀ H ₂₄ N ₄ O ₂)Cl]Cl ₂	09.20 (9.23)	61.5(63.8)	4.0(4.25)	9.85(9.90)	563.5
2	[Cr(C ₃₀ H ₂₄ N ₄ O ₂)Br]Br ₂	08.49(8.55)	58.0(59.2)	3.92(3.95)	8.2(8.55)	608
3	[Fe(C ₃₀ H ₂₄ N ₄ O ₂)Cl]Cl ₂	09.65(9.70)	62.8(63.5)	4.18(4.23)	9.63(9.70)	566.5
4	[Fe(C ₃₀ H ₂₄ N ₄ O ₂)Br]Br ₂	08.38(9.00)	55.0(58.9)	3.80(3.93)	8.96(9.00)	611
5	[Co(C ₃₀ H ₂₄ N ₄ O ₂)Cl]Cl ₂	10.44(10.54)	63.7(64.3)	4.10(4.29)	10.52(10.54)	559.5
6	[Co(C ₃₀ H ₂₄ N ₄ O ₂)Br]Br ₂	09.60(9.76)	58.3(59.6)	3.82(3.97)	9.64(9.76)	604

Table-2: Analytical Data of Cr³⁺, Fe³⁺ and Co³⁺ Complexes obtained from Hexane-1, 6-diamine and 2, 2-Dihydroxyindane-1, 3-dione.

S.No.	Complexes	Colour	Molar Conductance	Yield
1	[Cr(C ₃₀ H ₂₄ N ₄ O ₂)Cl]Cl ₂	Shinny Green Powder	103	53
2	[Cr(C ₃₀ H ₂₄ N ₄ O ₂)Br]Br ₂	Blackish Powder	110	59
3	[Fe(C ₃₀ H ₂₄ N ₄ O ₂)Cl]Cl ₂	Shinny Black	101	41
4	[Fe(C ₃₀ H ₂₄ N ₄ O ₂)Br]Br ₂	Black Powder	112	46
5	[Co(C ₃₀ H ₂₄ N ₄ O ₂)Cl]Cl ₂	Shinny Grey Powder	99	53
6	[Co(C ₃₀ H ₂₄ N ₄ O ₂)Br]Br ₂	Blackish Powder	108	43

IR Spectra

The complexes and the ligands were subjected to infrared radiations IR spectra to obtain the spectrum on FT-IR/FT-FIR spectrophotometer (Perkin Elmer Spectrum 400); range $4000-667\text{cm}^{-1}$ using KBr pellets at SAIF, CFL, Panjab University, Chandigarh and plots were obtained between %transmittance and wave number. A strong band appeared at $1716-1780\text{cm}^{-1}$ in all complexes. This has appeared due to the presence of carbonyl $>\text{C}=\text{O}$ group. The geminal hydroxyl groups of ninhydrin (2, 2-Dihydroxyindane-1, 3-dione) undergo dehydration on heating to produce carbonyl in all the metal complexes. A strong band was seen at $\sim 1405-1689\text{cm}^{-1}$ indicating $>\text{C}=\text{N}-$ stretching vibrations but this band position was not found in IR spectra of Hexane-1, 6-diamine and 2, 2-Dihydroxyindane-1, 3-dione from which these complexes were synthesized. This indicates the attachment of the carbonyl of dione with amino group of the diamine. The low value of $>\text{C}=\text{N}-$ stretching frequency gives an idea about the formation of macrocyclic frame and migration of lone pair present on nitrogen towards metal atom for coordination¹⁰⁻¹¹. The various peaks for all macrocyclic complexes were given as in Table-3.

Table-3: IR Spectra of All Metal Complexes

S. No.	Complexes	$\nu(\text{C}=\text{N})\text{cm}^{-1}$	$\nu(\text{C}=\text{O})\text{cm}^{-1}$	$\nu(\text{M}-\text{N})\text{cm}^{-1}$
1.	$[\text{Fe}(\text{C}_{30}\text{H}_{24}\text{N}_4\text{O}_2)\text{Cl}]\text{Cl}_2$	1679	1757	500
2.	$[\text{Fe}(\text{C}_{30}\text{H}_{24}\text{N}_4\text{O}_2)\text{Br}]\text{Br}_2$	1689	1780	484
3.	$[\text{Co}(\text{C}_{30}\text{H}_{24}\text{N}_4\text{O}_2)\text{Cl}]\text{Cl}_2$	1463	1716	439
4.	$[\text{Co}(\text{C}_{30}\text{H}_{24}\text{N}_4\text{O}_2)\text{Br}]\text{Br}_2$	1405	1752	527
5.	$[\text{Cr}(\text{C}_{30}\text{H}_{24}\text{N}_4\text{O}_2)\text{Cl}]\text{Cl}_2$	1636	1763	497
6.	$[\text{Cr}(\text{C}_{30}\text{H}_{24}\text{N}_4\text{O}_2)\text{Br}]\text{Br}_2$	1586	1720	415

Solubility was checked in the following solvents and the data collected as given in Table-4.

Table-4

S. No.	Solvent	Solubility
1.	Diethyl Ether	Not Soluble
2.	Methanol	Not Soluble
3.	Ethanol	Not Soluble
4.	Ethyl Acetate	Not Soluble
5.	Acetone	Not Soluble
6.	Benzene	Not Soluble
7.	Dimethyl Formamide	Soluble
8.	Dimethyl Sulphoxide	Soluble

¹H NMR Spectra

The ¹HMR spectra could not be obtained due to the insolubility of the complexes in general organic solvents. A clear solution could not be obtained.

Electronic Spectra and Magnetic Moment

Electronic spectra are very useful for the revelation of the geometry of the macrocyclic complexes which arise due to the absorption of radiation leading to d-d electronic transitions. The d-orbitals in transition metals are split into different energy levels. This split is due to the repulsions between the e_g and t_{2g} orbitals of transition metal and the electron cloud of the ligand. Hence electrons from lower energy levels are transited into a higher energy level with the absorption of energy from the UV-Vis region. The electronic transition takes only 10-15 sec due to which the atoms in the molecules remain in their positions. Hence, the molecular configuration remains unchanged. There is no change in vibrational K.E in the excited state concerning the ground state at the moment of absorption. The transitions occur from ν_0 to $\nu_1, \nu_2, \nu_3, \dots, \nu_n$. The different term symbols are used for exciting vibrational levels as ${}^4\text{B}_1, {}^4\text{E}_a, {}^4\text{A}_2$.

Cr^{3+} complexes: Cr^{3+} macrocyclic complexes show a magnetic moment at $\sim 4.0-4.2$ B.M. The electronic spectra of Cr^{3+} show three bands at 9900cm^{-1} , 15000cm^{-1} and 21000cm^{-1} . These spectra resemble with spectra of the square pyramidal. With the confirmation of the literature data, five coordinated square pyramidal geometry has been suggested. Thus, considering C_{4v} for these complexes, the spectral bands may be assigned as ${}^4\text{B}_1 \rightarrow {}^4\text{E}_a$, ${}^4\text{B}_1 \rightarrow {}^4\text{B}_2$, ${}^4\text{B}_1 \rightarrow {}^4\text{A}_2$, and ${}^4\text{B}_1 \rightarrow {}^4\text{E}_b$.¹²⁻¹⁵

Fe³⁺ complexes: Fe³⁺ complexes show the magnetic moment at ~ 5.25-5.65 B.M confirming the presence of five unpaired electrons ^{12, 13}. The spectra data indicates the three bands at 9500cm⁻¹, 16500cm⁻¹ and 28000 cm⁻¹. The analytical data reports the bands as d_{xy} → d_{xz}, d_{yz}, d_{xy} → dz².

Co³⁺ complexes: Co³⁺ complexes show magnetic moment at 5.95 B.M. This value of magnetic moment indicates the presence of not more than four unpaired electrons in Co³⁺. The electronic configuration was to be 3d⁶ 4s⁰. It has four unpaired electrons. The bands are shown in the spectra as 18000cm⁻¹, 25000 cm⁻¹ and 35000 cm⁻¹.

¹³C NMR Spectra

¹³C NMR spectra were collected from Bruker Avance Neo II 500 NMR spectrophotometer using DMSO as a solvent and TMS as reference. The ¹³C NMR spectra of all macrocyclic complexes were compared with spectra of Hexane-1, 6-diamine and 2, 2-Dihydroxyindane-1, 3-dione in terms of chemical shifts (ppm). A upward or shielding shift was observed at ~40.32 ppm which indicates the contribution of the electrons from the ligand towards metal atom. No change was to be found in the peaks of aryl carbon and any other carbon linked to donor atom.¹⁴

Mass Spectra

The mass spectrum of all the metal complexes, were reported on mass spectrometer at SAIF, CFL, Panjab University, Chandigarh using LC-MS Spectrometer Model Q-ToF Micro Waters. Mass spectra give various peaks that were assigned to different fragments and molecules. It gives molecular ion peaks at different values that correspond to [M]⁺. The peaks [M]⁺ and [M+4]⁺ values indicate the coordination of one halogen (Cl/ Br) inside the sphere and two halogens outside the coordination sphere representing primary valency and secondary valency successively.

[Fe(C₃₀H₂₄N₄O₂)Cl]⁺ = 563.5 and 565.5, [Fe(C₃₀H₂₄N₄O₂)Br]⁺ = 608 and 610, [Co(C₃₀H₂₄N₄O₂)Cl]⁺ = 566.5 and 568 [Co(C₃₀H₂₄N₄O₂)Br]⁺ = 611 and 613, [Cr(C₃₀H₂₄N₄O₂)Cl]⁺ = 559.5 and 561.5, [Cr(C₃₀H₂₄N₄O₂)Br]⁺ = 604 and 606.

Powder Method

Powder method is the technical method used for the detection of the crystal structure of the sample. They were obtained from SAIF, CFL, Panjab University, Chandigarh using XPERT-PRO PAN analytical with Cu as X-ray source and scanning range (0-80°C). Discs were used for the scanning of the powder samples. To keep away from moisture, special sample tubes were used. The samples of trivalent metal ions disclose amorphous nature due to broadening peaks. The unit cell of Cr³⁺ gives a= 4.9588 Å, b=4.9588 Å and c=13.5942 Å, α=90.0000, β= 90.0000 and γ=120.0000, density= 5.23g/cm³, the unit cell of Fe³⁺ gives a= 4.9890 Å, b=4.9890 Å and c=17.0620 Å, α=90.0000, β= 90.0000 and γ=120.0000, density=2.71g/cm³ and Co³⁺ gives a=6.7766 Å, b=6.7788 Å and c= 9.8978 Å and α=90.0000, β= 90.0000 and γ=120.0000 which indicates rhombohedral structure for Cr³⁺ and Fe³⁺ complexes and monoclinic system for Co³⁺ complexes¹⁷. The diffractograms depicting 2θ values and relative intensity using Origin 8 software were shown as¹⁸ (Fig-1).

Antibacterial Assay of Trivalent Cobalt, Iron and Chromium Complexes Derived From Hexane-1, 6-diamine and 2, 2-Dihydroxyindane-1, 3-Dione

The bacterial gram-positive strains; *Bacillus subtilis* (MTCC 8509) and *Bacillus stearothermophilus* (MTCC 8508), The bacterial gram-negative strains; *Escherichia coli* (MTCC 51) and *Pseudomonas putida* (MTCC 121) were purchased from culture collection and gene bank, Institute of Microbial Technology, Chandigarh, India. These bacterial samples were used for antibacterial study of the synthesized complexes.¹⁹⁻²⁰

Antibacterial Technique

Hole Diffusion technique was used to ascertain the antibacterial behaviour of newly synthesized complexes. Both Gram-positive bacteria and Gram-negative bacteria were tested by the same Hole Diffusion technique.²¹⁻²³ A laminar airflow chamber was also used. 20 ml of MHA (Mueller- Hinton-Agar) medium was dispersed into pre-sterilized petridishes, under aseptic conditions. The solidified medium was inoculated with microorganism suspended in peptone water. Holes of 6mm diameter were

punched in the media with the help of cork and these were filled with different solutions of different concentrations (ppm) using DMSO as a solvent. They were mentioned as a, b, c, d. Streptomycin and Chloramphenicol antibiotics were used as standard antibiotics and DMSO used a test control. At the last, the petridishes were stored in an incubator at 37°C for 24 hours. The diameter of circumference developed around the hole was measured the next day. The experiment was repeated thrice for determining MIC (minimum inhibitory concentration). The MIC was determined by subtracting the value of circumference of the solvent from the circumference of macrocyclic complexes.

Fig.-1

Antibacterial activities of trivalent Chromium, Iron and Cobalt complexes derived from Hexane-1, 6-diamine and 2, 2-Dihydroxyindane-1, 3-Dione. The comparison of MIC values of Gram-positive bacteria and Gram-negative bacteria with standard antibiotics (Chloramphenicol and Streptomycin) were listed in Table-5.

Table-5: Minimum Inhibitory Concentration (MIC) of Trivalent Metal Complexes Obtained from 2, 2-Dihydroxyindane-1, 3-dione and Hexane-1, 6-diamine against Test Bacteria by Using Hole Diffusion Technique

S. No.	Complexes	MIC			
		A	B	C	D
1	$[\text{Cr}(\text{C}_{30}\text{H}_{24}\text{N}_4\text{O}_2)\text{Cl}]\text{Cl}_2$	>16	>16	32	32
2	$[\text{Cr}(\text{C}_{30}\text{H}_{24}\text{N}_4\text{O}_2)\text{Br}]\text{Br}_2$	32	32	>64	32
3	$[\text{Fe}(\text{C}_{30}\text{H}_{24}\text{N}_4\text{O}_2)\text{Cl}]\text{Cl}_2$	08	02	02	08
4	$[\text{Fe}(\text{C}_{30}\text{H}_{24}\text{N}_4\text{O}_2)\text{Br}]\text{Br}_2$	02	02	04	04
5	$[\text{Co}(\text{C}_{30}\text{H}_{24}\text{N}_4\text{O}_2)\text{Cl}]\text{Cl}_2$	>64	32	32	32
6	$[\text{Co}(\text{C}_{30}\text{H}_{24}\text{N}_4\text{O}_2)\text{Br}]\text{Br}_2$	32	>32	32	16
7	Chloramphenicol	02	02	06	08
8	Streptomycin	02	02	04	04

Where,

A - *Bacillus subtilis* (MTCC 8509)

B - *Bacillus stearothermophilus* (MTCC 8508)

C - *Pseudomonas putida* (MTCC 121)

D - *Escherichia coli* (MTCC 51)

Chloramphenicol, Streptomycin-Standard Antibiotics

The comparison of MIC values of Gram-positive bacteria and Gram-negative bacteria with standard antibiotics were shown in the bar graph (Fig-2):

Fig.-2

Proposed Structure

Various analytical and spectral methods like elemental analyses, magnetic susceptibilities, conductance measurements, NMR, UV-Vis, infrared, XRD Spectra suggests a square pyramidal geometry for all the trivalent macrocyclic metal complexes as shown in Fig.-3 may be proposed.

Where, R = (-CH₂)₆-, X = Cl⁻/Br⁻, M = Cr³⁺, Fe³⁺, Co³⁺

Fig.-3

CONCLUSION

Based on the preparation, characterization and structural elucidation data it is proposed that the Template synthesis is a better yielding method of preparation. The cyclization and coordination are taking place simultaneously in template synthesis. Trivalent metal complexes of Chromium, Iron and Cobalt are square-pyramidal in geometry. They are ionic of the ratio 1:2 of cation to anion in DMSO and DMF. Iron complex as bromide are found to be effective antibacterial towards both gram-positive and gram-negative bacteria. These compounds can be used for further pharmaceutical studies.

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