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Synthesis, biological and molecular modeling studies of macrocyclic complexes of trivalent metal ions

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Abstract

The macrocyclic complexes of biological importance with 3d transition metals are synthesized by template methodology leading to the formation of the complex [MLX] X2; where L is macrocyclic ligand derived from 3,4-diaminotoluene, 2,4-thiazolidinedione, M=Cr (III) and Fe(III) X is Cl-, CH_3COO- or NO_3-. Characterization of these complexes are made with the assistance of elemental analyses, molar conductance measurements, magnetic susceptiblities measurements and infrared spectral studies. Molecular modelling was done by Avagadro 1.01 progarm and optimised geometry in which energy calculations of macrocyclic complexes were deterrmined. Synthesized complexes were also screened for their biological activities such as antimicrobial, antifungal and antioxidant activities.

Keywords: Macrocyclic; antimicrobial; modelling; template methodology.

Introduction

Prompted from their applications [1,2] and important significance in coordination chemistry [3] as well as in bioinorganic chemistry [4-6], macrocyclic metal complexes have been captivated or magnetized in depth analysis interest within the past decades. Many macrocyclic ligands like crown ethers [7], porphyrins [8] and polyazamacrocycles [9,10]; N4S2 donor macrocyclic[11] have been synthesized and characterised in previous couple of decades. Schiff base macrocycles were among the primary artificial metal macrocyclic complexes to be synthesized. However, condensation reaction by template methodology lies within the heart of macrocyclic chemistry [12,13]. These macrocyclic complexes have potential applications in areas like models for biological structures and functions as well as resonance imaging distinction enhancing agents [14] .The stabilization of unusual oxidation states of transition metal ions by macrocyclic ligand is of great significance [15]. The bio-mimicing ability of macrocyclic complexes with the naturally occurring macrocyclic systems such as iron-porphyrin core of haemoglobin and cobalt-corrin of vitamin B12 boost their relevance from the biological point of view [16]. Encouraged from these

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studies, macrocyclic complexes of Cr(III) and Fe (III) are synthesized.

Experimental

Material and methods

The metal salts were purchased from S.D. fine, Mumbai (India). 3,4-Diaminotoluene and 2,4-thiazolidinedione were purchased from Sigma Aldrich. Organic solvents like DMSO, acetone, methyl alcohol and DMF were of chemical agent grade and used as received.

Melting points were determined through capillaries in electrical melting point equipment. Microanalysis of carbon, hydrogen and nitrogen were meted out on EuroEA elemental analyser. Molar electrical phenomenon of the complexes was measured in DMSO on a digital conduction meter (HPG System, G-3001). Methods in the literature were used for the analysis of the metal content within the complexes. The magnetic measurements were calculated at STIC, Cochin. The IR spectra were recorded on FTIR (Agilent Technologies) within the vary 4000–400cm^{-1} at SAIF, Punjab University, Chandigarh.

Synthesis of the macrocyclic complexes

All of the complexes were synthesized by template methodology dissolving in metal salts (5mmol) in minimum amount of solvent. To the present stirred methanolic solution adde d 3,4-diaminotoluene(10mmol). The ensuing solution was refluxed for nearby half-hour. After that methanolic solution of 2,4-thaizolidinedione(10mmol) was mixed to the refluxing mixture and continued for 6-8 h. Then, the mixture was cooled to room temperature, filtered and washed with methanol, acetone and diethyl ether and dried *in vacuo*. The progress of the reaction was analysed by TLC(finally giving single spot).The yield of the reaction was 60-70%s.

Antioxidant activity evaluation (free radical scavenging activity)

DPPH (2,2-diphenyl-1-picrylhydrazyl) techniques were used to evaluate the free radical scavenging activity of the macrocyclic complexes [17]. Stock solution of 1 mM DPPH was prepared in methanol and the solutions of ascorbic acid and different concentrations of test compounds(0–500 lg/mL) were prepared using DMSO. To the 1 mL of samplesolution of different concentration 3 mL of methanolic solution of DPPH (0.1 mM) was added. The samples were incubated for 30 min at room temperature (26 ˚C). The control experiment was performed as indicated above without the test samples. The absorbance of test solutions was noted at 517 nm. Ascorbic acid was used as standard whereas DPPH was used as positive control and DMSO was used as negative control. The reduction of DPPH was calculated relative to the measured absorbance of control. % Inhibitionor % Radical scavenging activity was calculated using the following formula:

% Radical scavenging activity =$[(A_0 – A_c) /A_0]\times 100$ where A_0 is the absorbance of the control and Ac is the absorbance of the sample at concentration c.

Primary screening and determination of Minimum Inhibitory Concentration (MIC)

The antimicrobial activities of all the complexes were evaluated by the agar well diffusion method [18] and Minimum Inhibitory Concentration of the synthesized complexes against bacterial and yeast strains were tested

through a modified agar well diffusion method [19] as reported in the literature.

Results and discussion

Chemistry

The newly synthesized complexes are completely soluble in DMSO whereas the mentioned complexes are insoluble in ethanol, methanol, acetone and other common organic solvents. The complexes did not melt up to 215 ˚C. The CHN data support the monomeric nature of the complexes. The analytical data of the metal complexes corresponds to the formula that may be represented as: [M (C_{20} $H_{18}N_4S_2$ X]X2; where M = Cr(III), and Fe(III) and X = Cl^- , NO_3^- and CH_3COO^- as shown in Table 1. The test for anions was positive before as well as after decomposing the complexes, indicating their presence inside as well as outside the coordination sphere. Molar Conductivity measured in DMSO indicated them to be 1:2 electrolytes (150–180 ohm^{-1} cm^{-2} mol^{-1}) [20]. However, the analytical spectroscopic and magnetic moment data enable us to propose the structure of the complexes.

Table 1. Physical data of the synthesized complexes

S.No.	Mol.Formula	Mol. Wt.	Yield(%)	Mp	Colour
1	[$C_{20}H_{18}$Cl Fe N_6 S_2]	497.8	67	219	Reddish brown
2	[C_{22} H_{21} FeN_6 O_2 S_2]	521.4	70	234	Brown
3	[C_{20} H_{18} FeN_7 S_2O_3]	524.3	58	225	Dark Brown
4	[C_{20} H_{18}Cl CrN_6 S_2]	493.9	64	270	Greyish Black
5	[C_{22} H_{21} CrN_6 O_2 S_2]	517.5	73	264	Black
6	[C_{20} H_{18} CrN_7 O_3 S_2]	520.5	66	256	Back

Elemental analysis

Complex-I

[C_{20} H_{18}Cl Fe N_6 S_2] cal. M = 11.17, C = 48.06, H = 3.353, N = 16.81, found M = 11.11, C = 48.00, H=3.28, N = 16.27, $\mu_{eff.}$ = 5.68 B.M.

Complex II

[C_{22} H_{21} FeN_6 O_2 S_2] cal. M = 10.67, C = 50.48, H = 4.43, N = 16.06, found M = 10.23, C = 50.01.36, H=4.28, N = 16.27, $\mu_{eff.}$ = 5.72 B.M.

Complex III

[C_{20} H_{18} FeN_7 S_2O_3] cal. M = 10.61, C = 45.63, H = 3.83, N = 18.63, found M = 10.42, C = 45.36, H=3.68, N = 18.27, $\mu_{eff.}$ = 5.76 B.M.

Complex IV

[C_{20} H_{18}Cl CrN_6 S_2] cal. M = 10.48, C = 48.43, H = 4.06, N = 16.93, found M = 10.13, C = 48.36, H=4.0, N = 16.27, $\mu_{eff.}$ = 4.28 B.M.

Complex V

[C_{22} H_{21} CrN_6 O_2 S_2] cal. M = 10.01, C = 50.86, H = 4.46, N = 16.17, found M = 9.89, C = 50.36, H=4.28, N = 16.02, $\mu_{eff.}$ = 4.36 B.M.

Complex VI

[C_{20} H_{18} CrN_7 O_3S_2]cal. M = 9.95, C = 45.97, H = 3.86, N = 18.76, found M =

9.67, C = 45.36, H=3.28, N = 18.27, $\mu_{eff.}$ = 4.34 B.M.

IR spectra

The presence of a medium intensity band in the IR spectra of all the complexes in the region 1580-1620 cm^{-1} confirms the formation of macrocyclic Schiff's base [21] and the condensation of thecarbonyl group of 2,4-thiazolidinedione and the aminogroup of 3,4-diaminotoluene, as these bands may be assigned tov(C=N) stretching vibrations [22,23]. The medium intensity band in the range 3240-3280 cm^{-1} shows the presence of sec. (NH) group [24] of 2,4-thiazolidinedione. Strong intensity peaks at 1673 correspond to C=O group of the acetate moiety in the spectrum [25]. The lower value of v(C=N) in the complexes may be explained on the basis of drift of the lone pair electron density from the heteroatom(nitrogen) towards the central metal atom [26] indicating the coordination occurred through nitrogen of C=N (azomethine linkage). The weak intensity bands present in the region 2920–2950 cm^{-1} may be assigned to v(CH) stretching vibrations of the methyl groups of the3,4-diaminotoluene. The bands in the region 450-490cm^{-1} correspond to v(M-N) vibrations, respectively [27].

Antibacterial and antifungal activity

All the synthesized complexes are screened for their biological activity and located to their own smart biological activities. Compound 5 is effective against all the strains of microorganism and fungi. This indicates the impact of individual metal, its electron density, coordination potential, dipole moment and electrical phenomenon on its overall biological behaviour. Compound 1 which is additionally effective against Bacilli And Compound No. 2 shows smart activity against fungal strains. The MIC of the synthesized compounds is shown in Table 2 and Figure1

Table 2. Minimum Inhibitory concentration(MIC) of compounds(µg/cm^{-3}) by using modified agar well diffusion method

Compound No.	Bacillus Subtilis	Escherchia coli	Saccharomyces cerevisiae	Candida albicans
1	**8**	32	128	32
2	32	128	**8**	**8**
3	16	16	16	8
4	32	64	8	32
5	**8**	**8**	**8**	**16**
6	64	8	128	64
Ciprofloxacin	6.25	6.25	Nt	Nt
Amphotericin-B	Nt	Nt	12.5	12.5

Nt=not tested

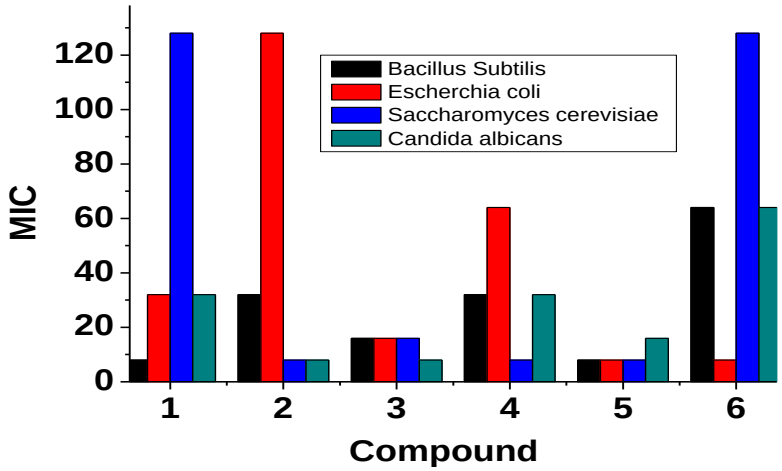


Figure 1. Bar graph showing MIC of the synthesized complexes

All the complexes were evaluated for inhibitor activity. Antioxidant activity directly varies with the concentration of the complexes as shown in Table 3. All the complexes show moderate to highly important activity. The extinction of DPPH radical results from the magnet behaviour of the metal ion concerned. Complexes 2 and 3 are the most effective inhibitor agents showing the IC_{50} 50µg/ml. The iron complexes possess higher antioxidative activity as compared to metal complexes which need lower IC_{50} values.

Table 3. Antioxidant activity

Compound	**Concentration(µg/ml)**				
	0	**50**	**100**	**250**	**500**
Ascorbic acid	1.323	0.634	0.562	0.460	0.240
1	1.323	0.856	0.780	0.664	0.432
2	1.323	0.598	0.320	0.280	0.198
3	1.323	0.352	0.434	0.346	0.267
4	1.323	0.746	0.568	0.408	0.386
5	1.323	0.867	0.760	0.618	0.466
6	1.323	0.664	0.592	0.458	0.306

Molecular modelling studies

Molecular modelling of the complexes of iron and chromium was done using Avagadro 1.01 program. Complexes are optimized using molecular mechanic method. Several cycles of the energy minimization was carried out for each structure. Optimized geometry and their energies values are listed below in Figure 2 and Table 4.

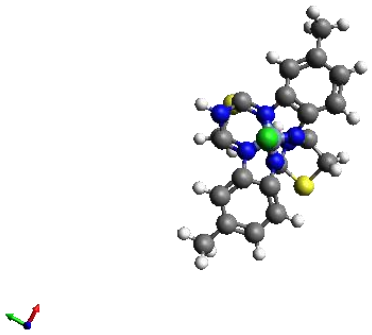
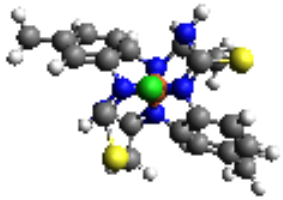
$[C_{20}\ H_{18}Cl\ CrN_6\ S_2]$	$[C_{20}\ H_{18}Cl\ Fe\ N_6\ S_2]$
	

Figure 2. Optimised geometry

Table 4. Energy data of the optimised geometry

Compounds	**Total electrostatic energy**	**Total Vander waals energy**	**Total Angle Bend. Energy**	**Total Bond Strech. energy**	**Total torsional energy**	**Total energy(KJ/Mol)**
$Cr(III)Cl_3$	1.717	137.902	1374.268	210.824	419.463	2144.174
$Fe(III)Cl_3$	2.113	202.459	1297.724	293.239	552.726	2348.25

Conclusion

The spectral and magnetic moment data favors square pyramidal geometry of the complexes. Molar conductance values show their non-electrolytic nature. Biological evaluation and the antioxidant property were evaluated and good results were found. Energy data and optimized geometry are obtained from Avagadro program.

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