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SYNTHESIS, SPECTRAL INVESTIGATION AND BIOLOGICAL EVALUATION OF NOVEL MACROCYCLIC LIGAND AND ITS TRANSITION METAL COMPLEXES

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ABSTRACT

A novel series of macrocyclic complexes of Mn(II), Co(II), Ni(II) and Cu(II) were synthesized by using condensation reaction between macrocyclic ligand and corresponding transition metal salts. The chemical composition of ligand was determined on the basis of analytical and spectral techniques i.e. elemental analyses, IR, mass and computational study i.e. molecular modelling studies. Data obtained by spectral studies revealed tetradentate nature [N_4] of ligand and ligand coordinated to metal ion through nitrogen donor atoms. Metal complexes were characterized by elemental analyses, molar conductance, magnetic susceptibility measurements, IR, electronic spectra, EPR spectra and molecular modelling study. The molar conductance data suggested non-electrolytic nature of metal complexes and formulated as [$M(L)X_2$] where M = Mn(II), Co(II), Ni(II), Cu(II) L = macrocyclic ligand X = Cl^-, NO_3^- anion. On the basis of characterization data, all metal complexes possessed octahedral geometry around the metal ion except Cu(II) complex which possessed tetragonal geometry. Geometry of ligand and its complexes was also optimized by using molecular modelling study and it supports to the spectral data results. Newly synthesized macrocyclic ligand and its metal complexes were screened to evaluate the biological activity against some selective microorganisms (bacteria and fungi). The biological experimental result suggested that metal complexes were more potent than ligand.

KEYWORDS: macrocyclic ligand, metal complexes, spectral data, molecular modelling, bacteria, fungi.

INTRODUCTION

Macrocyclic ligands and their complexes occupy a unique section in chemical science.[1] Macrocyclic ligands have several features that make them interesting in efforts to deal with different hard targets with extensive binding sites.[2] Development of new macrocyclic ligands and their composed reactions were carried out since 1961 and becomes phenomenal to provide exciting and novel chemistry.[3,4] The macrocyclic ligands are a growing class of compounds with varying chemistry, a wide range of different molecular topologies and sets of donor atoms. Macrocyclic chemistry represents an important role in biochemistry.[5] The significance of macrocyclic ligands extends from large number of life composing and naturally occurring complexes with enormous biological functions to vast numbers of synthetically made ones for diverse biological and non biological functions.[6] Macrocyclic ligands and their metal complexes have been explored for their antibacterial[7], fungicidal[8], anticonvulsant[9] and catalytic activities etc.[10] The available literature evidence about their antioxidant[11] and anti-HIV activities[12] also. These are also used as MRI contrast agents.[13] The thermodynamic and kinetic inertness of transition metal complexes of polyaza macrocyclic ligands have significant in various industrial fields.[14] Keeping in mind the above importance of these compounds, we designed, synthesized and characterized novel macrocyclic ligand and its transition metal complexes of Mn(II), Co(II), Ni(II) and Cu(II) metals. All synthesized compounds were also tested for their antimicrobial activity against selective pathogenic bacteria (S.lutea, E.coli, S.aureus) and fungi (A.niger, A.glaucus, U.triticii) species.

Materials and Experimental protocols

All chemicals i.e. diethyloxalate and 1,3-diaminopropane were commercially available and purchased from Aldrich. Metal salts were purchased from Merck and were used as received. Analytical grade solvents were purchased and used as such. Micro elemental analysis (CHN) was analyzed on Carlo-Erba 1106 elemental analyser. Molar conductance was measured on the ELICO (CM82T) conductivity bridge. Magnetic susceptibility was measured at room temperature on a Gouy balance using $CuSO_4.5H_2O$ as calibrant. IR spectra were recorded on FT-IR spectrum BX-II spectrophotometer in KBr and CsI medium. The electronic spectra were recorded in DMSO on Shimadzu UV-visible mini-1240 spectrophotometer. Electronic impact (EI) mass spectrum was recorded on JEOL, JMS-DX-303 mass spectrophotometer. EPR spectra of complexes were recorded at room temperature (RT) on E_4-EPR spectrometer using the DDPH as the g-marker at SAIF, IIT Bombay. Molecular modelling of ligand and its metal complexes was performed by using Gaussian PM3 level, in gas phase.

EXPERIMENTAL WORK

Synthesis of macrocyclic ligand

Hot ethanolic solution (20 mL) of diethyloxalate (0.05 mol) was mixed drop wise with hot ethanolic solution (50 mL) of 1,3-diaminopropane (0.05 mol) with constant stirring. This mixture was refluxed at 80^0C (+-5^0C) for 6 hrs in the presence of few drops of concentrated hydrochloric acid. On cooling, white coloured precipitate was formed. It was filtered out, washed with cold ethanol and dried under vacuum over P_4O_{10} Yield 78%, M.P. 240^0C.

Synthesis of complexes

Transition metal complexes of ligand were synthesized by addition of hot ethanolic solution of ligand (0.001 mol) and hot ethanolic solution of corresponding metal salts i.e. Mn(II), Co(II), Ni(II) and Cu(II) (0.001 mol) in 1:1 ratio. The mixture was refluxed for 5-8 hrs at 75-85°C through constant stirring. After cooling, coloured product was precipitated out, which was filtered and washed with cold ethanol and dried under vacuum over P_4O_{10}. M.P. <200^0C.

RESULTS AND DISCUSSION

On the basis of elemental analyses, complexes are assigned to possess the composition as shown in **Table 1.** The molar conductance measurement of the complexes in dimethylsulphoxide (DMSO) and dimethylformamide (DMF) corresponded to their non-electrolytic nature means anions are located inside the coordination sphere. Thus these complexes may be formulated as $[M(L)X_2]$, where M = Mn(II), Co(II), Ni(II), Cu(II), L = macrocyclic ligand and X = Cl^-, NO_3^- anions.

Table 1: Molar conductance and elemental analysis of the complexes

Compound	**Mol. Wt.**	**Molar Conductance**	**Colour**	**Elemental Analysis (%)**			
				C	**H**	**N**	**M**
Macrocyclic Ligand $C_{10}H_{16}N_4O_4$	256	-	White	46.78 (46.86)	6.19 (6.25)	21.79 (21.88)	-
$[Mn(L)Cl_2]$	418	15	Light pink	28.65 (28.71)	4.70 (4.78)	13.33 (13.33)	13.09 (13.16)
$[Mn(L)(NO_3)_2]$	471	18	Pale pink	11.61 (11.68)	4.19 (4.25)	17.91 (17.83)	11.61 (11.68)
$[Co(L)Cl_2]$	386	22	Dark green	30.98 (31.09)	4.07 (4.15)	14.59 (14.51)	15.14 (15.28)
$[Co(L)(NO_3)_2]$	439	18	Magenta	27.21 (27.33)	3.69 (3.64)	19.02 (19.13)	13.32 (13.44)
$[Ni(L)Cl_2]$	386	20	Light green	31.02 (31.09)	6.10 (6.13)	14.43 (14.51)	14.85 (14.90)
$[Ni(L)(NO_3)_2]$	439	16	Bluish green	27.41 (27.33)	3.59 (3.64)	19.18 (19.13)	13.29 (13.44)
$[Cu(L)Cl_2]$	391	09	New satin blue	30.58 (30.69)	4.00 (4.09)	14.41 (14.32)	16.30 (16.37)
$[Cu(L)(NO_3)_2]$	444	08	Opaline green	27.11 (27.03)	3.67 (3.60)	3.67 (3.60)	14.49 (14.41)

C-carbon, H-hydrogen, N-nitrogen, M-metal

MASS SPECTRUM OF THE LIGAND

The mass spectrum of the macrocyclic ligand is characterized by moderately to highly abundant molecular ions. It is obvious that the molecular ions are in good agreement with their suggested empirical formula. The mass spectrum of ligand shows a well-defined parent peak at m/z = 245 with a relative intensity of 13.5% Figure 1. The mass spectrum of ligand shows a molecular ion peak at 255 amu, corresponding to the macrocyclic moiety $(C_{10}H_{16}N_4O_4)^+$ and a series of peaks, due to different fragments at position 42, 56, 72, 128, 184 and 200 amu.

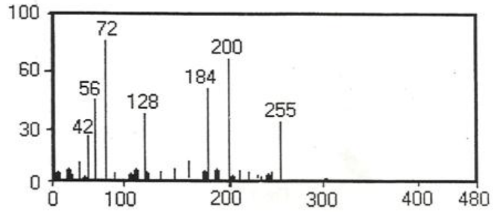


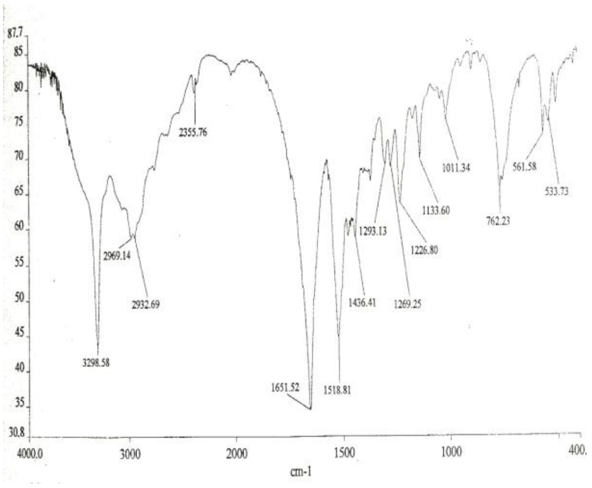
Figure 1: Mass spectrum of macrocyclic ligand

Infrared spectra

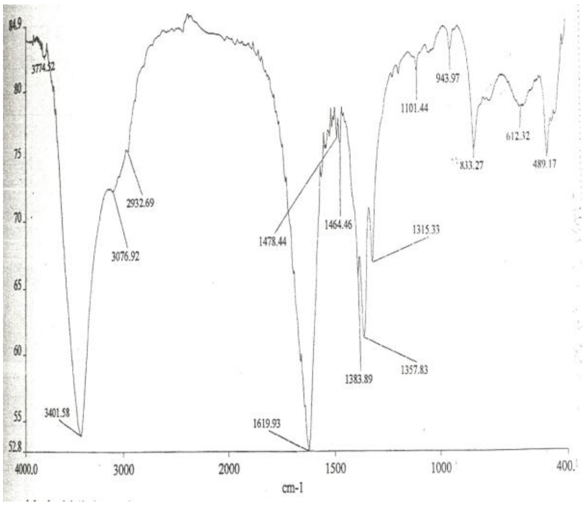
The IR spectra of the ligand do not show any band around 3400 cm^{-1} indicated the absence of free primary diamine and hydroxyl group, which suggested the complete condensation of keto group with amino group Appearance of four new bands in the IR spectra of the ligand, in the region 1635-1651 cm^{-1}, 1518 cm^{-1}, 1226 cm^{-1}, 762-779 cm^{-1}, are corresponded to amide I [ν(C=O)], amide II [ν(C-N) + δ(N-H)], amide III [δ(N-H)] and amide IV [φ(C=O)], respectively.[15,16] The appearance of a band at 3298 cm^{-1} may be attributed to [ν(N-H)] of the secondary amino group. The shifting, of this band (1651 cm^{-1}), towards lower side, (10-25 cm^{-1}) in the complexes is strong evidence for the involvement of nitrogen atom in coordination which is further supported by the presence of a medium intensity band in the range 463-492 cm^{-1}. On the basis of above IR spectral study we concluded that the ligand is tetradentate in nature and coordinated to metal ion through the nitrogen atoms.

IR Spectral Bands due to Anions

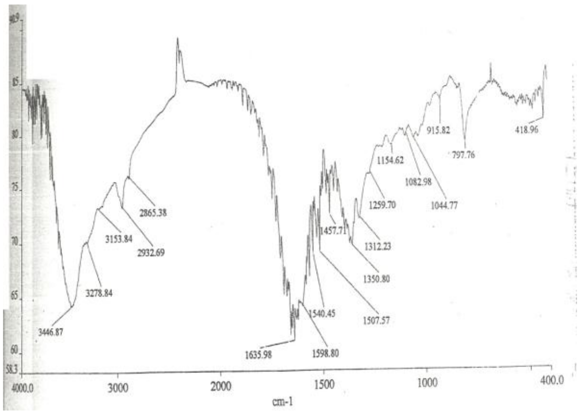
Infra-red spectra of the nitrato complexes of ligand with metal ions displayed three (N-O) stretching bands in the range 1418-1434 cm^{-1} (υ_5), 1302-1315 cm^{-1} (υ_1)and 1004-1016 cm^{-1} (υ_2). The separation of two highest frequency bands (υ_5-υ_1) is 116-119 cm^{-1}, suggested that both nitrate groups coordinated to the central metal ion in unidentate manner Figure 2.[17,18]



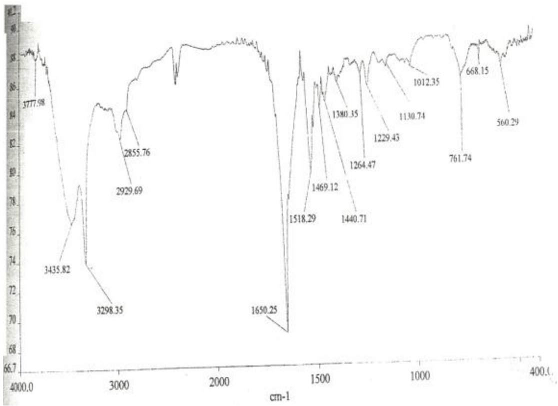
(a)



(b)



(c)



(d)

Figure 2: IR spectra of (a) Ligand, (b) $[Mn(L)(NO_3)_2]$ (c) $[Co(L)(NO_3)_2]$, (d) $[Ni(L)Cl_2]$

Electronic spectra

Mn (II)

Electronic spectra of Mn(II) complexes gives four bands in the range 18051-20132 cm^{-1} (υ_1), ~22553-24631 cm^{-1} (υ_2), ~27993-29975 cm^{-1} and ~33003-38610 cm^{-1}. These bands are characteristic of an octahedral environment around Mn(II) ion [18]. Band at 33003-38610 cm^{-1} corresponds to the charge transfer band. These bands may be assigned to the following transitions.

$^6A_{1}g \rightarrow {}^4T_{1}g$ (υ_1)
$^6A_{1}g \rightarrow {}^4Eg$
$^4A_{1}g$ (4G) (10B + 5C) (υ_2)
$^6A_{1}g \rightarrow {}^4Eg$ (4D) (17B + 5C) (υ_3)

Co (II)

The electronic spectra of the Co(II) complexes Figure 3(c) under study display three well defined bands lie in the range 9652-11223, 14362-15474 and 18051-20534 cm^{-1} Table 2 which corresponds to $^4T_{1}g(4F) \rightarrow {}^4T_{2}g(^4F)$ (υ_1), $^4T_{1}g(^4F) \rightarrow {}^4A_{2}g(^4F)$ (υ_2) and $^4T_{1}g(^4F) \rightarrow {}^4T_{1}g(^4P)$ (υ_3) transitions, respectively, characteristic to octahedral geometry.[19] These electronic spectral bands indicate that the complexes have octahedral geometry and might be possess D_{4h} symmetry.[20]

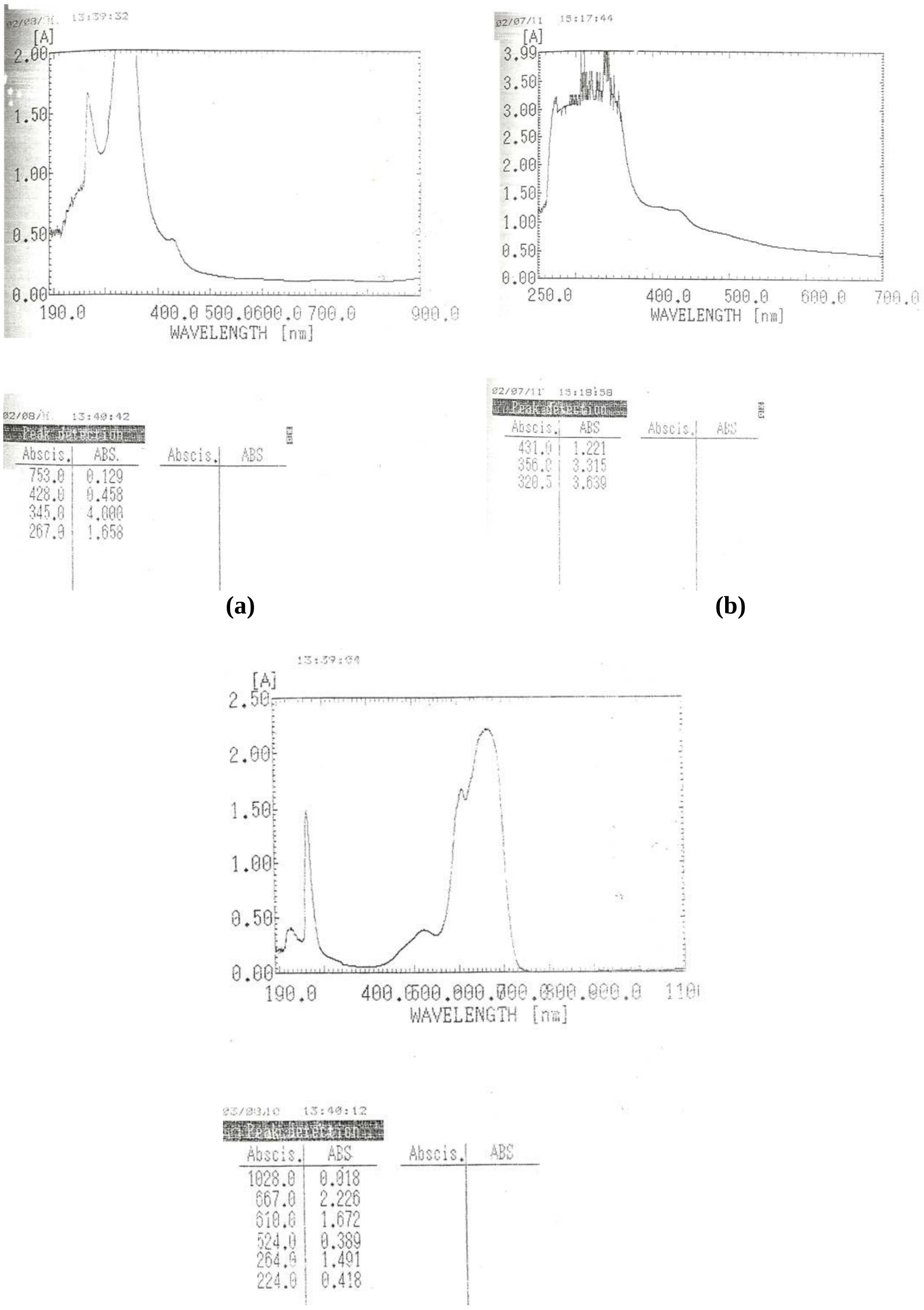
Ni (II)

Electronic spectra of Ni(II) complexes showed three bands in the range of 12674-13889 cm^{-1}, 14327-15601

cm^{-1} and 23041-26455 cm^{-1} assignable to $3A_2g(F) \rightarrow 3T_2g(F)$ (υ_1), $3A_2g(F) \rightarrow 3T_1g(F)$ (υ_2) and $3A_2g(F) \rightarrow 3T_1g(P)$ (υ_3) transitions respectively.[21-22] Six-coordinate Ni(II) complexes may possess O_h or D_{4h} symmetry. Thus complexes, under study, possess octahedral geometry.

Ligand field parameter

The experimentally observed transition energies and calculated values for various ligand field parameters are shown in Table 2. The value of parameter B and C were calculated from the transition $^6A_1g \rightarrow {}^4Eg\ {}^4A_{1}g\ (^4G)$ and $^6A_1g > {}^4Eg\ (^4D)$, because these transitions are free from the crystal field splitting and depend on B and C parameters, only.[23] The values of Dq were obtained with the help of curve, transition energies υ_3. Dq, as given by Orgel[24] using the energy due to the transition $^6A_{1g} \rightarrow {}^4T_{1g}$ (^4G). Slater Condon-shortly repulsion parameters F_2 and F_4 are related to Racah parameters**.** Parameters B and C as $B = F_2 - 5F_4$ and $C = 35\ F_4$ are calculated of Mn(II) complex only.[24] The observed values for parameter β and hx suggest that the complexes, reported here, have appreciable covalent character.[26]



02/08/ 13:40:42

Abscis.	ABS.
753.0	0.129
428.0	0.458
345.0	4.000
267.0	1.658

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Abscis.	ABS
431.0	1.221
356.0	3.315
320.5	3.639

(a) **(b)**

13:40:12

Abscis.	ABS
1028.0	0.018
667.0	2.226
610.0	1.672
524.0	0.389
264.9	1.491
224.0	0.418

(c)

Figure 3: Electronic Spectra of (a) $[Mn(L)Cl_2]$ (b) $[Mn(L)(NO_3)_2]$ (c) $[Co(L)Cl_2]$

Table 2: Electronic spectral bands (cm^{-1}) and ligand field parameters of the complexes

Complexes	λ_{max} (cm^{-1})	μ_{eff} (BM)	Ligand Field Parameters						
			Dq	B	β	F_4	F_2	hx	v_2/v_1
$[Mn(L)Cl_2]$	18349, 22883, 28329, 38462	5.89	1835	778	0.98	86.30	1209.50	0.29	1.25
$[Mn(L)(NO_3)_2]$	19685, 23474, 28011, 38610	5.93	1968	648	0.82	97.10	1133.65	2.57	1.19
$[Co(L)Cl_2]$	5578, 14992, 19084	4.64	697.25	996	0.89	-	-	-	-
$[Co(L)(NO_3)_2]$	9763, 14912, 19455	4.88	976	678	0.60	-	-	-	-
$[Ni(L)Cl_2]$	13831,15521, 25316	2.95	1383	532	0.51	-	-	-	-
$[Ni(L)(NO_3)_2]$	13717,14970, 25063	2.89	1371	528	0.51	-	-	-	-
$[Cu(L)Cl_2]$	10526,15986, 26247	1.95	-	-	-	-	-	-	-
$[Cu(L)(NO_3)_2]$	10542,17212, 28736	1.99	-	-	-	-	-	-	-

Electronic paramagnetic resonance spectra

The EPR spectra of Mn(II) complexes were recorded as polycrystalline sample at room temperature in the solution of DMF Figure 4. The polycrystalline spectra of the complexes show one broad isotropic band, which is approximately centred at the free electron ‘g’ value (2.0023). The EPR spectra of the Co(II) complexes under study were recorded polycrystalline sample at liquid nitrogen temperature, because the rapid spin lattice relaxation of Co(II) broadens the lines at higher temperatures. g- Values are presented in Table 3. The large deviation of the g-values from the spin only value (g =2.0023) is due to the large angular momentum contribution.

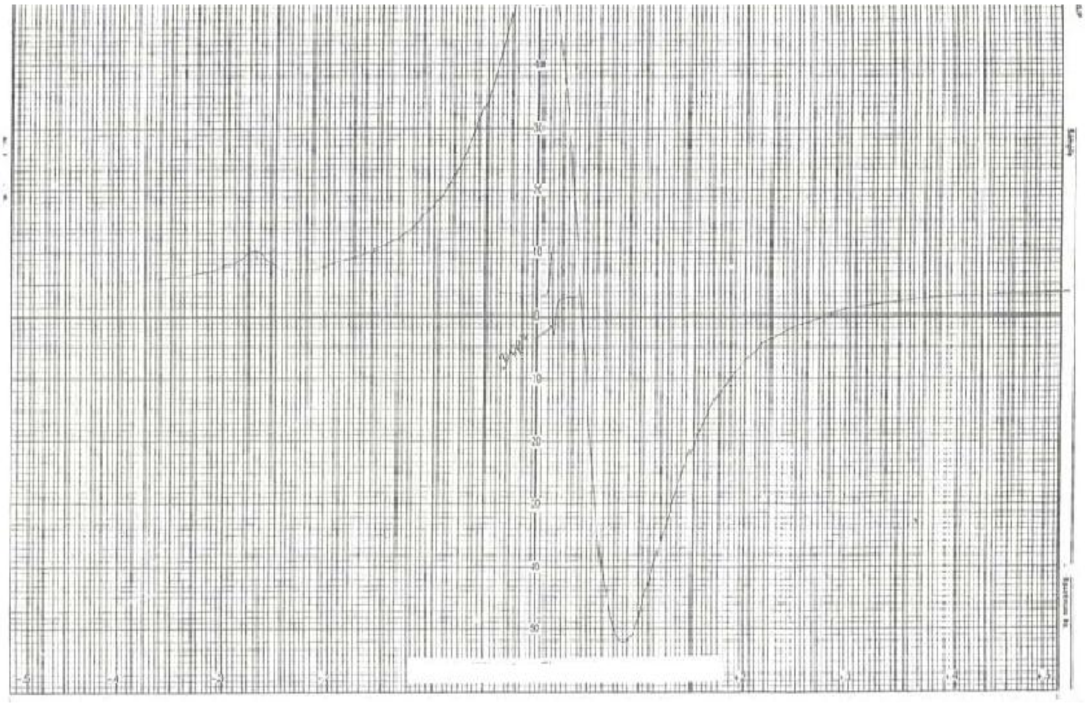


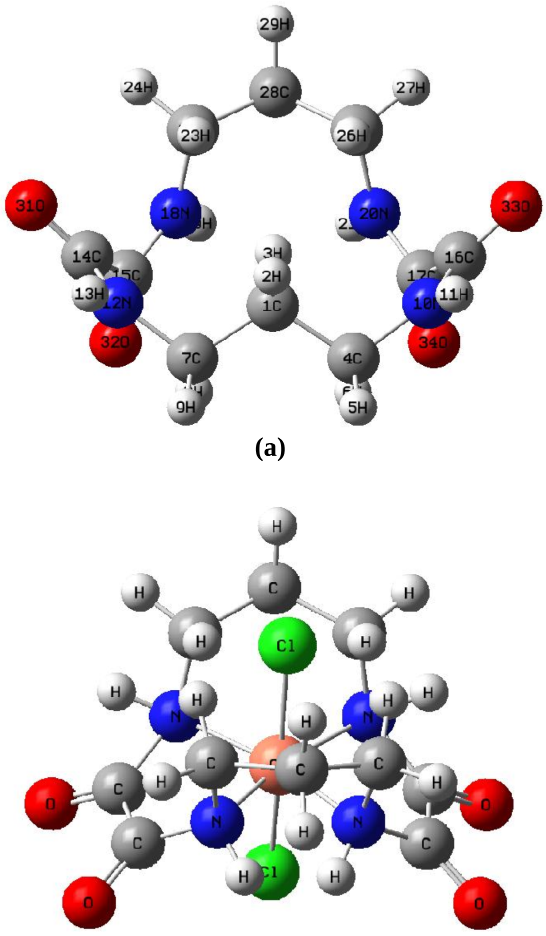
Figure 3: EPR spectrum of $[Mn(L)Cl_2]$ complex of macrocyclic ligand

Table 3: EPR spectra data of the complexes

Complexes	g	g	G	g_{iso}
$[Mn(L)Cl_2]$	-	-	-	1.9656
$[Mn(L)(NO_3)_2]$	-	-	-	1.9992
$[Co(L)Cl_2]$	2.0318	3.3173	-	2.4603
$[Co(L)(NO_3)_2]$	2.0124	3.856	-	2.4368
$[Cu(L)Cl_2]$	2.1760	2.0519	3.3911	2.0932
$[Cu(L)(NO_3)_2]$	2.2402	2.1345	1.7859	2.1697

MOLECULAR MODELLING

Geometry optimization of macrocyclic ligand was done by molecular modelling study. Molecular modelling of macrocyclic ligand was performed by using Gaussian PM3 level, in gas phase. Optimized geometries of compounds are given in Figure 4.



(a)

(b)

Figure 4: Optimized geometry of (a) macrocyclic ligand (b) Optimized geometry of Cu(II) complex

ANTIMICROBIAL EVALUATION

Antibacterial Activity

Antibacterial activity of the ligand and its complexes was evaluated against different species of bacteria i.e. S.lutea, S.aureus and E.coli. The antibacterial screening of ligand and its metal complexes was done by using paper disc diffusion method. The disc of Whatmann filter paper no. 4, with the diameter 6 mm, were soaked in the solution of tested compounds in DMSO (500 ppm). After drying, it was placed on nutrient agar plates. The inhibition areas were observed after 48 hrs. DMSO/DMF was used as a control and Gentamycin as standard drug for the comparison purpose. Results of antibacterial activity of metal complexes has been shown in Table 4.

Antifungal Activity

The antifungal activity of the macrocyclic ligand and its complexes, reported here, was checked by agar plate technique for A.niger, A.glaucus and U.triticii fungi.[27] The compounds were directly mixed with media at different concentration. The fungus was placed in the media with the help of an inoculums needle. The patri dishes were wrapped in polythene sheets, containing few drops of EtOH and kept in incubator at 32^{0}C ±3°C for 2 days. The growth of fungus was measured by the recording of diameter of fungal colony. Result of antifungal activity of complexes has been shown in Table 5.

Table 4: Antibacterial activity of the complexes at concentration 500 ppm

Complex	Bacterial growth inhibition in (%)		
	S.lutea	**E.coli**	**S.aureus**
$[Mn(L)Cl_2]$	45	80	NA
$[Mn(L)(NO_3)_2]$	35	40	NA
$[Co(L)Cl_2]$	40	50	90
$[Co(L)(NO_3)_2]$	85	NA	90
$[Ni(LA)Cl_2]$	80	80	NA
$[Ni(L)(NO_3)_2]$	90	90	NA
$[Cu(L)Cl_2]$	70	80	NA
$[Cu(L)(NO_3)_2]$	65	70	50

NA means no activity

Table 5: Antifungal activity of the complexes at concentration 500 ppm

Complex	Antifungal growth inhibition in (%)		
	A.niger	**A.glaucus**	**U.triticii**
$[Mn(L)Cl_2]$	80	35	NA
$[Mn(L)(NO_3)_2]$	30	70	NA

[Co(L)Cl_2]	90	90	NA
[Co(L)$(NO_3)_2$]	40	80	NA
[Ni(LA)Cl_2]	85	NA	30
[Ni(L)$(NO_3)_2$]	30	NA	60

CONCLUSION

On the basis of the physicochemical and spectral data, we assume that macrocyclic ligand behaves in tetradentate manner [N_4]. In the light of above discussed studies, we proposed six coordinated octahedral geometry for all synthesized metal complexes. Among all metal complexes [Ni(L)$(NO_3)_2$] complex showed highest antibacterial activity against bacteria S.lutea and E.coli. It was also assumed that only [Co(L)Cl_2] complex exhibit highest antibacterial activity against bacteria S.aureus. Table 4 and 5 indicated that [Co(L)Cl_2] complex exhibit highest antifungal activity against tested fungi A.niger and A.glaucus except Ni(II) complexes. Other complexes were inactive against the growth fungi U.triticii.

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