Synthesis, Characterization, Spectral Studies, Antifungal and Antibacterial Screening of Ca (II) and Ba (II) Macrocyclic Complexes Derived from α-Diketones and Diamine

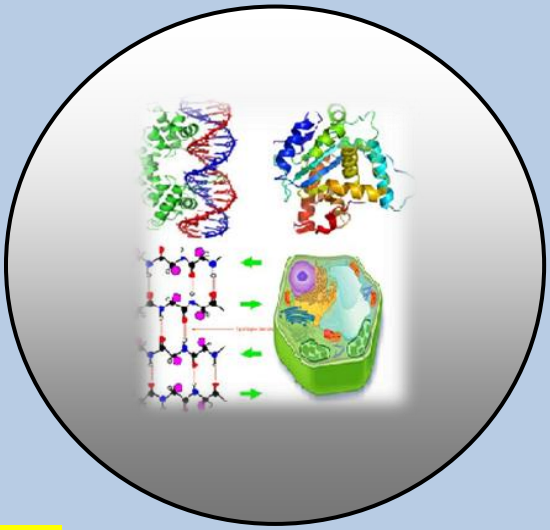
By

Mithlesh Agrawal and Swati Bugalia

ISSN 2319-3077 Online/Electronic
ISSN 0970-4973 Print

Global Impact factor of Journal: 0.756
Scientific Journals Impact Factor: 3.285
InfoBase Impact Factor: 2.93
Index Copernicus International Value
IC Value of Journal 6.01 Poland, Europe

J. Biol. Chem. Research
Volume 32 (2) 2015 Pages No. 823-834



Journal of Biological and Chemical Research

(An International Refereed/Peer Reviewed Journal of Life Sciences and Chemistry)

Indexed Abstracted and Cited in about 25 different Scientific Databases around the World

Published by Society for Advancement of Sciences®

J. Biol. Chem. Research. Vol. 32, No. 2: 823-834, 2015
(An International Refereed/Peer Reviewed Journal of Life Sciences and Chemistry)
Ms 32/2/91/2015

ISSN 0970-4973 (Print)
ISSN 2319-3077 (Online/Electronic)

Swati Bugalia
http:// www.sasjournals.com
http:// www.jbcr.in
jbiolchemres@gmail.com
info@jbcr.in

RESEARCH PAPER

Received: 11/09/2015 **Revised: 25/09/2015** **Accepted: 26/09/2015**

Synthesis, Characterization, Spectral Studies, Antifungal and Antibacterial Screening of Ca (II) and Ba (II) Macrocyclic Complexes Derived from α-Diketones and Diamine

Mithlesh Agrawal and Swati Bugalia
Department of Chemistry, University of Rajasthan, Jaipur, 302004, India

ABSTRACT

Some new macrocyclic complexes of Ca(II) and Ba(II) metal ions (derived from 1,16-diamine-4,7,10,13-tetraoxahexadecane and α-diketones viz 2,3-butanedione, 3,4-hexanedione or benzyl) have been synthesized and characterized with the help of elemental analyses, conductance measurements, decomposition temperature, IR, ^{1}H-NMR and Mass spectrometry. Based on these studies the complexes were found to have composition $[M(L^1)(L^2)].Cl_2$, {where M = Ca(II) or Ba(II), L^1 = 1,16-diamine-4,7,10,13-tetraoxahexadecane and L^2 = α-diketones viz 2,3-butanedione, 3,4-hexanedione or benzyl}. A tentative structure for these complexes is proposed and suggested coordination number six around the metal ion. The in vitro antibacterial activity of these complexes was performed on some pathogenic bacterial strains Escherchia coli(gram-negative), Bacillus subtilis(gram-positive) , Pseudomonas putida (gram-negative), while in vitro antifungal activities was tested against four fungal pathogens Microsporum gypseum, Alternaria alternata, Trichophyton rubrum, Trichophyton tonsurans.
Key words: Macrocyclic Complexes, Mass, Proton-NMR Spectra, Antibacterial and Antifungal Activities.

INTRODUCTION

The field of macrocyclic chemistry of metals is growing very fastly because of its importance in the area of coordination chemistry (Kumar et al., 2006; Comba et al., 2001; Kong et al., 2002; James et al., 1999; Valencia et al., 2001). Condensation reactions between carbonyl compounds and primary amines have played an important role for the synthesis of new macrocyclic ligands and its complexes (Agrawal et al., 1965; Sargeson, 1996; Colinson et al., 1996; Tsukube, 1996; Mitewa et al., 1994). These reactions are carried out in presence of suitable metal ions which may serve to direct the condensation preferentially to cyclic

product or to stabilize the macrocycles once formed. Macrocyclic ligand contains active donor groups (N, O or S), which coordinated to central metal ion and provide kinetic and thermodynamic stability to the complexes. As we know mixed donor (N,O- donor) macrocycles can form a stable complex with the transition metals and alkaline earth metal ions(Zhao et al., 1995). A number of macrocyclic natural compounds of alkali and alkaline earth metals have been reported which play important role in the metabolism of plants, respiration of fungal metabolism. The importance of Na^+, K^+, Mg^{2+} and Ca^{2+} ions in biochemical processes have been recently reviewed by Williams, (1970). Nowadays macrocyclic compounds play a vital role in bioinorganic chemistry, catalysis, extraction of metal from solution, and the activation of small molecules gave impetus to this phenomenon (Varghese et al., 2010; Pandey et al., 1998). Synthetic macrocyclic complexes mimic some naturally occurring macrocycles because of their resemblance to many natural macrocycles, such as metalloproteins, porphyrins and cobalamine (Chandra et al., 2008). Large number of important macrocyclic molecules have been reported which exhibit biological activities including antibacterial, antifungal, antitumor, anticancer (Sharma et al., 2013; Kumar et al., 2010; Kulkarni et al., 2009; Pandeya et al., 1999; Bagihalli et al., 2008; Singh et al., 2009; Jadhav et al., 2000; More et al., 2001; Ramesh et al., 2003; Silveria et al., 2008; Illan-Cabeza et al., 2008; Singh et al., 2007). Reaction of 2, 6-diacetylpyridine with diethylenetriamine in the presence of Ba^{+2}, Sr^{+2} or Ca^{+2} refluxing in methanol gives complexes of the macrocyclic ligand (Drew et al., 1981). Chandra and coworkers synthesized a novel tetradentate nitrogen donor [N_4] macrocyclic ligand and its complexes with first row transition metals, which gives an important information about spectral studies and biological approaches of macrocycles(Chandra et al., 2007). Gull et al., (2015) synthesized macrocyclic complexes having formula as $[M(C_{26}H_{28}N_8O_4)].X_2$, {where M= Co^{2+}, Cu^{2+} and Ni^{2+} and X= Cl^-} and antimicrobial studies of these complexes results that the metal complexes are effective drugs against the tested strains as compared to the macrocyclic ligands. Wankhede et al., (2012) have been reported macrocyclic complexes of Mg(II), Ca(II) and Ba(II) derived from condensing diethyl malonate with 1,2-diaminoethane and 1,3-diaminopropane. Prasad et al., (2004) have reported a series of large ring tetraaza-macrocyclic complexes of Ca (II) obtained by the reaction of α-diketones and diaminoalkanes. By keeping these facts in view the present paper describe the synthesis, characterization and biological activities of macrocyclic complexes $[M\ L^1\ L^2].Cl_2$, {where M= Ca(II) and Ba(II), L^1= 1,16-diamine-4,7,10,13-tetraoxahexadecane and L^2= α-diketones such as 2,3-butanedione, 3,4-hexanedione or benzil}. Complexes are made up by condensation reaction of diamine with α –diketones in butanolic medium in presence of metal ion salt. All complexes have been characterized by using spectral technique viz IR, proton NMR, Mass spectra and in vitro antimicrobial screening.

MATERIAL AND METHODS

Material

$CaCl_2$. $2H_2O$ (Himedia) and $BaCl_2$. $2H_2O$ (Merck) used were of AR grade. 2,3-butanedione (Merck), 3,4-hexanedione(Sigma-Aldrich), benzyl (Merck), ethanol, methanol and butanol were purified by distillation and amine *i.e.* 1,16-diamino-4,7,10,13-tetraoxahexadecane was synthesized in our laboratory by using 2-methyl propane2-ol, 3-amino-1-propanol, benzene (distillation), ditosyl ester, KOH pellets, sodium sulphate and potassium metal.

Physical Measurements

The mass spectra were recorded on a MSD1100VL mass spectrometery/ data system. Infra-red spectra of KBr pellets of the complexes were recorded in the region 4000-200cm^{-} on a Nicolet Magna- 550 FTIR spectrometer. Proton-NMR spectra were recorded in DMSO-d_6 on JEOL FX 90 QFT NMR Spectrometer at 90 MHz using TMS as a reference. Calcium was estimated volumetrically by EDTA using Eriochrome Black T as an indicator and Barium was determined gravimetrically as $BaSO_4$. Elemental analyses were also done by the help of analyzer. Molar conductance measured at room temperature in DMSO solutions using a glass cell having cell constant 1.0 and magnetic moment measurements were taken on a model 155 vibrating sample magnetometer.

Anti-microbial Screening

Anti-bacterial Studies

Escherchia coli (gram-negative) ATCC 25922, *Bacillus subtilis* (gram-positive) ATCC 6633, *Pseudomonas putida* (gram-negative) ATCC 2633 pathogenic species of bacteria were used for screening of newly synthesized complexes. *In vitro* antibacterial screening was performed by disc diffusion method (Wilkins et al., 1972) using nutrient agar medium. The nutrient agar medium was prepared by using agar-agar 20g, NaCl 5g, beef extract 5g, peptone 5g and distilled water 1000 mL, was pipette into the petri dish. After solidification, 5mL of warm seeded agar was applied. The seeded agar was prepared by cooling the molten agar to 38°C then adds the 10 mL of bacterial suspension. The complexes were dissolved in methanol in 500 and 1000 ppm concentrations. Paper discs of Whatman No. 1 filter paper measuring diameter of 5mm were soaked in these solutions of varied concentrations . The discs were dried and placed on the medium previously seeded with organisms in petri plates at suitable distance. The Petri plates were stored in an incubator at 36±2°C for 1 Day. These macrocyclic complexes were compared by using standard antibiotic Ciprofloxacin.

Anti-fungal studies

The antifungal screening of the synthesized compounds were checked *in vitro*. The tested pathogenic fungi, namely *Alternaria alternate* ATCC 6663, *Microsporum gypseum* ATCC 2819, *Trichophyton rubrum* ATCC 296 and *Trichophyton tonsurans* ATCC 8475, were obtained from the Seed Pathology Laboratory, Department of Botany, University of Rajasthan, Jaipur, India. The *in vitro* screening of the synthesized complexes was performed by using agar plate technique (Chauhan et al., 2002). The potato dextrose agar (PDA) medium was prepared in the laboratory to maintain fungal growth. Potato Dextrose Agar (PDA), medium was prepared by mixing 1000 ml of potato infusion to 20g each of agar and dextrose followed by autoclaving as usual. Solutions of the test compounds in methanol at 100 and 200 ppm were prepared and then mixed with the medium. The medium was then poured into petri plates and spores of fungi were placed on the medium with the help of inoculum's needle. These petri plates were placed in an incubator at 25±2°C. The activity was determined after 4 days (96 h) of incubation at room temperature (25°C). The antifungal screening data of all the synthesized macrocyclic complexes were compared with standard antibiotic (Fluconazole).

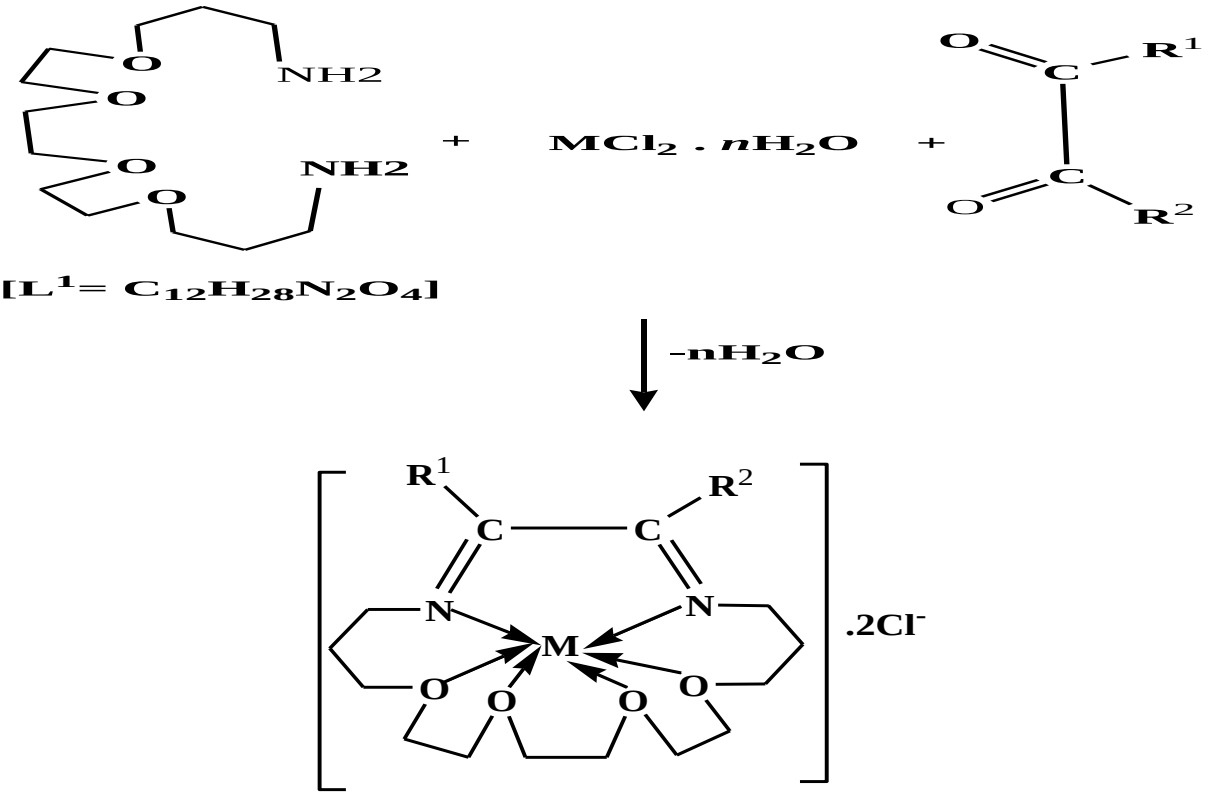
Synthesis of Macrocyclic complexes of Ca (II) and Ba (II)

Firstly we used a convenient method for the preparation of diamine *i.e.* 1, 16- diamino-4,7,10,13-tetraoxahexadecane,

which is made by the reaction of the ditosyl ester with 3-amino-1-propanol in the presence of potassium and KOH pellets in benzene as a solvent(Kern et al., 1979). Ditosyl ester was synthesized by the reaction of triethylene glycol, pyredene and p-toluene ptosylayl chloride in 1:1:1 molar ratios and recrystallized with pet-ether (Sekera et al., 1933). To a butanolic solution of Ca(II) and Ba(II) chloride (about 0.350≈ 0.450g. in 20 ml butanol) a butanolic solution of α-diketones such as 2,3-butanedione, 3,4-hexanedione or benzil (≈0.170g. in 12ml) and 1,16-diamino-4,7,10,13-tetrahexadecane (0.450g.in 15ml butanol) were added with constant stirring. This reaction mixture was stirred for 5-6 hours. pH of the solution measured by pH paper and it was found neutral in these complexes. The solid obtained was filtered, washed with n-butanol and dried under reduced pressure.

RESULTS AND DISCUSSION

The cyclocondensation reactions of hydrated metal chlorides [Metal = Ca(II) or Ba(II)] with 1,16-diamino-4,7,10,13-tetraoxahexadecane and α-diketones viz. as 2,3-butanedione, 3,4-hexanedione or benzil have been carried out in butanolic solution and can be represented as given in **scheme**.



M = Ca(II) or Ba(II)

R^1	R^2
CH_3	CH_3
C_2H_5	C_2H_5
Ph	Ph

Scheme- Metal complexes of 20-membered N_2O_4-donor macrocycles

The resulting macrocyclic complexes have been obtained as light colored solids which are quite stable and exhibit solubility in methanol, DMF and DMSO. Their molecular weights, yields, analyses and temperature of decomposition are recorded in Table-1. Molar conductance measured in DMSO found to be very low (11-21 $ohm^{-} cm^{2} mol^{-}$), showing their non electrolytic behavior. Magnetic moment results show that these complexes are diamagnetic in nature. Same kind of results about the magnetic susceptibility of the macrocyclic complexes of alkaline earth metals Mg (II), Ca (II) and Ba (II), reported by Wankhede et al., (2012).

Table 1. Analyses and characteristics of macrocyclic complexes derived from 1, 16-diamine-4,7,10,13-tetraoxahexadecane and α-diketones

Complexes Molecular formula	Formula Weight/ g	Colour and Decomposition temp. (°C)	Yield (%)	Molar Conductance ($\Omega^{-}cm^{2}mol^{-}$)
$C_{12}H_{28}N_2O_4$(Ligand[1])	264.36g	Light yellow -	65	-
$C_4H_6O_2$(Ligand[a])	86.41g	Light yellow -	-	-
$C_6H_{10}O_2$(Ligand[b])	114.14g	Light	-	-
$C_{14}H_{10}O_2$(Ligand[c])	210.23g	-	-	-
$C_{16}H_{30}N_2O_4CaCl_2$	425.41g	Dirty white 232°C	36	10.8
$C_{18}H_{34}N_2O_4CaCl_2$	453.46g	White color 214°C	47	11.2
$C_{26}H_{34}N_2O_4CaCl_2$	559.51g	Dirty white 228°C	53	14.7
$C_{16}H_{30}N_2O_4BaCl_2$	535.67g	Light brown 234°C	64	16.5
$C_{18}H_{34}N_2O_4BaCl_2$	550.70g	dirty white 246°C	53	16.7
$C_{26}H_{34}N_2O_4BaCl_2$	646.79g	Brown 238°C	59	20.2

Where a= 2,3-butanedione, b= 3,4-hexanedione and c= benzil

IR Spectra

IR spectra of all the Macrocyclic complexes have been recorded. In the spectra of macrocyclic complexes weak to medium intensity absorption bands observed in the region 400-500 cm^{-1}, which are absent in free ligands, may be attributed to υ_{M-O} vibrations. Similar kinds of bands in this region have been assigned to υ_{M-O} vibrations by Prasad et al., (2002) in 2+2 Cyclocondensation reaction of 1,7-diaminoheptane with α-diketones, *viz*. 2,3-butanedione, 3,4-hexanedione or 4,4'-dimethylbenzil, in the presence of Mg^{2+}, Ca^{2+}, Sr^{2+} and Ba^{2+} ions as templates yields a series of complexes of the type [ML(X2)] (where L = N_4 macrocycle having a 22-membered ring and X=Cl or NCS).

The chloro complexes exhibit bands at 430–440cm^{-1} which may be assigned to coordinated chloro groups(Nakamoto, 1970). All the complexes exhibit a strong band at 1580–1645 cm^{-1} due to -(C=N). reported bands at 1620–1640 cm^{-1} due to the coordinated imine groups in Ca(II), Sr(II)] and Ba(II) complexes of macrocycles derived from 2,6-diacetylpyridine and *o*-phenylenediamine. No absorption band at 1700 cm^{-1} characteristic of (C=O) is observed in any of the spectra of these complexes and the absence of absorption bands at 3200–3300 cm^{-1} shows the absence of unreacted primary amine groups. Thus the (C=O) and the NH_2 groups must have reacted, to give (C=N) linkages. Specific C-O-C etheric peaks were observed at 1065-1255 cm^{-1} in the IR spectra of the macrocyclic complexes where as bands observed at 1175-1225 cm^{-1} in free C-O-C etheric diamine. Ugras et al., (2006) reported a newly synthesized macrocyclic schiff base, which also have specific etheric peak due to the presence of etheric group. All the macrocyclic complexes synthesized during the present investigations exhibit bands at 2910–2940cm^{-1} which may be assigned to (C–H) vibrations. Similar bands in the region 2900–3000 cm^{-1} in Co (MePhTIM) have been reported by Eggleston et al., 1989).

^{1}H-NMR Spectra

The ^{1}H NMR spectral data of the ligands and their corresponding metal complexes have been recorded in DMSO-d_6 by using TMS as internal Standard. A peak in the region δ 2.44–2.65 ppm is observed in the spectra of all the complexes due to the residual protons of the solvent DMSO-d_6. In free diamines, peaks observed as follows: δ 1.59 ppm (s, H^a, 4H, -NH_2), 2.19 (m, H^b, 4H, NH_2-$\underline{CH_2}$-), 2.08 (m, H^c, 4H, CH_2-$\underline{CH_2}$-CH_2-), 3.26 (m, H^d, 4H), 3.43 (m, H^e, 4H), 3.47 (m, H^f, 4H) and 3.53 (m, H^g, 4H). In the corresponding metal complexes ^{1}H NMR peaks have been shift towards up field due to coordination of all donor atoms with central metal ion. Similar kinds of result have been reported for the synthesis of α,ω-diaminosubstituted oligo (oxyethylene)s by the use of ditosyl esters of α,ω-dihydroxy oligo (oxyethylene)s and potassium salt of ethanolamine in presence of benzene and t-butyl alcohol(Kern et al., 1979). In free 2,3-butanedione, the methyl protons appears at δ1.46 ppm. The up field shift of the methyl protons in the macrocyclic complex confirms the coordination of the nitrogen of the macrocycle to a central metal atom. In free 3,4-hexanedione ($CH_3^aCH_2^bCOCOCH_2CH_3$), the methyl protons appear as a triplet at δ1.14 ppm and the methylene protons as a quartet at δ2.77 ppm. In the complex the methyl protons (CH_3^a) of the ketone residue are shifted very slightly up field (0.98 ppm). This may be due to the fact that these protons are far removed from the C=N group and, hence, are not affected much by coordination of this group. The methylene protons (CH_2^b) of the ketone residue appear as a quartet at δ2.16 ppm. The up field shift of these CH_2 peaks supports the coordination of the C=N group to the metal atom. However, in complex sof benzil, NMR peaks are observed in between 7.25 to 7.72 ppm and this may be due to the non-equivalence of the aromatic protons as a result of restricted rotation.

Mass Spectra

EI-mass spectra for all the macrocyclic complexes of Ca(II) and Ba(II) have been recorded and spectra of $C_{18}H_{34}N_2O_4CaCl_2$ and $C_{26}H_{34}N_2O_4CaCl_2$ complexes are reproduced in fig-1 and 2. Spectrum of the $C_{18}H_{34}N_2O_4CaCl_2$ complex exhibits a peak at 453.3m/z with very low abundance (6.28%), which is its molecular ion/parental ion peak (calculated atomic mass $[C_{18}H_{34}N_2O_4Ca].Cl_2$, 453.469).

A peak with highest abundance, observed at 265.2m/z (100%) due to the diamine. Similarly at 303.2m/z (95%) a strong peak observed by the loss of $CaCl_2.H_2O$. Many other peaks *viz* 113.0(70%), 115.0(30%), 137.1(30%), 266.2(14%), 208.2(8%), attributable to different fragments of the complex. A peak observed with 50% abundance at 435.3m/z by the loss of $[M\text{-}OH]^+$. Same kind of peak observed at 265.3m/z with 100% abundance due to $(diamine)^+$ in the spectrum of $C_{26}H_{34}N_2O_4CaCl_2$ complex. A peak at 559.3m/z (10%) observed due to $[C_{26}H_{34}N_2O_4CaCl_2]^+$, is its molecular ion peak calculated atomic mass $[C_{26}H_{34}N_2O_4Ca].Cl_2$, 559.516). A peak at 208.1m/z (15%) observed due to $[Benzil]^+$ and many other peaks appeared at112.9m/z(45%), at 114.9m/z(25%), at 303.2(80%), at 435.3(60%), at 397.3m/z(20%) and at 513.4m/z(15%), which exhibit due to fragmentation of the complex. These all data suggest that 2 + 2 cyclocondensation reaction of α-diketones with 1,16-diamino-4,7,10,13-tetraoxahexadecane occur in the presence of Ca(II)chloride.

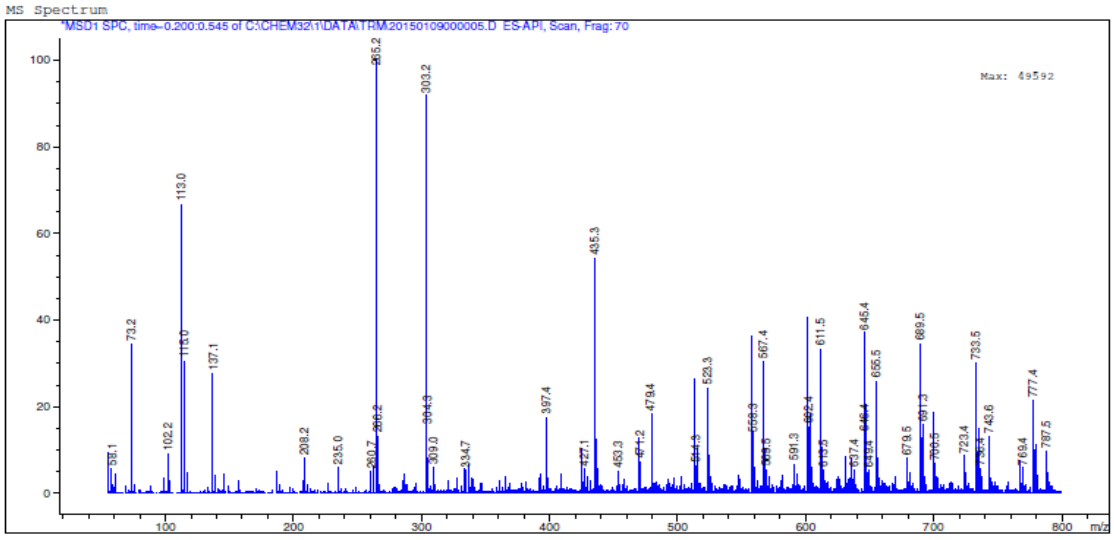


Figure 1. Mass spectrum of 20-membered Oxaaza macrocyclic complex $[C_{18}H_{34}N_2O_4Ca]Cl_2$.

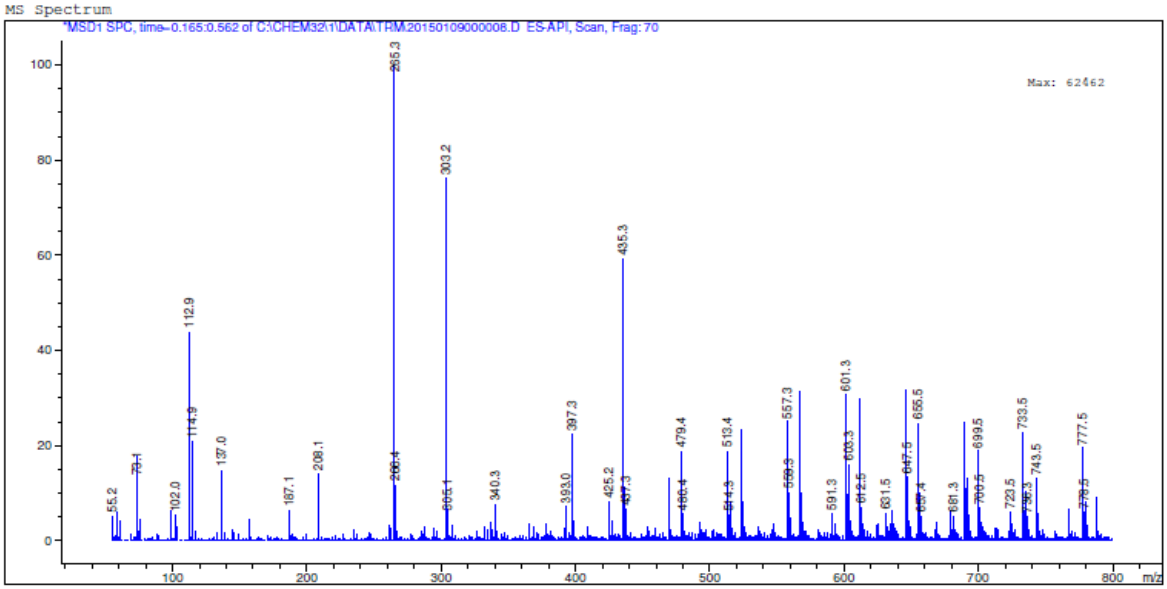


Figure 2. Mass spectrum of 20-membered Oxaaza macrocyclic complex $[C_{26}H_{34}N_2O_4Ca]Cl_2$.

Antibacterial and Antifungal Screening

All synthesized complexes were screened against pathogenic fungal and bacterial strains and the antimicrobial screening shows that the metal complexes exhibit antimicrobial properties against both fungal and bacterial strains. It is important to note that these complexes exhibit more inhibitory effects towards both of the bacterial as well as fungal strains as compare to the parent ligand. The increased activities of the metal complexes as compare to ligand can be explained on the basis of chelation theory.

Table 2. **Antibacterial activities of macrocyclic complexes**.

Complexes	Zone of Inhibition in MM(Conc. in ppm)					
	Bacterial Pathogens					
	E. coli(gm-ve)		*B.subtilis*(gm+ve)		*P. putida*(gm-ve)	
	500	1000	500	1000	500	1000
$C_{16}H_{30}N_2O_4CaCl_2$	+	++	++	++	+	++
$C_{18}H_{34}N_2O_4CaCl_2$	-	++	+	++	+	++
$C_{26}H_{34}N_2O_4CaCl_2$	++	+++	-	++	-	++
$C_{16}H_{30}N_2O_4BaCl_2$	+	++	++	++	+	++
$C_{18}H_{34}N_2O_4BaCl_2$	++	++	-	++	++	++
$C_{26}H_{34}N_2O_4BaCl_2$	+	+++	++	+++	-	++
Ciprofloxacin	++	+++	++	+++	++	++

Table 3. **Antifungal activities of macrocyclic complexes**.

Complexes	Zone of Inhibition in MM(Conc. in ppm)							
	Fungal Pathogens							
	A. alternata		*M. gypseum*		*T. rubrum*		*T. tonsurans*	
	100	200	100	200	100	200	100	200
$C_{16}H_{30}N_2O_4CaCl_2$	-	32.7	13	33.2	41	46.5	48	47.8
$C_{18}H_{34}N_2O_4CaCl_2$	12.5	18.7	14	23.6	27	27.6	29.3	29.8
$C_{26}H_{34}N_2O_4CaCl_2$	17	18.4	25.6	27.4	38	38.9	40	40.2
$C_{16}H_{30}N_2O_4BaCl_2$	26.7	26.8	33	48.7	51.1	51.6	52.1	52.9
$C_{18}H_{34}N_2O_4BaCl_2$	27.2	29.4	32	36.2	42.1	43.3	45.2	45.9
$C_{26}H_{34}N_2O_4BaCl_2$	32.1	45.3	42.1	43.2	53.2	53.5	55.1	56.7
Fluconazole	91±1.1	96±.8	93	94±1.3	92	95±1.2	92±0.7	97±1.1

According to chelation theory(Ei-Behery et al., 2007), chelation decreases the positive charge of metal ion by the partially sharing of its positive charge with donor atoms of the ligand and stability of the complex increases by the π-electron delocalization over the whole chelate ring. This increases the lipophobic character of the metal chelate and favors its permeation through the lipid layer of the microbial membranes and blocks the metal bonding sites on the enzymes of microorganism. All macrocyclic metal complexes were compared with standard antibiotic Fluconazole for fungi and Ciprofloxacin for bacteria. These complexes show better antimicrobial activities but less active as compared to the Fluconazole and Ciprofloxacin as standard drugs. Sharma et al., (2013) synthesized and tested the antifungal, antibacterial and anti fertility activities of macrocyclic complexes of Tin(II). The results indicate that Ba(II) complexes showed more effective and better antimicrobial activity than Ca(II) complexes. Table 2 & 3 representing antibacterial and antifungal activities for the complexes respectively.

CONCLUSIONS

Based on various physicochemical and spectral studies, it can be proposed that all complexes are nonelectrolytic, diamagnetic in nature and Macrocyclic ligand exhibit a hexacoordinated environment around the metal ion. Mass spectral study further confirms the proposed structure of the complexes because the fragmentation of complex into its precursors confirms that there is 2+2 cyclocondansation reaction occur in presence of metal ion. The IR spectral data reveal that a broad band appears at 1580-1645 cm^{-1} due to the presence of υ(C=N), which confirmed the cyclocondensation reaction of the both ligands in presence of metal salt.s All complexes are biologically active and exhibit antimicrobial activities. The enhancement in biological activity upon coordination may be elucidated on the basis of overtone's concept and chelation theory.

ACKNOWLEDGEMENTS

The authors are thankful to the Head, Department of Chemistry, University of Rajasthan, Jaipur, for providing laboratory facilities and IR analysis, The Head, Therachem Institute, Jaipur for Mass and NMR Spectral analysis, The Head, Banasthali Vidyapith, Banasthali, Rajasthan, for magnetic data and The Head, Department of Botany, University of Rajasthan, Jaipur, for antibacterial and antifungal screening.

REFERENCES

Bagihalli, G. B., Avaji, P. G., Patil, S. A. and Badami, P. S. 2008. Syntesis, spectral characterization, in vitro antibacterial, antifungal and cytotoxic activities of Co(II), Ni(II) and Cu(II) complexes with 1,2,4-triazole Schiff bases. *Eur. J. Med. Chem.* 43: 2639-2649.

Chandra, S. and Gupta, L. K. 2007. Synthesis spectroscopic and biological approach in the characterization of novel [N_4] Macrocyclic ligand and its transition metal complexes. *Trans. Met. Chem*. 32:558-563.

Chandra, S. and Pundir, M. 2008. Spectroscopic characterization of chromium(III), manganese(II) and nickel(II) complexes with a nitrogen donor tetradentate, 12-membered azamacrocyclic ligand. *Spectrochim. Acta A.* 69:1-7.

Chauhan, J. B., Subramanian, R. B. and Sanyal, P. K. 2002. Influence of heavy metals and a fungi side on growth profiles of nematophagous fungus, Arthrodotrys musiformis A potential biocontrol agent against animal parasitic nematodes. *Indian j. Environ. Toxicol.*12: 22-28.

Colinson, S. R. and Fenton, D. E. 1996. Metal complexes of bibracchial Schiff base macrocycles. *Coord Chem. Rev.* 148:19-40.

Comba, P., Luthar, S. M., Maas, O. and Pritzkow, V. A. 2001. Template synthesis of a tetraazamacrocyclic ligand with two pendant pyridinyl groups: properties of the isomers of the metal-free ligand and of their first-row transition metal compounds. *Inorg. Chem.* 40:2335-2345.

Curtis, N. F. and Curtis, Y. M. 1965. Some Nitrato-Amine Nickel (II) Compounds with Monodentate and Bidentate Nitrate Ions. *Inorg. Chem.* 4:804-809.

Drew, M. G. B., Nelson, J. and Nelson, S. M. 1981. Metal-ion-controlled transamination in the synthesis of macrocyclic Schiff-base ligands. Part 2. Stepwise synthesis, ring expansion/contraction, and the crystal and molecular structure of a ten-co-ordinate barium(II) complex. *J. Chem. Soc., Dalton Trans.* 1678-1684.

Eggleston, D. S. and Jackels, S. C. 1980. Tetra substituted [14]-1,3,8,10-tetraene N4 macrocyclic complexes: synthesis, organic precursor, and template reaction mechanism *Inorg. Chem.* 19:1593-1599.

EI-Behery, M. and EI-Twigry, H. 2007. Synthesis, magnetic, spectral and antimicrobial studies of Cu(II), Ni(II), Co(II), Fe(III) and UO_2(II) complexes of a new Schiff base hydrazone derived from 7-chloro-4-hydrazinoquinoline. *Spectrochimica Acta A.* 66:28-36.

Gull, P. and Hashmi, A. A. 2015. Biological activity studies on metal complexes of Macrocyclic Schiff base ligand: Synthesis and spectroscopic characterization. *J. Braz. Chem. Soc.* 00:1-7.

Illan-Cabeza, N. A., Hueso-Urena, F., Moreno-Carretero, M. N., Martinez-Martos, J. M. and Ramirez-Exposito, M. J. 2008. Synthesis, characterization and antiproliferative activity of metal complexes with the Schiff base derived from the condensation 1:2 of 2,6-diformyl-4-methylphenol and 5,6-diamino-1,3-dimethyluracil. *J. Inorg. Biochem*. 102:647-655.

Jadhav, V. D., Phule, R. M., Archana, Y. V. and Vibhute, Y. B. 2000. Synthesis and antimicrobial activity of some new Schiff bases. *Orient. J. Chem.* 16:553-556.

James, S., Kumar, D. S. and Alexander, V. 1999. Synthesis of lanthanide(III) complexes of 20-membered octaaza and hexaaza Schiff-base macrocyles. *J. Chem. Soc. Dalton Trans.* 999: 1773-1778.

Kern, W., Iwabuchi, S., Sato, H. and Bohmer, V. 1979. A convenient synthesis of α-ω-diamino substituted oligo (oxyethylene)s. *Makromol, Chem.* 180:2539-2542.

Kulkarni, A., Patil, S. A. and Badami, P. S. 2009. Synthesis, characterization, DNA cleavage and in vitro antimicrobial studies of La(III), Th(VI) and Vo(IV) complexes with Schiff bases of coumarin derivatives. *Eur. J. Med. Chem.* 44:2904.

Kumar, G., Kumar, D., Devi, S., Johari, R. and Singh, C. P. 2010. Synthesis, spectral characterization and antimicrobial evaluation of Schiff base Cu(II), Ni(II) and Co(II) complexes. *Eur. J. Med. Chem.* 45:3056.

Kumar, R. and Singh, R. 2006. Coordination chemistry of copper(II) complexes with N_4, N_4S_2, and N_4O_2 donor macrocyclic ligands: Biological aspects—antifungal, synthesis, spectral studies, and magnetic moments. *Russ. J. Coord. Chem*. 32:192-198.

Kong, D., Huang, X. and Xie, Y. 2002. . Synthesis, stability and structural characterization of a new Macrocyclic ligand with four neutral pendent groups: 1,4,7,10-tetrakisbenzyl-1,4,7,10-tetraazacyclo dodecane (L) and its Co and Cu complexes. *Inorg. Chimic. Acta* 340:133-138.

Mitewa, M. and Bentechev, P. R. 1994. Coordination chemistry of N_6 macrocycles. *Coord Chem. Rev.* 135/136:129-163.

More, P. G., Bhalvankar, R. B. and Pattar, S. C. 2001. Synthesis and biological activities of Schiff bases of aminothiazoles. *J. Indian Chem. Soc.* 78:474-475.

Nakamoto, K. 1970. *Infrared Spectra of Inorganic and Coordination Compounds,* Wiley Inter Science, New York, p. 214.

Pandey, G. K., Srivastava, S., Pandey, O. P. and Sengupta, S. K. 1998. Template synthesis and spectroscopic studies on oxovanadium(iv) acyclic and macrocyclic complexes. *Indian J. Chem.* 37A: 447-451.

Pandeya, S. N., Sriram, D., Nath, G. and Clercq, E. D. 1999. Synthesis and antimicrobial activity of Schiff and Mannich bases of isatin and its derivatives with pyrimidine. *Il Farmaco* 54:624-628.

Prasad, R. N., Agrawal, M. and Malhotra, S. 2004. Ca(II) complexes of tetraazamacrocycles derived from 3, 4-hexenedione and diaminoalkanes. *J. Serb. Chem. Soc*. 69:661-668.

Prasad, R. N. and Gupta, S. 2002. Synthesis and characterization of 2,3,13,14-tetramethyl (ethyl or p-tolyl)-1,4,12,15-tetraazacyclodocosa-1,3,12,14-tetraene complexes of Mg(II), Ca(II), Sr(II) and Ba(II). *J. Serb. Chem. Soc.* 67(7):523-530.

Ramesh, R. and Maheswaran, S. 2003. Synthesis, spectra, dioxygen affinity and antifungal activity of Ru(III) Schiff base complexes. *J. Inorg. Biochem.* 96:457-462.

Sargeson, A. M. 1996. The potential for the cage complexes in biology. *Coord Chem. Rev.* 151:89-114.

Sekera, V. C. and Marvel, C. S. 1933. Higher alkyl sulfonates. *Urbana, illionis* 55:345-349.

Sharma, K., Agarwal, S. and Gupta, S. 2013. Antifungal, sntibacterial and antifertility activities of biologically active Macrocyclic complexes of Tin(II). *Int. J. Chem. Tech. Res*. 5:456-463.

Silveira, V. C., Luz, J. S., Oliveira, C. C., Graziani, I., Ciriolo, M. R. and Ferreira, A. M. C. 2008. Double-strand DNA cleavage induced by oxindole-Schiff base copper(II) complexes with potential antitumor activity. *J. Inorg. Biochem.* 102:1090-1103.

Singh, K., Bharwa, M. S. and Tyagi, P. 2007. Synthesis and characterization of cobalt(II), nickel(II), copper(II), and zinc(II) complexes with Schiff base derived from 4-amino-3-mercapto-6-methyl-5-oxo-1,2,4-triazine. *Eur. J. Med. Chem.* 42:394-402.

Singh, D. P., Kumar, K. and Sharma, C. 2009. Antimicrobial active macrocyclic complexes of Cr(II), Mn(III) and fe(III) with their spectroscopic approach. *Eur. J. Med. Chem.* 44:3299-3304.

Singh, D. and Kumar, R. 2007. Trivalent metal ion directed synthesis and characterization of Macrocyclic complexes. *J. Serb. Chem. Soc* 72: 1069-1074.

Tsukube, H. 1996. Armed crown ether complexes in supramolecular assembly. *Coord Chem. Rev.*148:1-17.

Ugras, H. I., Basaran I., Kilic, T. and Cakir, U. 2006. Synthesis, complexation and antifungal, antibacterial activity studies of a new Macrocyclic Schiff base. *J. Heterocyclic. Chem.* 43:1679-1684.

Valencia, L., Adams, H., Bastida, R., Fenton, D. E. and Macias, A. 2001. Synthesis and characterization of silver, zinc and cadmium compounds with an N_2O_2 Schiff base macrocycles: the crystal and molecular structure of the silver(I) and cadmium(II) complexes. *Inorg. Chimica Acta.* 317:45-52.

Varghese, S. and Muraleedharan, M. K. 2010. Spectroscopic and antimicrobial studies of some 2-hydroxylbenzilidene-3-aminophenol complexes. *Int. J. app Bio and Pharmal Tech.* 1:347-353.

Wankhede, D. S., Wagh, P. B. and Shankarrao, O. 2012. Synthesis, characterization and biological activities of Macrocyclic complexes of alkaline earth metals such as Mg(II), Ca(II) and Ba(II). *Asian. J. Bio. Pharma. Res.* 2:126-134.

Wilkins, T. D., Holdeman, L. V., Abramson, I. J. and Moore, W. E. C. 1972. Standardized single-disc method for antibiotic susceptibility testing of anaerobic bacteria. *Antimicrob. Agents. Chemothe*. 6:451-459.

Williams, R. J. P. 1970. *Quart. Rev* 24:331; *Advan. Chem. Ser.* 100 : (1971) 155.

Zhao, B., Wu, Y. J. and Tao, J. C. 1995. The synthesis of new nitrogen-oxygen donor macrocycles and liquid membrane transport of alkali cations. *Polyhedron.* 14:3557-3561.

Corresponding author: Swati Bugalia, Department of Chemistry, University of Rajasthan, Jaipur – 302004, India
Email: mithagr@gmail.com, swati.bugalia@gmail.com