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Research Article

SYNTHESIS AND STRUCTURAL CHARACTERIZATION OF 16-MEMBERED SCHIFF BASE MACROCYCLES

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ABSTRACT

Novel tetraazamacrocyclic complexes of Cu(II), Co(II), Ni(II) and Zn(II) has been synthesized from the reaction of ethylenediamine with Meldrums acid and divalent metal ions using solid-supported perchloric acid ($HClO_4$-SiO_2) as a catalyst. The complexes were characterized by IR, ^{1}HNMR, EPR spectra, magnetic moments, conductance, thermal analysis and powder XRD analysis. The antimicrobial studies of these complexes against *Staphylococcus typhi*, *Staphylococcus aurieus*, *Escherichia coli*, *Bacillus subtilis* species by Minimum Inhibitory Concentration (MIC) method revealed that these complexes possess potent antibacterial activity.

Keywords: Complexes, Meldrums acid, Thermal analysis, Magnetic moments, Antimicrobial.

1. INTRODUCTION

The diversified role played by the naturally occurring macrocycles in biological systems is well known. Several macrocyclic complexes have been reported to possess remarkable antibacterial, antifungal and anti-inflammatory activities [1-2] and are used as dyes and pigments, MRI contrast agents and models for naturally occurring macrocycles [3-6]. In addition, macrocyclic nickel complexes find use in DNA recognition and oxidation [7] while copper complexes find use in DNA binding and cleavage [8]. Generally, macrocyclic complexes of type [$M(C_{16}H_{28}N_4)X_2$], where M = Cu(II), Co(II), Ni(II), Zn(II) and X = Cl,$^-$ NO_3,$^-$ CH_3COO^- are prepared by refluxing ehylenediamine, acetonyl acetone and metal salt in methanol or ethanol (template method) [9].

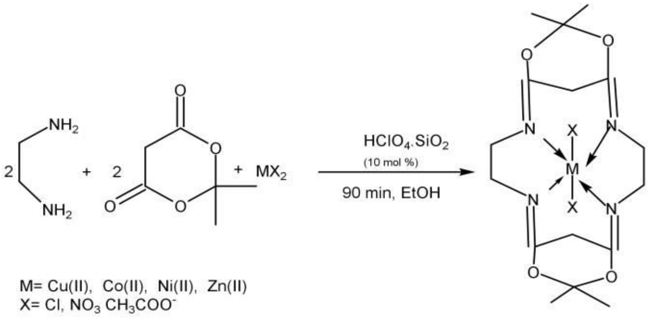
2. EXPERIMENTAL

2.1. Material and methods of analysis

IR spectra (400-4000 cm^{-1}) were recorded on Shimndzu FTIR spectrophotometer using KBR discs, and the absorption bands are expressed in cm^{-1}. ^{1}H NMR spectra were recorded in DMSO-d_6 with tetramethyl silane as an internal standard. Molar conductivity of 10^{-3} M solution in DMSO was obtained on C-100 Elico digital conductivity meter at room temperature. Magnetic susceptibilities were recorded on Guoy balance using AR grade $CuSO_4$ and $FeSO_4$ as standard. EPR spectra of complexes are performed in solid state at room temperature on Varian-E-4X band EPR spectrophotometer. TG/DTA scans were recorded on Mettler-Toledo-851 TGA-DTA instrument at linear heating rate of 10° per minute under nitrogen atmosphere in a temperature range 25-1000°C. X-ray powder diffraction patterns of complexes were recorded in the 2θ range of 10-80° on Bruker X-D-8 advanced diffractometer and XRD scans with the help of powder X-programme. Analytical grade chemicals brought from Sigma-Aldrich, INC. were used throughout this work.

2.2. Present Work

Novel macrocyclic complexes of type [$M(C_{20}H_{32}N_4)X_2$] and [$M(C_{16}H_{24}N_4O_4)X_2$] have been synthesized by non-template method utilizing solid-supported perchloric acid ($HClO_4$-SiO_2) as a catalyst at room temperature (Scheme 1). The investigated complexes were characterized and evaluated for their antimicrobial activity against four bacterial strains.



Scheme 1

2.3. Typical Procedure for the synthesis of $[Cu(C_{16}H_{24}N_4O_4)Cl_2]$

A mixture of ethylenediamine (10 mmol), copper chloride (5 mmol) and meldrums acid along with 10 mol% solid-supported perchloric acid in ethanol (50 mL) was stirred at room temperature for 90 min. The resulting colored complex along with insoluble catalyst was filtered, washed with ethanol, acetone and petroleum ether. To separate the catalyst, complex was dissolved in DMSO (2 x 15 mL) and then filtered. The filtrate was then concentrated under reduced pressure to afford shiny blue colored copper complex, which was dried over calcium chloride (65% yield).

3. RESULTS AND DISCUSSION

3.1. Chemistry

The analytical data suggest the formula of macrocylic complexes as $[M(C_{16}H_{24}N_4O_4)X_2]$ where M = Co(II), Ni(II), Cu(II), Zn(II) and X = Cl^{-1}, NO_3^{-1} and CH_3COO^{-1}. The anion test is positive after decomposing the complexes with concentrated HNO_3, indicating their presence inside the coordination sphere [9]. Conductivity measurements in DMSO indicate them to be non electrolytic in nature (10-20 $ohm^{-1}cm^2mol^{-1}$) [10]. The melting points of all complexes were above 200ºC and all complexes are intensively colored. Magnetic movement values suggest octahedral environment around metals (Table 1) [11].

Table 1: Analytical data of $M(C_{16}H_{24}N_4O_4)X_2]$type Complexes

Mol. for. of complex	Mol. Wt.	Colour	Melting Point	Elemental Analysis %C	Elemental Analysis %H	Elemental Analysis %N	Mol. Cond Mohs $cm^2 Mol^{-1}$	M.M. B. M.
$[Cu(C_{16}H_{24}N_4O_4)Cl_2]$	470.83	Blue	225	40.83 (40.34)	5.13 (4.87)	11.89 (11.56)	11	1.77
$[Cu(C_{14}H_{24}N_4O_4)(CH_3Coo)_2]$	523.94	Dark Blue	230	36.67 (36.21)	4.61 (4.21)	16.04 (15.76)	09	1.76
$[Cu(C_{14}H_{24}N_4O_4(NO_3)_2]$	518.02	Blue	233	46.37 (46.00)	5.83 (5.39)	10.81 (10.43)	13	1.78
$[Co(C_{14}H_{24}N_4O_4)Cl_2$	466.23	Brown	236	42.21	5.18 (4.97)	12.01 (11.76)	08	4.80
$[Co(C_{14}H_{24}N_4O_4)(NO_3)_2]$	519.33	Brown	234	37 (36.87)	4.65 (4.26)	16.18 (15.87)	15	4.83
$[Co(C_{14}H_{24}N_4O_4)(CH_3COO)_2]$	513	Black	239	46.78 (46.20)	5.88 (5.34)	10.91 (10.39)	14	4.82
$[Ni_9C_{14}H_{24}N_4O_4)Cl_2]$	466	Light Green	243	41.23 (40.87)	5.19 (4.90)	12.02 (11.78)	12	2.80
$[Ni(C_{14}H_{24}N_4O_4)(NO_3)_2]$	519.11	Green	249	37.02 (36.65)	4.66 (4.28)	16.18 (15.87)	07	2.82
$[Ni(C_{14}H_{24}N_4O_4)(CH_2COO)_2]$	513	Green	250	40.80 (40.30)	5.89 (5.57)	10.91 (10.34)	09	2.85
$[Zn(C_{14}H_{24}N_4O_4)Cl_2]$	472.66	Buff	246	40.65 (40.23)	5.11 (5.07)	11.85 (11.34)	12	-
$[Zn(C_{14}H_{24}N_4O_4)(NO_3)_2]$	525.77	Buff	255	36.55 (36.10)	4.60 (4.21)	15.98 (15.45)	12	-
$[Zn(C_{14}H_{24}N_4O_4)(CH_3COO)_2]$	519	Buff	253	46.20 (45.89)	5.81 (5.53)	10.77 (10.62)	14	-

3.2. Infrared spectra

The infrared spectra of complexes (Table 2) do not exhibit broad peak in the region 3230-3260 cm^{-1} for ν (NH_2) and strong peak in the region 1700-1720 cm^{-1} for ν (C=O) group. This confirms the condensation of acetyl dimedone/meldrums acid and amino groups of ethylene diamine [12-13]. The appearance of two new peaks in the region 1565-1606 cm^{-1} and 1000-1350 cm^{-1} for ν (C=N) and ν (C-N) respectively supports the formation of macrocyclic frame [14]. Further, the presence of peak in the region 420-460 cm^{-1} for ν (M-N) indicates coordination of azomethine nitrogen [15-16].

Table 2: IR spectra of complexes

Compound	v(C=N)	v(C-N)	v(M-N)
$[Zn(C_{16}H_{24}N_4O_4)Cl_2]$	1575-1610	1000-1310	420-460

3.3. NMR Spectra

The ^1H NMR spectrum of $[M(C_{16}H_{24}N_4O_4)X_2]$ type complexes shows signal of $-NCH_2CH_2N-$ protons (8H) at δ = 2.00 ppm, $-CCH_2C-$ protons (4H) at δ = 2.60 ppm, while $-CH_3$ protons (12H) appeared at δ = 3.25 ppm

3.4. EPR Spectra

The EPR spectra of the $[Ni(C_{16}H_{24}N_4O_4)(NO_3)_2]$ complex in powder form at room temperature shows isotropic signals with $g_{\parallel}=1.9995$, $g_{\perp} = 1.9955$, and $g_{iso} = 1.9968$, $A_{\parallel}= 6.66G$, $A_{\perp} = 13.33G$, and exchange coupling interaction constant $G = 0.3846$. This finding indicates that the observed 'g' values for the complex are less than 2.3 in agreement with the covalent character of the metal ligand bond [17-20]. The trend $g_{\parallel} > g_{\perp} > 2.0023$ observed for the Co(II) and Ni(II) complexes indicated that unpaired electron is localized in the dx^2-y^2 orbital [21-23].

Table 3: ^{1}H NMR spectra of complexes

Compound	$-CH_3$	$-NCH_2$ CH_2N-	$-CCH_2$ $C-$	$-CCH_2$ $C-$
$[Zn(C_{16}H_{24}N_4O_4)(NO3)_2]$	3.25	2.00	2.30	-

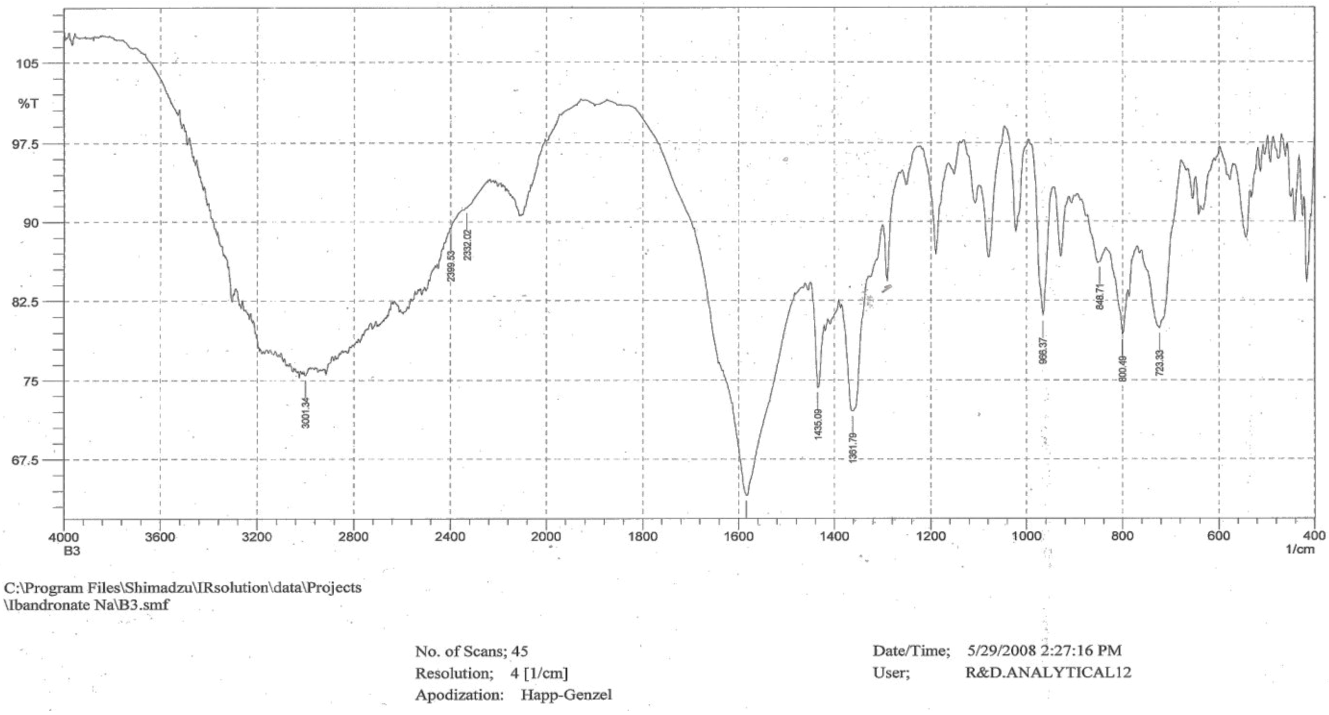


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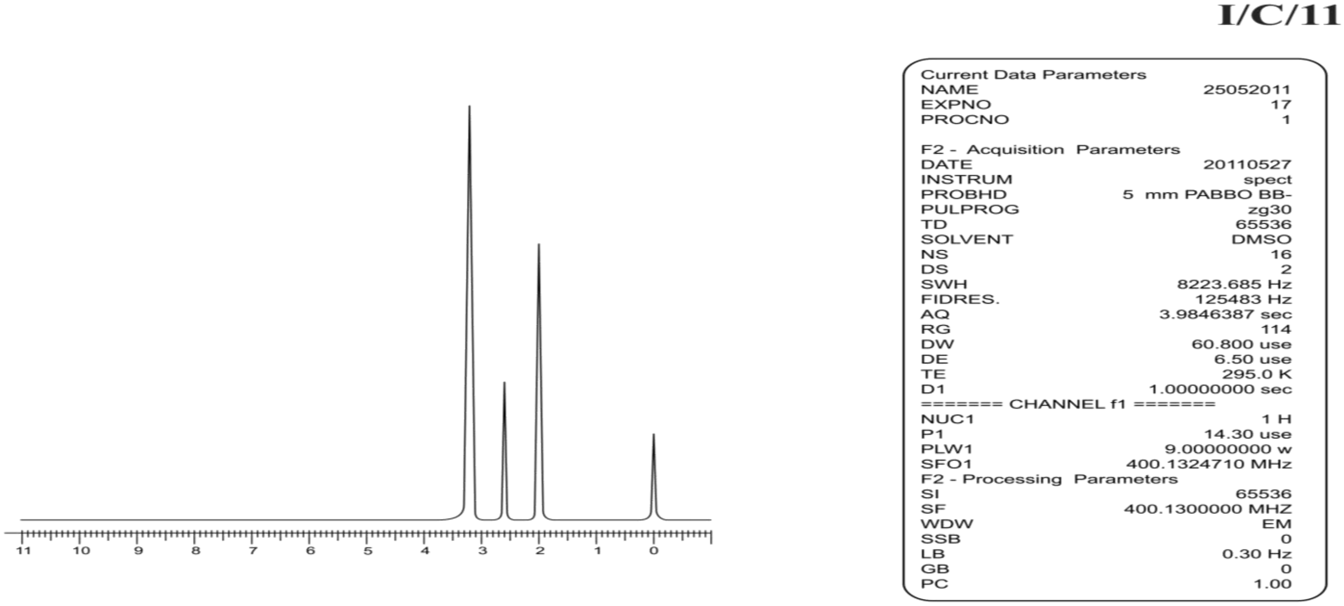
Fig. 1: IR Spectrum



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DS                          2
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FIDRES.             125483 Hz
AQ              3.9846387 sec
RG                        114
DW                 60.800 use
DE                   6.50 use
TE                    295.0 K
D1             1.00000000 sec
======= CHANNEL f1 =======
NUC1                      1 H
P1                  14.30 use
PLW1             9.00000000 w
SFO1           400.1324710 MHz
F2 - Processing  Parameters
SI                      65536
SF             400.1300000 MHZ
WDW                        EM
SSB                         0
LB                    0.30 Hz
GB                          0
PC                       1.00
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Fig. 2: ^{1}H NMR Spectra

Table 4: EPR parameters for metal complexes

Complex	Gyromatric ratio g	A gauss	G	e/gm *10 ^{21}
$(Cu(C_{24}H_{26}N_6O_4)(NO_3)_2]$	$g_{\|\|} = 1.9995$ $g_{\perp} = 1.9955$ $g_{av} = 1.9968$	$A_{\|\|} = 6.66$ $A_{\perp} = 13.33$	03846	1.5048

3.5. Powder X-ray analysis

Powder XRD diffractogram of Ni(II) complexes were recorded in the range 20-80° at wavelength 1.5447° A. The diffractogram and associated data depict the 2θ value for each peak, relative intensity and inter-planar spacing (d-values). Major refluxes were used to determined corresponding interplaner distances. The X-ray diffraction pattern of Ni(II) complexes with respect to major peaks having relative intensity greater than 10% has been indexed by using computer programme. Miller indices (hkl), unit cell parameteplers and unit cell volume were also obtained from above indexing method. The unit cell of Ni(II) complex yielded values of lattice constants a =11.3927, b =6.1167, c = 10.5121 and unit cell volume 665.21°A^3. Also, in association with these cell parameters, the conditions such as $a \neq b \neq c$ and $\alpha = \gamma = 90^0 \neq \beta$ required for sample to be monoclinic were tested and found satisfactory. In conclusion the complexes Ni(II) have monoclinic crystal system [24-30].

The experimental density values of complexes were determined using specific gravity method and found to be 0.7761 g cm^{-3} for the Ni(II) complexes respectively.

Using the experimental density values, ρ, the molecular weight of the complexes, M, Avogadro's number, N, and the volume of unit cell, V, the number of molecules per unit cell, n, were calculated using the equation $\rho = nM/NV$ and they were found to be one. With these values, the theoretical densities were computed and found to be 0.7787 g cm^{-3} for respective complexes. Comparison of experimental and theoretical density value shows good agreement within the limits.

3.6. Thermal Analysis

On TG curve of $[Co(C_{16}H_{24}N_4O_4)(NO_3)_2]$ complex, mass loss of 11.31% (calc. 12.93%) in the range 25-220°C indicating the removal of non-coordinated water and partial part of nitrate. An endothermic peak on DTA curve at 110°C also corresponds to dehydration and partial loss of nitrate. The second step of the decomposition between 220-290°C with 39.13% mass loss (calc. 39.57%) is attributed to the removal of the coordinated nitrate and organic moiety of the complex. An exothermic peak in the DTA curve at 230°C was observed. The third step, from 290 to 400°C with mass loss 43.48% (calcd. 43.24%) corresponds to removal of remaining part of coordinated ligand. For this a broad exothermic peak was observed in DTA. The mass loss continued with slow decomposition of the remaining part upto 800°C corresponding to final residue of cobalt oxide. Amount of copper oxide found in residue is close agreement with calculated [31-40].

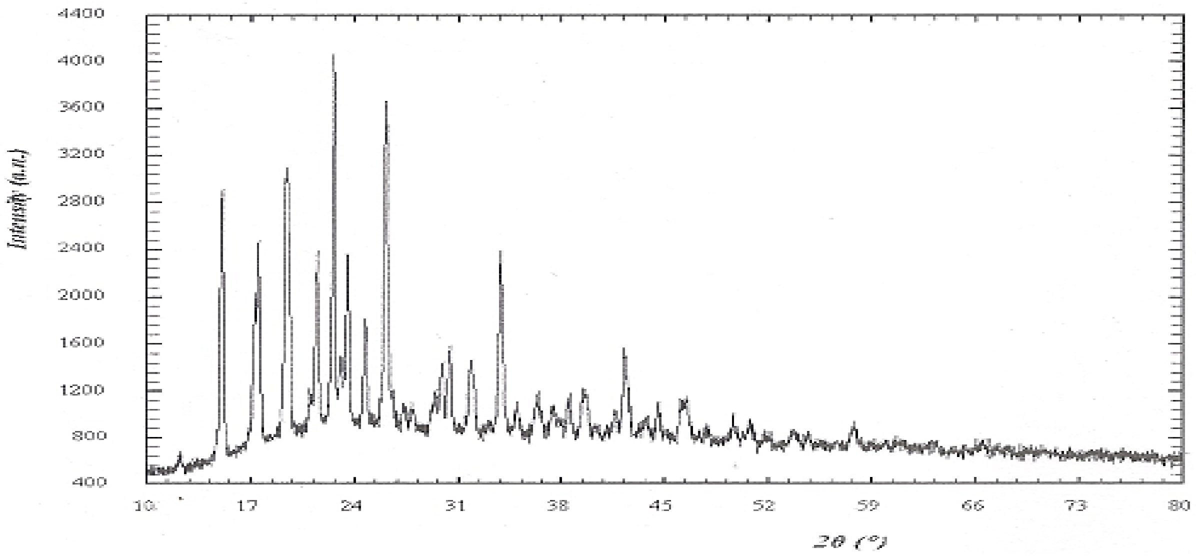

Fig. 3: Powder X-ray analysis

Table 5: Millar indices and interplaner distances

Complex	h k l	2θ obseraved	2θ calculated	d
$[Ni(C_{16}H_{24}N_4O_4)(NO_3)_2]$	1 0 1	15.033	15.022	5.8886
	2 0 0	17.140	17.128	5.1690
	2 1 0	22.491	22.492	3.9499
	2 0 2	30.332	30.311	2.9443
	2 1 2	33.745	33.738	2.6539
	1 0 4	42.232	42.244	2.1381

Table 6: Thermal decomposition and kinetic parameters

Complex	DTA Peak °C	Temp. range °C	Mass loss (%) obser (calcu)	Nature of decomposition	Order of reaction	Δ E Kg/mole	ΔS JK/ molde	ΔG KJ/mole	Frequency factor Z
$[Co(C_{16}H_{24}N_4O_4)(NO_3)_2]$	110	0-220	11.31 (12.93)	NO_3-&H_2O	1.9	6.977	-276.292	21.161	$3.211x10^{-2}$
	230	220-290	39.13 (39.57)	NO_3-&Ligand	1.1	11.195	-252.529	27.617	$7.306x10^{-1}$
	310	290-400	43.48 (43.24)	Meldrums acid	0.5	27.213	-224.667	43.319	$2.296x10^{-1}$

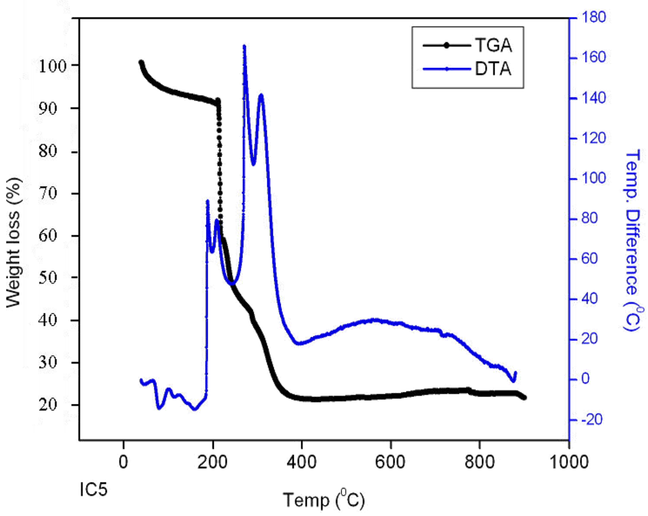

Fig. 4: TGA and DTA curve of $[Co(C_{16}H_{24}N_4O_4)(NO_3)_2]$ complex

3.7. Kinetic Data

The kinetic and thermodynamic parameters viz, order of reaction (n), energy of activation (E_a), three exponential factor (Z) etc. for non-isothermal decomposition of metal complexes were determined by the Horowitz-Metzar approximation method. The data obtained are given in (table 6). The calculated values of the activation energy of the complexes are relatively low, indicating the autocatalytic effect of the metal ion on the thermal decomposition of the complex. The negative activation entropy values suggest that the activated complex were more ordered than the reactants and that the reaction were slow. The more ordered nature may be due to polarization of bonds in activated state.

3.8. Antimicrobial activity

The *in vitro* antibacterial activities of synthesized complexes have been studied by disc diffusion method. The antibacterial activities were done at 100 μg /ml concentrations in DMF solvent using four bacterial strains *S. typhi* (MTCC3858), *S. aureus* (MTCC 737), *E. coli* (MTCC1687) and *B. subtilis* (MTCC441) by the minimum inhibitory concentration (MIC) method [41].

Table 7: Antibacterial activity of complexes of type $[M(C_{16}H_{24}N_4O_4)X_2]$

Complexes	Inhibition zone (mm)			
	S. typhi	*S. aureus*	*E. coli*	*B. subtilis*
$[Cu(C_{16}H_{24}N_4O_4)Cl_2]$	9	10	7	7
$[Cu(C_{16}H_{24}N_4O_4)(NO_3)_2]$	10	9	10	8
$[Cu(C_{16}H_{24}N_4O_4)(CH_3COO)_2]$	12	10	9	8
$[Co(C_{16}H_{24}N_4O_4)Cl_2]$	18	27	15	11
$[Co(C_{16}H_{24}N_4O_4)(NO_3)_2]$	17	16	15	12
$[Co(C_{16}H_{24}N_4O_4)(CH_3COO)_2]$	15	15	13	10
$[Ni(C_{16}H_{24}N_4O_4)Cl_2]$	17	14	15	14
$[Ni(C_{16}H_{24}N_4O_4)(NO_3)_2]$	16	14	12	12
$[Ni(C_{16}H_{24}N_4O_4)(CH_3COO)_2]$	22	19	16	17
$[Zn(C_{16}H_{24}N_4O_4)Cl_2]$	15	11	12	11
$[Zn(C_{16}H_{24}N_4O_4)(NO_3)_2]$	13	11	11	9
$[Zn(C_{16}H_{24}N_4O_4)(CH_3COO)_2]$	11	12	9	8
Cefodox	22	27	22	20
Linazoid	25	28	22	20

All the strains were procured from CSIR, Institute of Microbial Technology, Sector MA, Chandigarh-160036, India. The bacterial strains were incubated for 72 h at 27°C. Standard antibacterial (Cefodox and

Linazoid) were used for comparison under similar conditions. Activity was determined by measuring the diameter of the zone of inhibition (mm) (Table 7).

Table 7 indicated that Co(II) and Ni(II) complexes are more active against the bacterial strains *S. aureus* and *S.typhi* as compared to other bacterial strains. Cu (II) and Zn (II) complexes were found to be moderately active against all bacterial strains.

4. CONCLUSION

From analytical and spectral data of new series of macrocyclic ligand complexes, it is concluded that macrocyclic complexes acts as tetradentate with nitrogen donor transition metal complexes of the type [M ($C_{16}H_{24}N_4O_4$)X_2]. Where M= Co(II),Cu(II),Ni(II) and Zn(II). The infrared and magnetic moment data indicates octahedral environment at the metal centers. The EPR spectra of Ni (II) complexes shows sharp peaks indicating no distortion and g value indicate sufficient covalent nature of metal ligand bond. Powder X-ray diffraction studies of complexes indicates monoclinic system and lattice type P2/M. The number of water molecules and thermal stability of complexes was determined by thermal analysis. The complexes would be expected to exhibit the physiological properties with enhanced intensity.

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Conflict of interest

The authors confirm that this article content has no conflict of interest.

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