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Antibacterial activities of transition metal complexes along with their formation and description

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Abstract
Macrocyclic ligands are polydentate ligands containing donor atoms attached to cyclic backbone and showed significance in various biological studies. macrocyclic complexes of transition metals, Ni(II), Cu(II), Fe(III), and Mn(II) were synthesized in methanolic media using template method. These complexes were non-hygroscopic and consist of crystalline solids. Structural identification of these complexes was done using analytical techniques and IR Spectroscopy. The antibacterial activities of macrocyclic complexes (1-6) were screened against both Gram-negative bacteria and Gram-positive bacteria. In the present study we have reported that these synthesized complexes showed slight antibacterial activity except macrocyclic complex (6) which showed moderate antibacterial activity.

Keywords: Transition metals, macrocyclic complexes, UV-Vis and IR Spectroscopy, antibacterial activities

Introduction
Macrocyclic complexes have received considerable attention because of their relationship to biomimetic and catalytic systems and the applications in biology, medicine and chemical techniques [M.P. Reddy *et al*, 2012 [1], D. E. Fenton and H. Okawa, 1993 [2] The importance of macrocyclic complexes is well recognized. Coordination chemistry of macrocyclic complexes has been a fascinating area of current research interest to the inorganic chemists all over the world [S. Chandra *et al*, 2009] [3]. Because of their intense colors and chemical inertness, the macrocycles are of great importance as pigments and dyeing agents [S. Karaboce*et al*, 2006; K. Shankar *et al*, 2009] [32-5]. Its biological significance has given rise to the studies of macrocycles and there is new trend in the study of their complexation chemistry with a vast variety of metal ions [D. Singh et al, 2010; S. Chandra *et al*, 2006] [7]. Intrinsic structural properties of macrocyclic complexes mimic the synthetic models of metalloporphyrins and metallocorrins [E. Kubaszewski and T. Malinski 1992, R. Vaum *et al*, 1982]. The studies to achieve peripheral substitution providing points of attachments for further structural modification opens up new vistas for synthesis of more complex compounds providing possible applications in medicine [J. Eilmes, 1985; S. A. J. Collen*et al*, 1997]. The study of these synthetic model compounds plays an important role in the understanding of biological functions of these macrocycles [S. Cunha, *et al*, 2005]. Macrocyclic complexes's versatile coordination behavior, their pharmacological properties has made it a subject of attention and extensive study [E.V. Caemelbecke*et al*, 2005; E. Kimura, 1993] [15]. In both human being and animals, antibiotics are used as an important medicinal molecule to cure infections [D. Guillemot, 1999; T. Rosu *et al*, 2006]. In the recent studies, it has been observed that if there is a regular usage of antibiotics it results in an ever increasing therapeutic problem [R. Correa *et al*, 1998; G. Turhan-Zitouni, *et al*, 2001] [19]. This can be reduced with the help of antibiotic resistance inhibitors as macrocyclic complexes. Keeping the importance of the macrocyclic complexes and their antibacterial activities, the present article has been taken into account [S. Blain *et al*, 1990] [2].

Material and Methods
All chemicals used in this study were of AnalaR grade. Six macrocyclic complexes were synthesized and characterized.

Synthesis of macrocyclic complexes

All complexes were synthesized using template method [B.H.M. Mruthyunjayaswamy *et al*, 2005] [21] by condensation of acetone/diacetyl in the presence of respective metals salts (Chloride, sulphate). To a methanolic solvent (=50), o-phenylene diamine/3, 5 diamino benzoic acid with acetone/diacetyl followed by metal salt in ratio 2:2:1 were added in round bottom flask and refluxing was carried out for 6-8 hours. The change in colour was appeared. The round bottom flask was kept aside for its cooling. The filtration and washing were carried out by methanol and dried in vacuum. The coloured complexes were obtained and taken for further studies [F. Rafat *et al*, 2004; N. Raman *et al*, 2008] [23].

Table 1: Elemental analysis of macrocyclic complex

Macrocyclic Complex (molecular Formula)	Color	Yield (%)	Elemental Analysis							
			C%		H%		N%		M%	
			Cal	Found	Cal	found	Cal	Found	Cal	Found
C-I$C_{22}H_{26}N_4NiCl_2O_8$	Purple	45	43.72	42.0	4.30	4.0	9.27	9.10	13	12
C-II$C_{22}H_{26}N_4NiCl_2O_8$	Blue	40	41.40	41.20	3.54	3.50	8.05	8.0	11.05	11
C-III$C_{22}H_{26}N_4NiCl_2O_8$	Blue	44	41.37	40.20	3.78	3.75	9.64	9.0	9.35	9.0
MC-VI$C_{22}H_{26}N_4NiCl_2O_8$	Green	50	52.42	51.50	4.46	4.40	10.0	9.50	10.78	10.35
MC-V$C_{22}H_{26}N_4NiCl_2O_8$	Pale green	42	70.98	70.80	4.22	4.0	7.78	7.75	9.02	8.9
C-VI$C_{22}H_{26}N_4NiCl_2O_8$	Violet	40	56.96	56.0	4.52	4.5	12.07	12.02	9.70	9.30

All the complexes were analysed for elemental data (C, H, and N), colours and yields. The UV-Vis measurements were carried out using a spectrophotometer (Systronics UV-Vis spectrophotometer 117). Infrared spectra were recorded as KBr pellets on a Nicolet NEXUS Aligent 1100 FT-IR Spectrometer, using 50 scans and were reported in cm–1. For all complexes coordination of azomethine nitrogen was supported by lowering of $V_{C=N}$ to 7–10 cm^{-1} as compared to free ligand in IR spectra.

Biological activity

The synthesized target compounds were evaluated for their *in vitro* antibacterial activity against bacterial culture of *Escherichia coli* and *Vibrio cholerae*, *Staphylococcus aureus* and *Bacillus subtilis*. The test isolates were taken from the MTCC (Microbial Type Culture Collection) and included *Escherichia coli* and *Vibrio cholerae*, *Staphylococcus aureus* and *Bacillus subtillus.* An Agar-diffusion method was used for the determination of the preliminary antibacterial activity. In this technique, the filter paper (Whatsmann no. 1) sterile disc of 5 mm diameter impregnated with test macrocyclic complexes (10 mg/ml of DMSO) were placed in nutrient agar plate at 37 ºC for 12 h. The inhibition zones around the dried impregnated disks were measured after 12 hrs. The The antibacterial activity was classified as highly active (>14 mm), moderately active (10-14 mm) and slightly active (6-10 mm) and less than 5 mm was taken as inactive. The minimum inhibitory concentration (MIC) of the compounds was determined using a micro broth dilution method. In the broth dilution MIC method, various concentrations of the compounds were inoculated with a standard suspension of test bacteria. Following an overnight incubation at 37 °C, the MIC was determined by observing the lowest concentration of the compounds that would inhibit visible growth of the test bacteria. Growth was determined photometrically by measuring the optical density (OD) at 600 nm.

$$\text{Percentage of growth} = \frac{OD\ of\ organism\ grows\ with\ sample}{OD\ of\ control}$$

Results and Discussion

The present studies described the six macrocyclic complexes (I-VI) of different metals synthesis and their antibacterial activities. These complexes were crystalline solids and non-hygroscopic. The formulae for these macrocyclic complexes were assigned on the basis of analytical data (Table-1) and enable us to predict the possible structure of the synthesized complexes.

Table 2: UV-Vis Spectral data of Macrocyclic complexs (nm)

Molecular Formula	λmax (nm)
$C_{22}H_{26}N_4NiCl_2O_8$	548.4
$C_{24}H_{25}N_4CuCl_2O_{12}$	402
$C_{20}H_{22}N_4$ $CuCl_2O_8$	374
$C_{24}H_{25}N_4FeCl_2O_4$	520
$C_{42}H_{30}N_4FeCl_2O_4$	425
$C_{22}H_{21}N_4NiCl_2O_8$	389

Electronic absorption spectral data of the complexes in dimethyl sulfoxide (DMSO) at room temperature are presented in table 2. The electronic spectra of complexes in DMSO show bands in the visible–ultraviolet region. The absorption bands below 400 nm are practically identical and can be attributed to π-π* transitions in the azomethine (-C=N) group. The Ni(II) complexes possess square-planar geometry and Cu(II) complexes possess show octahedral geometry around the central metal ions [S. Chandra and L.K. Gupta 2004; S. Chandra and S.D. Sharma 2002]. The absorption bands observed within 350-550 nm range are most probably due to the transitions of n- π* of imine group [E. Konig, 1971]. The electronic spectra of the Ni(II) and complexes show an absorption band at 380-550 nm attributed to the 2Eg →$2T_2$g transition, characteristic for tetragonally elongated octahedral or square planar geometry [B.N. Figgis and M.A. Hitchman, 2000; A.A.A. Emara and M.I.A. Omima, 2007] [28]. The electronic absorption bands of the presented Ni(II) and Co(II) complexes in the visible region exhibit solvent dependence behavior. The observed red shifts in the low energy d-d band of Ni(II) and Co(II) complexes in DMSO can be interpreted in terms of weak ligand field strength [C. Preti and G.Tosi,1976].

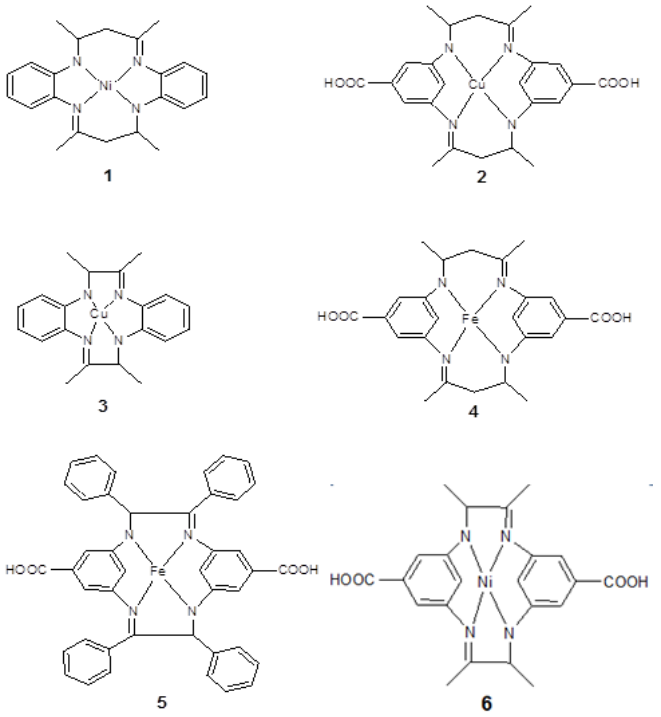

Fig 1: Proposed Structures of Dicataionic form of Macrocyclic Complexes, where 1-6 are macrocyclic complexes I-IV

Infrared spectra were recorded as KBr pellets on a Nicolet NEXUS Aligent 1100 FT-IR Spectrometer, using 50 scans and were reported in cm^{-1}. For all complexes coordination of azomethine nitrogen was supported by lowering of $V_{C=N}$ to 7–10 cm^{-1} as compared to free ligand in IR spectra. Results of IR-spectroscopy were summarized in table 3.

Table 3: Infrared Spectral data of Macrocyclic complexes (cm^{-1})

S. No.	Macrocyclic Complexes	v (NH)	v (ClO4)
1	$C_{22}H_{26}N_4NiCl_2O_8$	3240s	1097(s,b) 623m
2	$C_{24}H_{25}N_4CuCl_2O_{12}$	3220s	1092(s,b) 620m
3	$C_{20}H_{22}N_4$ $CuCl_2O_8$	3210m	1090(s,b) 618m
4	$C_{24}H_{25}N_4FeCl_2O_4$	3200s	1100(vs,b) 620s
5	$C_{42}H_{30}N_4FeCl_2O_4$	3210s	1100(vs,b) 620s
6	$C_{22}H_{21}N_4NiCl_2O_8$	3230s	1080(vs,b) 620s

Where s=strong, vs =very strong, b=broad, m= medium

Complex I showed IR bands near 1097 cm^{-1} together with a band at 623 cm^{-1} suggesting the presence of non-coordinated perchlorate ion. Complex II showed IR bands near 1092 cm^{-1} together with a band at 620 cm^{-1} indicated the presence of non-coordinated perchlorate ion, complex III showed IR bands near 1090 cm^{-1} together with a band at 618 cm^{-1} suggesting the presence of non-coordinated perchlorate ion. Complex IV showed IR very strong bands near 1100 cm^{-1} together with a band at 620 cm^{-1} suggesting the presence of non-coordinated perchlorate ion (Table 3). Complex V showed IR very strong bands near 1100 cm^{-1} and another band at 620 cm^{-1} suggesting the presence of non-coordinated perchlorate ion. Complex VI showed IR bands near 1080 cm^{-1} together with a band at 620 cm^{-1} suggesting the presence of non-coordinated perchlorate ion. The proposed macrocyclic complexes are **(1)** 1,4,8,11 dibenzotetraaza-tetradeca 7,14-Diene Ni(II) Macrocyclic complex, **(2)** 1,5,9,13-tetraaza dibenzoichexadeca 8,16 Cu(II) Macrocyclic complex, (3) 1,4,7,10-tetraaza dibenzododeca 6,12 diene Cu(II) Macrocyclic complex, (4) 1,5,9,13-tetraaza dibenzoichexadeca 8,16 diene Fe(III) Macrocyclic complex, (5) 1,5,8,12 tetraazadibenzoic 6,7,13,14 tetra benzo 7,14-duene Fe(III) Macrocyclic complex, (6) 1,5,8,12 tetraaza dibenzoic 6,7,13,14 tetramethyl tetradeca 7,14-diene Ni(II) Macrocyclic complex and figure-1 showed corresponding molecular structures.

Antibacterial activity

The antibacterial activity of macrocyclic complexes against pathogens at concentration 10mg/ml are given in table 4. The macrocyclic complexes (I-VI) showed a slight activity against all the four selected bacterial culture.

However, it was found that the macrocyclic complex-VI with Ni complex (at conc. 10 mg/mL) revealed a better activity (moderate activity) against all the four bacterial cultures. The antibacterial activity of complexes were observed in increasing order bacterial Antibactrial activity of the metal chelates can be explained on the basis of chelation theory [S. Chandra *et al*, 2011] [30]. The results obtained clearly indicated that among the series of metal chelates, macrocyclic complex-VI was moderate active towards growth inhibition of Gram-negative and Gram-positive bacteria under this investigation. This might be due to delocalization of π-electrons which show broad biological activity [M.R. Ahmed *et al*, 2013] [31] and is of special interest as the chelation tends to make the ligand more potent bacterial agent [K. Shankar *et al*, 2009] [32-5].

Table 4: Antibacterial activity of Macrocyclic complexes (conc. 10 mg/mL)

Macrocyclic Complex	*E. coli*	*Bacillus subtillus*	*Staphylococcus aureus*	*Vibrio choleraei*
1	10	10	10	9
2	10	9	9	9
3	11	10	9	10
4	11	9	8	10
5	10	10	10	9
6	13	12	10	11
Ampicillin (10 µg/mL)	52	52	45	43

Conclusion

The above study is a former evaluation of antibacterial activity of macrocyclic complexes. It also shows that the complexes have the capability to generate new antimicrobial metabolites. The discovery of new chemical classes of antibiotics is the result of macrocyclic complexes demonstrating antibacterial activity; which in future can be used as selective agent for maintaining human or animal health & also provides biochemical tools for the study of infectious disease.

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