

STUDY OF SOME NOVEL MACROCYCLIC CHELATES OF Co(II) AND Ni(II): SYNTHESIS, CHARACTERISATION AND BIOLOGICAL ACTIVITY

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Macrocyclic chelates of Co(II) and Ni(II) with nitrogen containing macrocyclic ligands ($L_1=1, 5, 8, 12$ - tetraaza – 6, 7, 13, 14 – dibenzo – 2, 4, 9, 11-tetramethylcyclotetradeca – 1, 4, 8, 11 – tetraene, and $L_2=1, 4, 8, 11$ -tetraaza – 2, 3, 9, 10 – tetramethylcyclotetradeca - 1, 3, 8, 10 - tetraene) have been synthesized and characterised on the basis of elemental analyses, magnetic susceptibility and molar conductance measurements, IR and uv – visible spectral investigations. The Co (II) chelates have been formulated as $[Co(L_1)(H_2O)_2]Cl_2$ and $[Co(L_2)(H_2O)_2]Cl_2$ while the Ni(II) chelates have been formulated as $[Ni(L_1)Cl_2]$ and $[Ni(L_2)Cl_2]$. All the synthesized metal chelates have been found to be paramagnetic. Co(II) chelates are 1:2 electrolyte while Ni(II) chelates are non – electrolytic in nature. Magnetic susceptibility values and the range of uv – visible spectral bands have suggested octahedral configuration of ligands around the metal ions. Nature of metal – ligand bonding has been established from IR – spectral investigations. The synthesised metal chelates displayed antibacterial activities. Ni(II) chelates exhibited antifungal activities, however, Co(II) chelates were not effective in restricting the fungal growth effectively..

Key Words: Macrocyclic ligands, metal chelates, biological activities, IR and uv - visible spectra, etc.

1. Introduction

Macrocyclic ligands and their metal chelates have been the area of research interest for inorganic and bioinorganic chemists since last few decades due to their resemblance with naturally occurring macrocyclic metal chelates of biological importance such as metalloproteins, cobalamine, chlorophylls, etc. Macrocyclic compounds act as hosts for metal ions, neutral molecules and organic cations [1]. They are useful in making metal-selective electrodes and also in phase-transfer catalysis [2]. Macrocyclic metal chelates are also useful as antiviral, antibacterial, antifungal [3], anticarcinogenic [4] and antifertile [5] agents. Macrocyclic chelates of lanthanides are used as MRI contrast agents [6]. The metal chelates of macrocyclic ligands have useful applications as dyeing materials [7], light emitting devices [8], DNA binding agents [9] and in various pharmacological studies [10]. By modifying the ring-size, the nature of donor atoms (N, S, O or P) and the ring substituents, a great variety of macrocyclic ligands and their metal chelates of vital importance can be synthesised. Macrocyclic compounds are being widely used in detecting tumour lesions due to their chelating properties. Metal chelates of macrocyclic ligands are used in chelation therapy for removing toxic heavy metals from biological systems. They also help in DNA nuclease activities as DNA modifying agents which recognise the DNA [11-13]. Keeping in view the wide range of applications of macrocyclic compounds and their metal chelates, we report the synthesis, characterisation and microbiological studies of some novel macrocyclic metal chelates.

2. Experimental

2.0 Materials and Methods

All chemicals used were of analytical grade purchased from Sigma Aldrich and were used as received without any further purification. The microanalysis of C, H, N of the ligands and complexes were done by elemental analyser EUROEA (Model EA3000). The magnetic susceptibility measurements of metal chelates were done using vibrating sample magnetometer (Model PAR155). The molar conductance measurements of the synthesised metal chelates were done using digital conductivity meter (HPG system, G- 3001). Metals were analysed by the methods available in literature [14]. The IR spectra were recorded within the range of 4000-400 cm⁻¹ using Agilent Technologies FTIR spectrophotometer (Carvy 630).

The electronic spectra of metal chelates were recorded on Hitachi 300 spectrophotometer. All the bacterial and fungal strains used in this study were received from Institute of Microbial Technology, Chandigarh. The agar-agar and malt yeast agar were used as culture medium for bacterial and fungal strains respectively. The antifungal and antibacterial studies were done in accordance with the methods available in literature [15]. Molar masses of synthesised metal chelates were determined by cryoscopic method.

2.1 Synthesis of Metal Chelates

The metal chelates of the macrocyclic ligands 1, 5, 8, 12 – tetraaza – 6, 7, 13, 14 – dibenzo – 2, 4, 9, 11 – tetramethylcyclotetradeca – 1, 4, 8, 11 – tetraene (L_1) and 1, 4, 8, 11 – tetraaza- 2, 3, 9, 10 - tetramethylcyclotetradeca – 1,3,8,10 –tetraene (L_2) with Co(II) and Ni(II) were synthesised by template condensation of the constituents of the ligands under the influence of the metal ions. Here, the coordination spheres of the metal ions provide proper chemical and steric environment for the condensation rather than polymerisation of the constituents of the ligands.

2.1.0: Synthesis of chelates of 1, 5, 8, 12 – tetraaza – 6, 7, 13, 14 – dibenzo – 2, 4, 9, 11 – tetramethylcyclotetradeca – 1, 4, 8, 11 – tetraene (L_1) with Co(II) and Ni(II)ions:

0.02 Mole of pentane- 2,4-dione and 0.02 mole of 1,2- diamino benzene were dissolved separately in minimum volume of ethanol. Both the solutions were mixed and filtered. An aqueous solution of 0.01 mole of cobalt(II) chloride hexahydrate / nickel(II) chloride hexahydrate was added slowly to the ethanolic solution containing pentane- 2,4-dione and 1,2-diaminobenzene with constant stirring. This mixture was refluxed for about 4 hours on a water bath using water condenser. It was then left for about 24 hours when a coloured solid was separated out. The precipitate was filtered, washed with water and ethanol and then recrystallised from dimethyl formamide (DMF). It was then dried at 110°C in an electric oven. The m.p. of synthesised metal chelates were recorded. The metal chelates were found to be insoluble in water and in common organic solvents such as benzene, toluene, methanol, ethanol, carbon tetrachloride and ether. However, they were found soluble in DMF and DMSO. The yield obtained was ~ 60-65%.

2.1.1: Synthesis of chelates of 1, 4, 8, 11 – tetraaza – 2, 3, 9, 10 – tetramethylcyclotetradeca – 1, 3, 8, 10 – tetraene(L₂) with Co(II) and Ni(II) Ions

0.02 Mole of butane- 2, 3-dione and 0.02 mole of propane- 1, 3-diamine were dissolved separately in minimum volume of ethanol. The two solutions were mixed and filtered. To the ethanolic solution of butane-2, 3-dione and propane-1, 3-diamine was added an aqueous solution of 0.01 mole of cobalt(II) chloride hexahydrate/nickel(II) chloride hexahydrate. The mixture was then refluxed for about 4 hours. The solution was then left overnight when coloured crystals were separated. The crystals were filtered, washed with cold water as well as with ethanol. The product was recrystallised from dimethylformamide (DMF). It was then dried at 110°C in an electric oven. The m.p. of the newly synthesised metal chelates were recorded. These metal chelates were found to be insoluble in water and in common organic solvents such as benzene, toluene, methanol, ethanol, carbon tetrachloride and ether. However, they were found soluble in dimethyl formamide (DMF) and dimethylsulphoxide (DMSO). The yield was approximately 70-75%.

3. Results and Discussion

3.0 Microanalytical data: From microanalytical data (Table-1), the stoichiometries of synthesised metal chelates were established. The experimental molar masses proved beyond doubt the monomeric nature of metal chelates. The micro analytical data and the observed molar masses of metal chelates were in good agreement with the proposed molecular formula (Table-1) of the respective metal chelates.

Table- 1

Micro analytical Data of Metal Chelates

Sl. No.	Metal Chelate	% Found (% Calculated)					Molar mass found (calculated)	Colour	m. p.
		C	H	N	Cl	M			
1.	[Co(L ₁)(H ₂ O) ₂]Cl ₂	51.27 (51.77)	5.56 (5.49)	10.72 (10.98)	13.68 (13.92)	11.67 (11.55)	510.38 (509.93)	Blue	209.4
2.	[Co(L ₂)(H ₂ O) ₂]Cl ₂	40.72 (40.58)	6.85 (6.76)	13.22 (13.53)	17.48 (17.15)	13.97 (14.24)	414.65 (413.93)	Blue	178.2
3.	[Ni(L ₁)Cl ₂]	54.97 (55.73)	5.16 (5.06)	12.14 (11.82)	15.21 (14.98)	12.22 (12.39)	472.82 (473.69)	Light Green	193.8
4.	[Ni(L ₂)Cl ₂]	44.71 (44.48)	6.20 (6.35)	14.94 (14.83)	18.26 (18.79)	15.29 (15.54)	376.52 (377.69)	Light Green	164.5

3.1 Molar Conductance

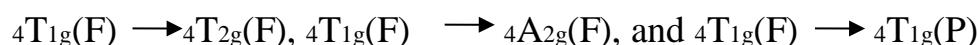
The molar conductance of the metal chelates were measured in 10^{-3} M DMF solution at room temperature. The chelates of cobalt(II) had their molar conductance values in the range $164\text{-}170 \text{ ohm}^{-1}\text{cm}^2\text{mol}^{-1}$ indicating their 1:2 electrolytic nature [16]. The electrolytic nature of the chelates of cobalt(II) is due to the presence of two chloride ions outside the coordination sphere. The presence of two chloride ions outside the coordination sphere was further confirmed by the addition of AgNO_3 solution to the solution of metal chelates in DMF leading to the formation of two moles of white precipitate of AgCl per mole of the metal chelate. The molar conductance values of nickel(II) chelates were in the range of $24\text{-}28 \text{ ohm}^{-1}\text{cm}^2\text{mol}^{-1}$ indicating their non-electrolytic nature [17]. Accordingly, all the coordination compounds were reasonably formulated as given in Table-1.

3.2 Magnetic Susceptibility

The observed magnetic moments of Co(II) chelates were in the range 4.88-4.96 BM which was much higher than the spin only magnetic moment (μ_s) corresponding to three unpaired electrons in Co(II). This suggested a high spin octahedral environment of ligands around Co(II). The higher values of magnetic moments were due to the orbital contributions to the magnetic moment from ${}^4\text{T}_{1g}$ ground term in octahedral environment [18]. The observed magnetic moments of Ni(II) chelates were in the range 2.92- 3.10 BM indicating high spin octahedral environment of ligands around Ni(II). In octahedral field, the ground term is ${}^3\text{A}_{2g}$ with no orbital contribution to magnetic moment. The higher values of magnetic moments over the spin only value(μ_s) corresponding to two unpaired electrons in Ni(II) may be due to contribution from first-order Zeeman effect.

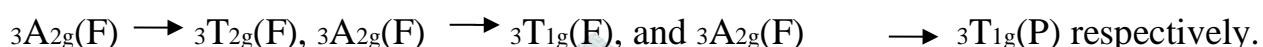
3.3 Electronic Spectra

The free ion ground term for Co(II) is ${}^4\text{F}$ with ${}^4\text{P}$ as the first excited term. Under the influence of a cubic ligand field, ${}^4\text{F}$ splits into ${}^4\text{T}_{1g}(F)$, ${}^4\text{T}_{2g}(F)$ and ${}^4\text{A}_{2g}(F)$ states and the ${}^4\text{P}$ term transforms into ${}^4\text{T}_{1g}(P)$ state only. In our present investigation, the chelates of Co(II) display three spectral bands in the region $9000\text{-}9500 \text{ cm}^{-1}$, $18900\text{-}19200 \text{ cm}^{-1}$ and $22150\text{-}22400 \text{ cm}^{-1}$ in their electronic spectra. These bands were assigned corresponding to the electronic transitions



respectively [19]. These spectral data were in good agreement with the data reported for spin free octahedral complexes of Co(II) [20,21].

The free- ion ground term of Ni(II) is 3F with 3P as the first excited term. Under the influence of a cubic field, 3F term splits into $^3T_{1g}(F)$, $^3T_{2g}(F)$ and $^3A_{2g}(F)$ states while 3P term transforms into $^3T_{1g}(P)$ state only. In our present study, the electronic spectra of Ni(II) chelates displayed three spectral bands in the region $8570\text{-}8675\text{ cm}^{-1}$, $13685\text{-}14200\text{ cm}^{-1}$ and $24000\text{-}25400\text{ cm}^{-1}$ which were assigned to the electronic transitions



The range of spectral bands were in good agreement with octahedral geometry around Ni(II) [22].

3.4 I. R. Spectra

The two bands present in 1, 2- diaminobenzene and propane- 1, 3-diamine around 3350 cm^{-1} and 3390 cm^{-1} corresponding to ν_{NH_2} symmetric and antisymmetric modes of vibrations respectively were absent in the spectra of the chelates of Co(II) and Ni(II). The disappearance of these bands and appearance of a new band at 1680 cm^{-1} corresponding to $\nu_{>C=N}$ (azomethine) mode of

vibration in the chelates of Co(II) and Ni(II) suggested the condensation of $-NH_2$ and $>C=O$ groups of the components of the ligands during template formation of metal chelates. Spectral bands in far I.R. region at 532 cm^{-1} and 530 cm^{-1} in the chelates of Co(II) and Ni(II) respectively were observed which were assigned to ν_{Ni-N} and ν_{Co-N} modes of vibrations respectively [23]. This indicated coordination of the ligands to the metal ions through nitrogen atoms. There were broad bands in the chelates of Co(II) in the region $3350 - 3600\text{ cm}^{-1}$. These bands were assigned to ν_{OH} mode of vibrations of coordinated water molecules. The coordination of water to the metal ion was further supported by the appearance of a band around 830 cm^{-1} , a characteristic of the wagging mode of vibration of the coordinated water molecule. The appearance of a band around 440 cm^{-1} in the chelates of Co(II), assignable to ν_{Co-O} mode of vibrations[24], also suggested coordination of water molecule to Co(II) ion.

A band observed around 350 cm^{-1} in the chelates of Ni(II) was assigned to $\nu_{\text{Ni}-\text{Cl}}$ mode of vibration [25]. This confirmed the coordination of Cl^- ion to Ni(II) in chelates of Ni(II).

On the basis of elemental analyses, magnetic susceptibility and molar conductance measurements, electronic (uv-visible) and I.R. spectroscopic investigations, the following high spin octahedral geometries (Fig.1 – Fig.4) were proposed for the metal chelates:

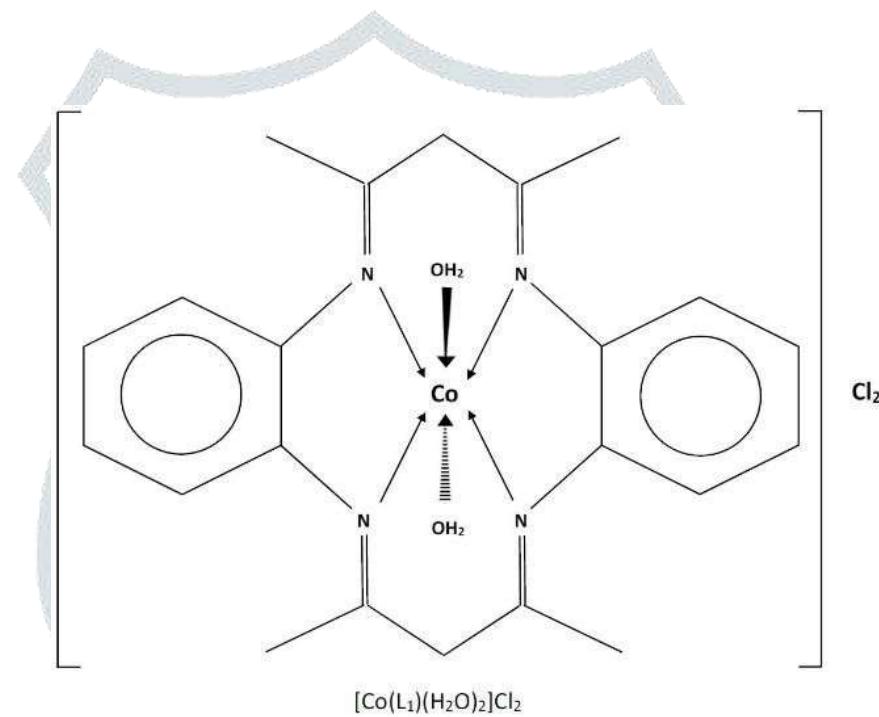


Fig. 1

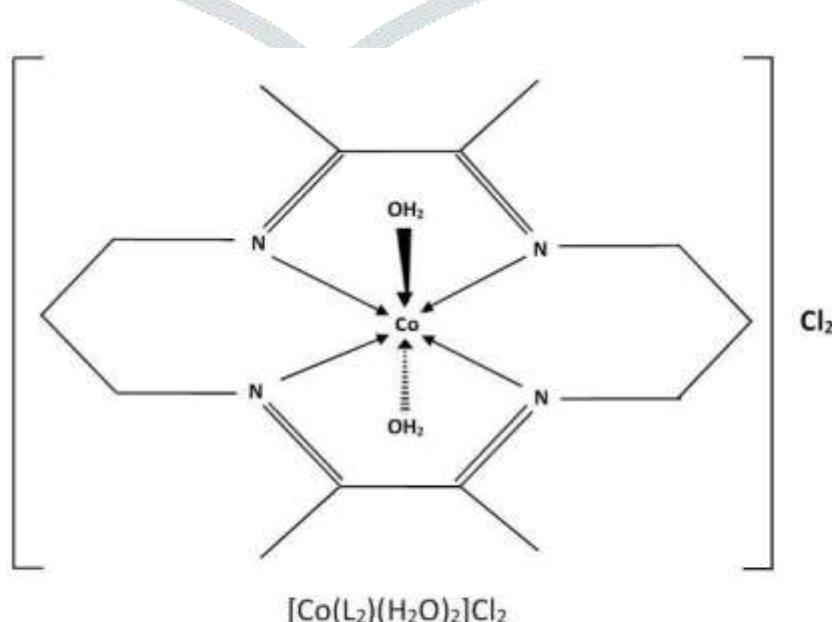


Fig. 2

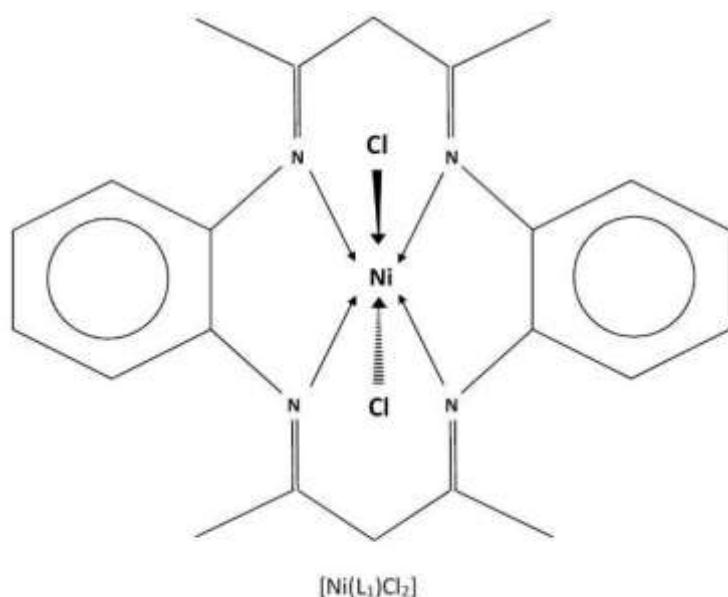


Fig. 3

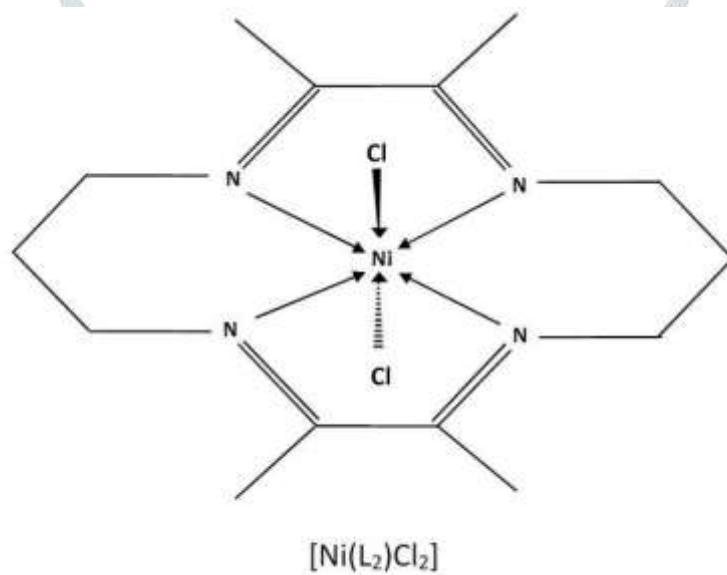


Fig. 4

4.0 Bioactivity

Two gram positive bacteria, i.e. *Bacillus subtilis* (MTCC 8509) and *Staphylococcus aureus* (MTCC 3160); two gram negative bacteria, i.e., *Escherichia coli* (MTCC 51) and *Pseudomonas aeruginosa* (MTCC 2488) and two fungal strains, i.e. *Candida albicans* and *Saccharomyces cerevisiae* were selected for the study of bioactivity of the newly synthesised macrocyclic chelates of Co(II) and Ni(II). In-vitro antimicrobial activities of

metal chelates are presented in Table-2 and Table-3. The antibacterial and antifungal activities of macrocyclic metal chelates were assessed using standard drugs ciprofloxacin and amphotericin - B by measuring the size of diameter in mm and percentage growth of inhibition respectively.

Table-2

In- Vitro Antimicrobial Activity of Metal Chelates (Diameter of Growth of Inhibition In mm)

Sl. No	Metal chelates	Gram- positive bacteria		Gram-negative bacteria		Fungal strains	
		Bacillus subtilis	Staphylococcus aureus	Escherichia coli	Pseudomonas aeruginosa	Candida albicans	Saccharomyces evisiae
1.	[Co(L ₁)(H ₂ O) ₂]Cl ₂	20	21	30	32	42.2	44.8
2.	[Co(L ₂)(H ₂ O)] Cl ₂	17	17.5	39.8	33.1	37.5	34.8
3.	[Ni(L ₁) Cl ₂]	28.6	36.2	34.4	38.3	25.9	26.3
4.	[Ni(L ₂) Cl ₂]	27.9	32.4	31.8	27.9	41.2	42.4
5.	Ciprofloxacin	24.0	26.6	25.0	22.0	-	-
6.	Amphotericin-B	-	-	-	-	16.6	19.3

Table- 3

Minimum Inhibitory Concentration (MIC) of Metal Chelates

Sl. No	Metal chelates	Gram- positive bacteria		Gram-negative bacteria		Fungal strains	
		Bacillus subtilis	Staphylococcus aureus	Escherichia coli	Pseudomonas aeruginosa	Candida albicans	Saccharomyces evisiae
1.	[Co(L ₁)(H ₂ O) ₂]Cl ₂	5.94	5.82	10.80	16.24	24.34	22.62
2.	[Co(L ₂)(H ₂ O) ₂]Cl ₂	5.46	5.22	12.56	18.52	29.42	26.25
3.	[Ni(L ₁)Cl ₂]	8.10	9.25	14.82	14.86	22.68	24.44
4.	[Ni(L ₂)Cl ₂]	10.56	11.92	9.56	20.24	35.28	31.80
5.	Ciprofloxacin	6.25	6.25	6.25	12.5	-	-
6.	Amphotericin- B	-	-	-	-	12.5	12.5

The antimicrobial studies indicated that the chelates of Co(II) were more effective against gram- positive bacteria in comparison to the standard drugs. No metal chelate was found to be effective against gram- negative bacteria and fungal strains.

5.0 Conclusion

Octahedral geometries have been established for the synthesised metal chelates on the basis of various physico-chemical investigations. All the metal chelates have been found to be paramagnetic. The chelates of Co(II) have 1:2 electrolytic nature whereas those of Ni(II) are non-electrolyte. Co(II) chelates are effective against gram-positive bacteria but all the metal chelates are ineffective against gram-negative bacteria and fungal strains.

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