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Research Article

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One pot template synthesis, characterization and biological assay of tetraaza (N_4) macrocyclic complexes of transition metal ions derived from acetylacetone / succinic acid with o-phenylenediamine

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ABSTRACT

Two novel series of the macrocyclic complexes [5, 7, 12, 14-Me_4-2, 3 9, 10- Bzo_2 [14]-1, 4, 8, 11-N_4- 2, 4, 7, 9, 11, 14-hexene] M(II) ***(1a-d)*** *and [2, 5, 10, 13-tetraoxo-7, 8, 15, 16-Bzo_2 [16]-1, 6, 9, 14-N_4-7, 16- diene] M(II)* ***(2a-d)****, where M(II)=Co(II), Ni(II), Cu(II) and Zn(II), were synthesized by the reaction of acetylacetone / succinic acid and o-phenylenediamine in presence of metal salts by adopting template method. The synthesized macrocyclic complexes were characterized by repeated melting point determinations, running single spot on TLC, elemental analyses, IR, magnetic moment values and electronic spectral studies. The electronic spectral studies and magnetic moment values suggested distorted octahedral geometry for Cu(II) and octahedral geometry for Co(II) and Ni(II) macrocyclic complexes. The antimicrobial activity of the complexes have been screened by serial dilution method in vitro against two bacteria Staphylococcus aureus and Pseudomonas aeruginosa and two fungi Aspergillus niger and Aspergillus flavus to access their biocidal potential.*

Keywords: Synthesis, spectral, IR, electronic spectral, macrocyclic complexes, template method, antimicrobial activity

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INTRODUCTION

The coordination chemistry of macrocyclic compounds, containing azomethine moiety, is an important area of research because complexes of macrocyclic compounds are thermodynamically more stable in comparison to open chain analogues [1,2]. They differ from open chain analogues due to some structural factors such as cavity size, stereo chemical rigidity and flexibility. The show co-ordination ability [3] with the metal ion present in the biological systems, hence the penetration power of macrocyclic complexes increased by replacing their metal ions from the metal present in the biological system. These complexes kills microbes more efficiently due to which they show some interesting properties in the biological systems such as antitumor, antibacterial, antiviral, antifungal and anticarcinogenic activities [4-8]. They have great importance in various industrial applications and in a number of biological processes such as photosynthesis and dioxygen transport [9], catalytic properties. They possess potential applications as metal extractant, radiotherapeutic and a high potential in antitumor therapy. The macrocyclic complexes also have great importance due to their use as dyes and pigments; MRI contrasts agents and models for naturally occurring macrocycles [10-13]. Macrocyclic nickel complexes are used in DNA recognition and oxidation [14], while macrocyclic copper complexes are used in DNA binding agents [15]. Some of macrocyclic complexes have been reported to exhibit the antibiotic and anti-inflammatory activities [16]. Macrocyclic metal complexes have close relationship with natural products such as chlorophyll, hemoglobin and vitamin B_{12} [17]. The macrocyclic

systems are of significant interest not only for their pharmacological properties but also for their capacity for chemical recognition of anion and metal ions of biochemical, medical and environmental importance [6]. Keeping the above applications in mind it has been decided to synthesize some new macrocyclic complexes with a view to search a good antimicrobial agent. In continuation of our previous work [18-21] in this paper we have reported the synthesis, characterization and biological assay of macrocyclic complexes of Co(II), Ni(II), Cu(II) and Zn(II) ions by adopting the template condensation reaction of acetylacetone / succinic acid with o-phenylenediamine.

EXPERIMENTAL SECTION

All the chemicals and solvents used were of AR grade. Metal salts were purchased from E. Merck. All the complexes were prepared by one pot template synthesis in order to produce high yield.

***Synthesis of* [5, 7, 12, 14-Me_4-2, 3 9, 10- Bzo_2 [14]-1, 4, 8, 11-N_4- 2, 4, 7, 9, 11, 14-hexene] M(II) macrocyclic complexes (1a-d):** 2.0 ml acetylacetone (0.02 mol) was dissolved in 25 ml ethanol. To this, 15 ml aqueous solution of 2.48 g cobalt acetate tetrahydrate (0.01mol) was mixed. The mixture was refluxed for 2 h and 20 ml ethanolic solution of o-phenylenediamine (2.16 g, 0.02 mol) was added dropwise with continuous stirring. The contents of the flask were refluxed for 6 h. On cooling colored precipitate was obtained which was filtered, washed with water, ethanol followed by diethyl ether and recrystallized from ethanol: chloroform (2:1). Finally, it was dried over anhydrous $CaCl_2$ in a vacuum desiccator. Similarly, metal complexes of Ni(II), Cu(II) and Zn(II) were synthesized by using respective metal salts.

***Synthesis of* [2, 5, 10, 13-tetraoxo-7, 8, 15, 16-Bzo_2 [16]-1, 6, 9, 14-N_4-7, 16- diene] M(II) *macrocyclic complexes* (2a-d):** 20 ml ethanolic solution of o-phenylenediamine (1.08 g, 0.01mol) was taken. To this, 15 ml aqueous solution of (1.24 g, 0.005 mol) cobalt acetate tetrahydrate was mixed. The solution was refluxed for 1 h and 1.18 g succinic acid (0.01mol), dissolved in 20 ml absolute alcohol, was added drop by drop with vigorous shaking. The contents of flask were again refluxed for 5 h. On cooling colored precipitate was obtained which was filtered, washed with water, ethanol followed by diethyl ether and recrystallized from ethanol: chloroform (2:1). Finally, it was dried over anhydrous $CaCl_2$ in a vacuum desiccator. Similarly, Metal complexes of Ni(II), Cu(II) and Zn(II) were synthesized by using their metal salts .

Antimicrobial Activity:

The antimicrobial studies of the synthesized macrocyclic complexes were screened against the bacteria *Staphylococcus aureus* (gram +ve), *Pseudomonas aeruginosa* (gram -ve) and fungi *Aspergillus niger* and *Aspergillus* flavus by adopting Serial Dilution Method [22] in suitable nutrient medium (1.5 g peptone, 0.75 g yeast extract, 0.37 g beef extract, 0.37 g agar only for slant and 0.25 g dextrose in 250 ml distilled water for bacteria and 2.5 g peptone, 5.12 g agar only for slant 5.0 g dextrose in 250 ml distilled water for fungi). Graded diluted solutions of the test compounds, with the microorganisms under examination using aseptic condition, were incubated at 37 ^oC for 24 h in case of bacteria and at 28 ^oC for 96 h in case of fungi in a B.O.D. incubator. The test tube having the highest dilution, i.e. lowest concentration showing no visible turbidity was chosen for the MIC value. Ciprofloxacin was used as standard drug for antibacterial and Griseofulvin drug for antifungal screening.

RESULTS AND DISCUSSION

The purity of synthesized metal complexes was ascertained by running their TLC for single spot on silica gel-G plates and by determining the repeated melting point of the recrystallized samples in open capillaries and thus uncorrected. The complexes were soluble in DMF and DMSO but insoluble in common organic solvents and water. C, H, N analyses were carried out at SAIF, CDRI Lucknow using elemental analyzer (presented in Table 1). The IR spectra were recorded in the range of 4000- 400 cm^{-1} on 'Bruker' spectrophotometer by using KBr pellets. The electronic spectra of the complexes in DMF/ DMSO were recorded on UV-VIS-NIR spectrophotometer cary 5E. The magnetic susceptibilities were measured at room temperature on a Gouy balance using $CuSO_4.5H_2O$ as calibrant.

IR spectral Studies

All the complexes exhibited medium sharp intensity bands in the region 3107.94-3039.54 cm^{-1}, 1450.13-1394.37 cm^{-1} and 760.75-736.67 cm^{-1} which may be attributed due to C-H, C=C stretching vibrations of aromatic ring [23,24] and C-H bending vibrations of dimethylene moiety respectively [25]. The macrocyclic complexes **1a-d**

exhibited absorption band in the region 2930.71-2920.69 cm^{-1} which may be attributed due to C-H stretching vibrations of CH_3 group. IR spectra of all macrocyclic complexes exhibited bands in the region 3451.20-3333.86 cm^{-1} and 891.80-842.42 cm^{-1} indicated the presence of coordinating water molecules. The coordinated water molecules in coordination sphere have been further confirmed by heating the metal complexes in vacuum at 100 ºC over P_2O_5. In the macrocyclic complexes of **1a-d** a medium intensity band in the region 1569.61-1555.72 cm^{-1} may be attributed due to >C=N- stretching vibrations of azomethine linkage [26,27]. This region was lower as compared to normal region i.e. 1620-1600 cm^{-1} which indicated that the N atom of azomethine linkage has been participated in the coordination. In the IR spectra of macrocyclic complexes of **2a-d** the band due to >NH stretching [28,29] vibrations appeared in the region 3291.11-3169.11 cm^{-1}.The position of this band was higher in comparison to normal value which indicated the involvement of >NH group in coordination with metal ion. Band appeared in the region 1278.01-1211.93 cm^{-1} may be attributed due to C-N stretching vibrations. In the IR spectra of all macrocyclic complexes two new bands also appeared in the region 517.90-492.86 cm^{-1} and 494.6-455.3 which may be attributed due to the formation of M-N and M-O stretching vibrations [30,31] respectively.

Electronic spectral studies

The electronic spectra of Co (II) complexes displayed three bands in the region 545-558, 662-674, 774-782 nm corresponding to transitions $^4T_{1g} \rightarrow {}^4T_{1g}(P)$, $^4T_{1g} \rightarrow {}^4A_{2g}$ (F) and $^4T_{1g} \rightarrow {}^4T_{2g}$ (F) respectively which suggested octahedral geometry [32] for these complexes. The magnetic susceptibility values of these complexes were found 4.81-4.79 BM which further suggested the octahedral geometry.

In the electronic spectra of Ni (II) complexes three bands in the region, 426-480, 554-645, 773-790 nm corresponding to transitions $^3A_{2g} \rightarrow {}^3T_{1g}(P)$, $^3A_{2g} \rightarrow {}^3T_{1g}$ (F) and $^3A_{2g} \rightarrow {}^3T_{2g}$ appeared. Appearance of these bands indicating octahedral geometry [32]. The magnetic susceptibility values of these complexes were found 3.34-3.27 BM which was very close to the value for their octahedral environment around the metal ion.

The electronic spectra of Cu (II) complexes exhibited three bands in the region, 385-482, 612-627 and 776-792 nm corresponding to transitions $^2B_{1g} \rightarrow {}^2A_{1g}$, $^2B_{1g} \rightarrow {}^2B_{2g}$, and $^2B_{1g} \rightarrow {}^2E_{1g}$ which may be due to the John teller distortion. These bands indicated distorted octahedral geometry [33]. The magnetic susceptibility values of Cu(II) complexes were found 1.90-1.83 B.M which further suggested the distorted octahedral geometry.

As accepted Zn(II) complexes did not exhibit significant bands due to diamagnetic nature.

On the basis of elemental analyses, IR, electronic spectral data and magnetic moment values the probable structures of macrocyclic complexes **1a-d** and **2a-d** have been shown in Fig.1 and 2.

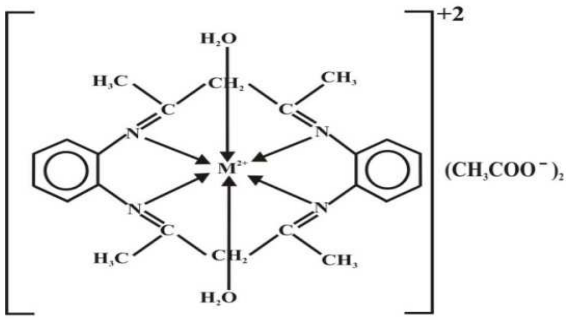

Fig.1: 1a-d

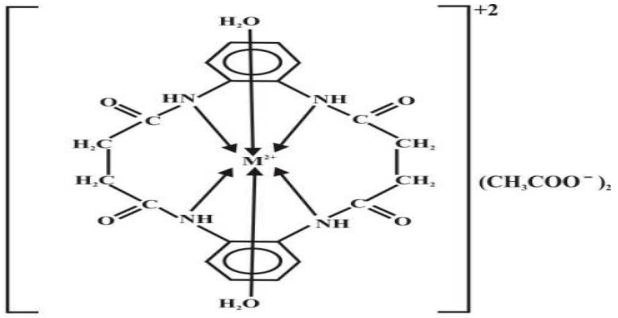

Fig.2: 2a-d

Results of antimicrobial activities

A comparative study of MIC values (**Table.2**) indicated that all the synthesized macrocyclic complexes exhibited remarkable activity against both bacteria and fungi. The remarkable antimicrobial activity of the complexes may be due to their chelation [34] which reduces the polarity of the metal ion by partial sharing of its positive charge with the donor groups and possibly π-electron delocalization within the whole macrocyclic ring thus increases the liphophilic nature [35] of the central metal atom, which in turn, favors its permeation through the lipid layer of cell membrane restricting the multiplicity of the microorganism. Among the complexes, Cu (II) macrocyclic complexes were found most active against both bacteria. In case of fungi, Zn(II) macrocyclic showed maximum antifungal activity. However, these complexes were found less potent as compared with ciprofloxacin (Antibiotic drug) and antifungal activity of the compound was compared with griseofulvin (Antifungal drug) both taken as standard for comparison.

TABLE 1: Physical and analytical data of macrocyclic complexes 1a-d &2a-d.

S.No	Complexes	Molecular Formula	Molecular Weight	Colour	Percentage Composition			
					Carbon C/(F)	Hydrogen C/(F)	Nitrogen C/(F)	M.P./ D.T. (±2) ^{o}C
1.	1a	$[Co(C_{22}H_{24}N_4).2H_2O](Ac)_2$	556.93	Dark brown	56.02 (57.13)	6.10 (7.30)	10.05 (11.07)	250
2.	1b	$[Ni(C_{22}H_{24}N_4).2H_2O](Ac)_2$	556.69	Black	56.04 (57.01)	6.10 (5.31)	10.05 (9.34)	200
3.	1c	$[Cu(C_{22}H_{24}N_4).2H_2O](Ac)_2$	561.54	Black	55.56 (56.32)	6.05 (6.95)	9.97 (10.76)	310
4.	1d	$[Zn(C_{22}H_{24}N_4).2H_2O](Ac)_2$	563.40	Dark brown	55.37 (56.32)	6.03 (5.25)	9.93 (8.81)	275
5.	2a	$[Co(C_{20}H_{20}N_4O_4).2H_2O](Ac)_2$	592.93	Black	48.57 (49.60)	5.05 (6.06)	9.44 (8.53)	320
6.	2b	$[Ni(C_{20}H_{20}N_4O_4).2H_2O](Ac)_2$	592.69	Dark brown	48.59 (49.27)	5.06 (4.18)	9.44 (10.33)	200
7.	2c	$[Cu(C_{20}H_{20}N_4O_4).2H_2O](Ac)_2$	597.54	Dark Green	48.19 (49.86)	5.02 (6.11)	9.37 (10.49)	300
8.	2d	$[Zn(C_{20}H_{20}N_4O_4).2H_2O](Ac)_2$	599.40	Black	48.04 (48.93)	5.00 (4.79)	9.34 (8.35)	260

Table 2: The Minimum Inhibitory Concentration ($X10^{-3}$ mole) values of complexes 1a-d &2a-d

S.No	Compounds	Bacteria		Fungi	
		Staphylococcus aureus	*Pseudomonas aeruginosa*	*Aspergillus niger*	*Aspergillus flavus*
1.	$[Co(C_{22}H_{24}N_4).2H_2O](Ac)_2$	22.4	22.4	44.8	44.8
2.	$[Ni(C_{22}H_{24}N_4).2H_2O](Ac)_2$	22.4	22.4	44.9	44.9
3.	$[Cu(C_{22}H_{24}N_4).2H_2O](Ac)_2$	22.2	22.2	22.2	22.2
4.	$[Zn(C_{22}H_{24}N_4).2H_2O](Ac)_2$	44.3	44.3	22.1	22.1
5.	$[Co(C_{20}H_{20}N_4O_4).2H_2O](Ac)_2$	21.0	21.0	42.1	42.1
6.	$[Ni(C_{20}H_{20}N_4O_4).2H_2O](Ac)_2$	21.0	21.0	42.1	42.1
7.	$[Cu(C_{20}H_{20}N_4O_4).2H_2O](Ac)_2$	20.9	20.9	20.9	20.9
8.	$[Zn(C_{20}H_{20}N_4O_4).2H_2O](Ac)_2$	41.7	41.7	20.8	20.8
9	Ciprofloxacin	9.4	9.4	-	-
10	Griseofulvin	-	-	8.8	8.8

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