



RESEARCH ARTICLE

**Macrocyclic Complexes of Bioactive Divalent and Trivalent Transition Metal Ions
Using Diethyl Malonate and Malonyldihydrazide**

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ABSTRACT

A series of seven macrocyclic complexes is synthesized by template condensation of diethyl malonate and malonyldihydrazide in methanolic medium in the presence of transition metal ions such as Cr(III), Mn(II), Fe(III), Co(II), Ni(II), Cu(II) and Zn(II). The synthesized complexes have been characterized with the help of molar conductance, magnetic susceptibility measurements, IR, electronic, and ¹H-NMR Spectra. On the basis of studies made a six coordinated octahedral geometry has been proposed for all these complexes. The synthesized complexes were also screened for their antifungal activity against human fungal pathogen *Candida albicans* and most of them have been found to exhibit significant antifungal activity.

KEYWORDS

Diethyl Malonate, Malonyldihydrazide, Template Method, Octahedral, Antifungal Activity

INTRODUCTION

The area of research on synthesis of macrocyclic complexes has gained importance since last few decades. Synthesis of variety of macrocyclic complexes in recent years by research workers in this field has motivated others to concentrate in this area. The interest in the field of synthesis of macrocyclic complexes is due to naturally occurring macrocyclic derivatives for many fundamental biological processes such as photosynthesis, transfer of oxygen in mammalian and all respiratory systems¹⁻². This observation has prompted many researchers to synthesize macrocyclic complexes expecting them to perform similar functions.

Numbers of macrocyclic molecules are also known to show biological activities such as antibacterial^{3,5-6}, antifungal^{4,6-7}, antidibetic⁸⁻⁹, and anticancer¹⁰⁻¹¹. Macrocyclic complexes are also synthesized in view to find applications in various fields such as to study DNA cleavage¹²⁻¹³, catalytic applications¹⁴⁻¹⁶, preparation of ion selective electrode¹⁷, radioimmunotherapy & other medicinal applications¹⁸⁻¹⁹.

It is not always possible to synthesize or isolate macrocyclic ligand and use it for complex preparation as is normally done in complex chemistry. In such situations template method is widely used where normally transition metal ions act as templating agents²⁰⁻²². In this method the components forming the macrocyclic ligand are reacted in presence of metal salts to produce the macrocyclic complex directly. In the present paper same method is utilized to synthesize

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macrocyclic complexes using diethyl malonate and malonyldihydrazide in presence of transition metal ions such as Cr (III), Mn (II), Fe (III), Co (II), Ni (II), Cu (II) and Zn (II). The synthesized complexes are characterized using molar conductance, magnetic susceptibility measurements, IR, electronic and ¹H-NMR spectra. On the basis of studies made an octahedral geometry is proposed for all the complexes. The synthesized complexes have also been examined for their efficacy against the human fungal pathogen, *Candida albicans*.

MATERIALS AND METHODS

The entire chemicals used in present study were of AR grade. Diethyl malonate, hydrazine hydrate and metal salts were procured from S. D. fine chemicals, and Spectrochem private limited respectively. All solvents used were distilled and dried using molecular sieves before use.

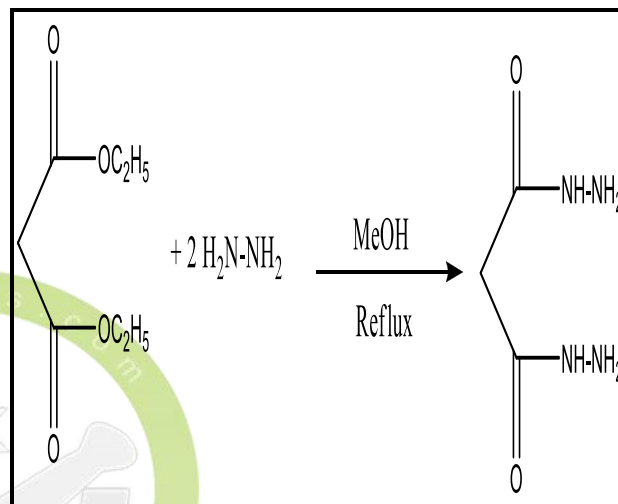
The Molar conductance of complexes was measured by preparing 10⁻³ M solutions in DMF solvent using Equiptronics conductivity meter with inbuilt magnetic stirrer model (Eq-664) at room temperature. Magnetic susceptibilities were determined on the SES Instrument's magnetic susceptibility Guoy balance (model EMU-50) at room temperature using copper (II) sulphate as a standard. These magnetic susceptibility values were utilized to calculate magnetic moments using spin only formula $\mu_{\text{eff}} = (n(n+2))^{1/2}$ for all the synthesized complexes.

IR spectra were recorded as KBr pellets in the region of 4000-400 cm⁻¹ on a Perkin Elmer Spectrophotometer. Electronic spectra were recorded in DMSO on a Shimadzu UV-1600 spectrophotometer. ¹H-NMR spectra was recorded on BRUKER AVANCE II 400 NMR Spectrometer using DMSO d⁶ (Spectroscopic grade) as a solvent. Chemical shifts are given in ppm relative to tetramethylsilane (TMS).

Synthesis of Malonyldihydrazide

Synthesis of malonyldihydrazide was carried out using the method reported earlier²³. It was prepared by reacting diethylmalonate (1 mol) with hydrazine hydrate (2 mol) in methanolic

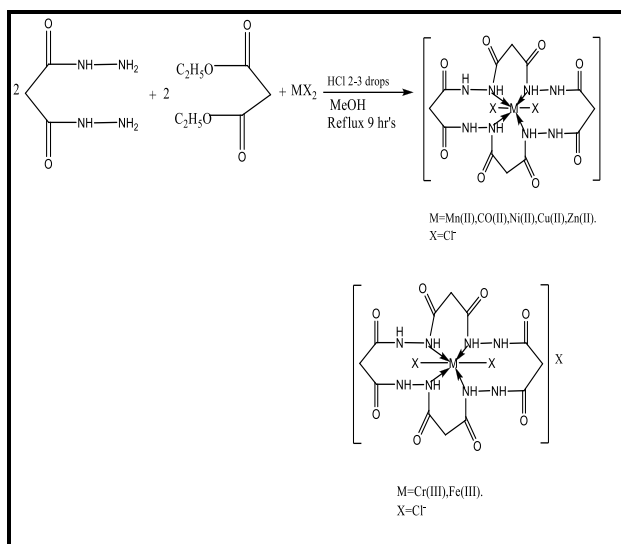
solvent. The reaction mixture was refluxed for 5-7 hrs. Progress of the reaction was checked by thin layer chromatographic technique using solvent system ethyl acetate (10%) + Pet ether (90%). After complete disappearance of starting material the reaction mixture was cooled for one hour. After cooling for one hour white crystalline product was obtained. It was filtered, washed with methanol and recrystallized from ethanol. Melting point was checked. (M. P. = 149 °C).



Scheme 1: Synthesis of malonyldihydrazide

Synthesis of Macrocyclic Metal Complexes

Synthesis of macrocyclic metal complexes was carried out using template method. A hot methanolic solution (15 ml) of respective transition metal salts (5 mmol) was mixed with a hot solution (15 ml) of malonyldihydrazide (10 mmol 1.32 g). The resulting mixture was refluxed for 20 minutes. After refluxing for 20 minutes, in the same solvent diethyl malonate (10 mmol, 1.60 ml) was added in presence of few drops of Conc. HCl. The resulting mixture was then left under reflux for 9 hours. After refluxing for 9 hours appropriate complexes precipitated out on cooling the solution. Those were then filtered, washed with methanol and recrystallized from ethanol. The purity of the complexes was checked by taking TLC (solvent system (9:1) CHCl₃+MeOH). The synthesized complexes were obtained in 60-80 % yield. The general scheme (Scheme 2) of the synthesis of macrocyclic metal complexes is given as below.



Scheme 2: Synthesis of Macrocyclic Metal Complexes of Cr(III), Mn(II), Fe(III), Co(II), Ni(II), Cu(II) and Zn(II) using Template method

***In vitro* Antifungal Assay**

The newly synthesized macrocyclic metal complexes have been studied for their antifungal activity against *Candida albicans* ATCC 90028 by microbroth dilution method²⁴. In this various concentrations of test compounds were prepared in RPMI-1640 medium by double dilution in the 96 well plates. Each well contained an inoculum of 1×10^3 cells ml^{-1} and the final volume of RPMI-1640 medium maintained in each well was 200 μl . The wells without addition of compounds served as a negative control while wells with fluconazole (a standard antifungal) were treated as a positive control. Microplates were incubated at 35 °C for 48 hours and read spectrophotometrically at 620 nm using microplate reader (Multiskan EX, Thermo Electron Corp. USA). The lowest concentration of the drug which caused minimum fifty percentage reduction in the absorbance compared to that of control was considered as minimum inhibitory concentration.

RESULTS AND DISCUSSION

The general composition of the synthesized macrocyclic metal complexes can be represented as $[\text{M}(\text{C}_{12}\text{H}_{12}\text{N}_8\text{O}_8)\text{Cl}_2]$ (where $\text{M}=\text{Mn}(\text{II}), \text{Co}(\text{II}), \text{Ni}(\text{II}), \text{Cu}(\text{II})$ and $\text{Zn}(\text{II})$) and $[\text{M}(\text{C}_{12}\text{H}_{12}\text{N}_8\text{O}_8)\text{Cl}_2] \cdot \text{Cl}$ (where $\text{M}=\text{Cr}(\text{III})$ and $\text{Fe}(\text{III})$). All the synthesized complexes were

thermally stable and coloured. Observations such as colour, melting point, % yield, solubility behavior for all the synthesized complexes were recorded.

Solubility Behaviour

Solubility behaviour of all the synthesized complexes was checked using different solvents such as water, methanol, ethanol, chloroform, acetone, acetonitrile, DMSO and DMF. The complexes were found to be soluble in DMSO and DMF whereas in remaining solvents they were found to be insoluble.

Molar Conductance

On the basis of solubility molar conductance values for all the complexes were measured by preparing 10^{-3} M solutions in DMF as a solvent. Low values (i.e. $13\text{-}27 \text{ ohm}^{-1} \text{ cm}^2 \text{ mol}^{-1}$) for divalent Mn(II), Co(II), Ni(II), Cu(II) and Zn(II) metal complexes and high values (i.e. 63 & 87 $\text{ohm}^{-1} \text{ cm}^2 \text{ mol}^{-1}$) for trivalent Cr(III) and Fe(III) complexes were obtained. The low values for divalent metal complexes indicate towards their nonelectrolytic behavior²⁵ whereas high values for trivalent metal complexes indicate towards their 1:1 electrolytic nature²⁶.

Magnetic Properties

The magnetic data of all the synthesized complexes is reported in Table 1. The observed magnetic moment values for Mn(II) and Fe(III) complexes were 5.94 and 5.33 B.M. respectively indicating towards d^5 configuration and five unpaired electrons in an octahedral environment. The magnetic moment values of Cr(III) and Co(II) complexes were found to be 3.84 and 4.27 B.M. respectively corresponding to three unpaired electrons²⁷. In case of Ni(II) and Cu(II) complexes observed magnetic moment values were 2.94 and 2.13 B.M. respectively corresponding to two and one unpaired electrons in these complexes²⁷. Zn(II) complex has been found to be diamagnetic.

IR Spectra

IR spectra of all the synthesized complexes have been recorded in the range $4000\text{-}400 \text{ cm}^{-1}$. The complexes in the present study are having one

Table 1: Physico-chemical Data of Macrocyclic Complexes

Sr. No.	Molecular Formula	Colour	Melting Point (°C)	Yield (%)	Molar conductance (ohm ⁻¹ cm ² mol ⁻¹)	Magnetic moment (μ _{eff} B. M.)
1	C ₁₂ H ₁₂ Cl ₃ CrN ₈ O ₈	Dark brown	242	62	63	3.84
2	C ₁₂ H ₁₂ Cl ₂ MnN ₈ O ₈	Light yellow	245	71	27	5.94
3	C ₁₂ H ₁₂ Cl ₃ FeN ₈ O ₈	Black	251	68	87	5.33
4	C ₁₂ H ₁₂ Cl ₂ CoN ₈ O ₈	Light Red	220	76	19	4.27
5	C ₁₂ H ₁₂ Cl ₂ NiN ₈ O ₈	Blue	240	79	14	2.94
6	C ₁₂ H ₁₂ Cl ₂ CuN ₈ O ₈	Dark green	225	75	17	2.13
7	C ₁₂ H ₁₂ Cl ₂ ZnN ₈ O ₈	White	238	68	13	Diamagnetic

Table 2: IR spectroscopic data (Cm⁻¹) of the synthesized metal complexes

Sr. no.	Molecular formula	ν(N-H)	Amide I ν(C=O)	Amide II δ (N-H) bending	ν(M-N)
1	C ₁₂ H ₁₂ Cl ₃ CrN ₈ O ₈	3200	1691	1641	465
2	C ₁₂ H ₁₂ Cl ₂ MnN ₈ O ₈	3165	1700	1610	500
3	C ₁₂ H ₁₂ Cl ₃ FeN ₈ O ₈	3179	1673	1641	475
4	C ₁₂ H ₁₂ Cl ₂ CoN ₈ O ₈	3209	1644	1644	520
5	C ₁₂ H ₁₂ Cl ₂ NiN ₈ O ₈	3199	1691	1648	530
6	C ₁₂ H ₁₂ Cl ₂ CuN ₈ O ₈	3250	1690	1623	475
7	C ₁₂ H ₁₂ Cl ₂ ZnN ₈ O ₈	3250	1700	1648	478

free CO-NH group of amide which is not involved in coordination with the metal and another CO-NH group which is formed after condensation of free -NH₂ group of malonyldihydrazide with diethyl malonate & in which there is coordination of the ligand to the metal through nitrogen. Both these group should show bands in the same region around 3150-3350 cm⁻¹ (with small changes in frequencies) which makes the observation and explanation little bit difficult. Still in the present study the spectra of complexes showed a broad

band with medium to strong intensity in the region 3150-3300 cm⁻¹ which can be assigned to ν(N-H) stretching for the -NH group coordinated to the metals.

The complexes showed a strong band in the region 1640-1700 cm⁻¹ which can be assigned to ν(C=O) of NH-NH-CO-CH₂ moiety. Similar observation was reported by Hossain et. al²⁸ in a research paper on macrocyclic synthesis including malonodihydrazide with different aldehydes in presence of metal perchlorates. In that research paper they have reported similar

type of band in the range 1649-1674 cm^{-1} for $\nu(\text{C}=\text{O})$ of NH-NH-CO-CH₂ moiety. Coordination of the ligand to the metal through nitrogen in complexes has been found to have variable values in the region 400-600 cm^{-1} depending on the environment surrounding the metal atom. Srivastava et. al.²⁹ in their paper have reported $\nu(\text{M}-\text{N})$ stretching frequency to be observed in the region 410-445 cm^{-1} . Hossain et. al.²⁸ in their research paper has reported an observation of a medium band at 407-412 cm^{-1} region which was attributed to $\nu(\text{M}-\text{N})$ indicating coordination of the ligand to metal through nitrogen atom.

Al-Obaidi and Al-Hiti³⁰ in their paper has reported the appearance of a medium intensity band in the range 550-500 cm^{-1} and attributed it to the $\nu(\text{M}-\text{N})$. In the paper published by Howlader and others³¹, coordination of ligand to the metal through nitrogen has been reported to have still lower values i.e. below 400 cm^{-1} (380-310 cm^{-1}). In the present paper a medium intensity band observed in the region 450-550 cm^{-1} can be ascribed to the $\nu(\text{M}-\text{N})$.

The $\nu(\text{M}-\text{Cl})$ band is usually reported to be observed below 400 cm^{-1} region³²⁻³³. Due to instrument limitation, the said region was not scanned for present investigation. The IR spectroscopic data of the synthesized metal complexes is represented in Table 2.

¹H-NMR Spectra

¹H-NMR spectra were also recorded for all the synthesized complexes to help in confirming the structures using DMSO-d₆ as a solvent against tetramethylsilane (TMS) as a standard.

In complexes the 8-NH protons are in similar environment and the 8 protons of four CH₂ groups are also in similar environment. Hence two different peaks for respective set of protons can be expected in the spectra of complexes. Actually the spectra of all the complexes show three peaks out of which a peak observed in the region 2.5-2.6 ppm was due to the residual protons of the solvent DMSO-d₆³⁴.

The remaining portion of the spectra of all the complexes match with our expectation and show

two peaks only. A singlet observed at δ 8.00-8.2 (8H) was due to 8 protons of NH groups³⁵⁻³⁶. Similarly another singlet observed at δ 3.20-3.40 (8H) was due to four CH₂ groups present in the structure³⁷.

Electronic Spectra

Electronic spectra of all the synthesized metal complexes were recorded by preparing solutions in DMSO. The Cr(III), Mn(II) and Co(II) metal complexes showed two d-d transition each at 449, 547 nm (for ⁴A_{2g}→⁴T_{2g}(F) and ⁴A_{2g}→⁴T_{2g}(P) transitions), at 480, 610 nm (for ⁶A_{1g}→⁴T_{1g}(⁴G) and ⁶A_{1g}→⁴E_g transitions) and at 290, 445 nm (for ⁴T_{1g}(F)→⁴T_{1g}(P), ⁴T_{1g}→⁴A_{2g} transitions) respectively indicating towards octahedral environment^{13,38-39}.

Electronic spectrum of Fe (III) complex shows three spectral bands at 615 nm may be assigned to the ⁶A_{1g}→⁴T_{2g} transition and another band appears at 485 nm assigned to ⁶A_{1g}→⁴T_{1g}(E) pointing towards octahedral geometry of the complex⁴⁰⁻⁴¹.

The electronic spectrum of Ni(II) and Cu(II) metal complexes has showed bands in the range 430-550 nm and 410-550 nm corresponding to the transitions ³A_{2g}(F)→³T_{1g}(F) and ²E_g→²T_{2g} indicating towards the octahedral geometry of these complexes^{27,28}.

Antifungal Activity

All the macrocyclic metal complexes except (Mn(II) macrocyclic complex), exhibited inhibitory activity against planktonic growth of *C. albicans* in a concentration dependent manner (Table-4).

Among the seven, Co(II) macrocyclic complex was most promising in inhibiting growth of *C. albicans* at 0.125 mg/ml. Cr(III) macrocyclic complex and Fe(III) macrocyclic complex were equally effective at 0.25 mg/ml. Ni(II) macrocyclic complex caused more than 50 % reduction in growth at 0.5 mg/ml. Cu(II) macrocyclic complex and Zn(II) macrocyclic complex showed MIC at 1 mg/ml (Table 3). Fluconazole exhibited MIC at 1 $\mu\text{g}/\text{ml}$.

Table 3: Electronic data of the synthesized metal complexes

Sr. No.	Metal complex	Transitions	Wavelength (nm)
1.	$C_{12}H_{12}Cl_3CrN_8O_8$	$^4A_{2g} \rightarrow ^4T_{2g}(F)$ $^4A_{2g} \rightarrow ^4T_{2g}(P)$	449 nm 547 nm
2.	$C_{12}H_{12}Cl_2MnN_8O_8$	$^6A_{1g} \rightarrow ^4T_{1g}(^4G)$ $^6A_{1g} \rightarrow ^4E_g$	480 nm 610 nm
3.	$C_{12}H_{12}Cl_3FeN_8O_8$	$^6A_{1g} \rightarrow ^4T_{1g}(E)$ $^6A_{1g} \rightarrow ^4T_{2g}$	485 nm 615 nm
4.	$C_{12}H_{12}Cl_2CoN_8O_8$	$^4T_{1g}(F) \rightarrow ^4T_{1g}(P)$ $^4T_{1g} \rightarrow ^4A_{2g}$	290 nm 445 nm
5.	$C_{12}H_{12}Cl_2NiN_8O_8$	$^3A_{2g}(F) \rightarrow ^3T_{1g}(F)$	430-550 nm
6.	$C_{12}H_{12}Cl_2CuN_8O_8$	$^2E_g \rightarrow ^2T_{2g}$	410-550 nm
7.	$C_{12}H_{12}Cl_2ZnN_8O_8$	-----	-----

Table 4: Minimum Inhibitory Concentration (MIC) of synthesized macrocyclic complexes compounds against *C. albicans* ATCC 90028

Sr. No.	Metal complex	MIC (mg/ml)
1.	$C_{12}H_{12}Cl_3CrN_8O_8$	0.25
2.	$C_{12}H_{12}Cl_2MnN_8O_8$	NA
3.	$C_{12}H_{12}Cl_3FeN_8O_8$	0.25
4.	$C_{12}H_{12}Cl_2CoN_8O_8$	0.125
5.	$C_{12}H_{12}Cl_2NiN_8O_8$	0.5
6.	$C_{12}H_{12}Cl_2CuN_8O_8$	1
7.	$C_{12}H_{12}Cl_2ZnN_8O_8$	1
8.	Fluconazole	0.001

(NA: Not achieved up to highest concentration tested)

CONCLUSION

In present paper we have reported a series of seven macrocyclic complexes synthesized by template condensation of diethyl malonate and malonyldihydrazide in methanolic medium in the presence of Cr(III), Mn(II), Fe(III), Co(II), Ni(II), Cu(II) and Zn(II) ions. These synthesized complexes have been characterized with the help of molar conductance, magnetic susceptibility measurements, IR, electronic, ¹H NMR Spectra. On the basis of studies made a six coordinated octahedral geometry has been proposed for all these complexes. Most of the complexes have been found to exhibit significant antifungal activity against *Candida albicans*.

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