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Macrocyclic complexes: synthesis and characterization

DHARMPAL SINGH* and KRISHAN KUMAR

Department of Chemistry, National Institute of Technology, Kurukshetra – 136 119, India

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Abstract: A novel series of complexes of the type $[M(C_{28}H_{24}N_4)X]X_2$, where $M = Cr(III)$, $Fe(III)$ or $Mn(III)$, $X = Cl^-$, NO_3^- , CH_3COO^- and $(C_{28}H_{24}N_4)$ corresponds to the tetradentate macrocyclic ligand, were synthesized in methanolic media by the template condensation of 1,8-diaminonaphthalene and 2,3-butanedione (diacetyl) in the presence of trivalent metal salts. The complexes were characterized by elemental analyses, conductance and magnetic measurements, and UV/Vis and IR spectroscopy. Based on these studies, a five-coordinate square pyramidal geometry for all the prepared complexes is proposed. All the synthesized macrocyclic complexes were tested for their *in vitro* antifungal activity against some fungal strains viz. *Aspergillus niger* and *A. fumigatus*. The results obtained were compared with the standard antifungal drug fluconazole.

Keywords: antifungal activity; 2,3-butanedione; template synthesis; macrocyclic Schiff-base complexes.

INTRODUCTION

A number of nitrogen donor macrocyclic derivatives have long been used in analytical, industrial and medical applications.¹ Macrocyclic compounds and their derivatives are interesting ligand system because they are good hosts for metal anions, neutral molecules and organic cation guests.² The metal-ion and host–guest chemistry of macrocyclic compounds are very useful in fundamental studies, e.g., in phase transfer catalysis and biological studies.³ *In situ*, one pot template condensation reactions lie at the heart of macrocyclic chemistry.⁴ Therefore, template reactions have been widely used for the synthesis of macrocyclic complexes,⁵ where, generally, transition metal ions are used as the templating agent.⁶ The metal ions direct the reaction preferentially towards cyclic rather than oligomeric or polymeric products.⁷ Synthetic macrocyclic complexes mimic some naturally occurring macrocycles because of their resemblance to many natural macrocycles, such as metalloproteins, porphyrins and cobalamine.^{8,9} Transition

* Corresponding author. E-mail: dpsinghchem@yahoo.co.in
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metal macrocyclic complexes have received great attention due to their biological activities, including antiviral, anticarcinogenic,⁹ antifertile,¹⁰ antibacterial and antifungal.¹¹ Macrocyclic metal complexes of lanthanides *e.g.*, Gd(III), are used as MRI (magnetic resonance imaging) contrast agents.¹² In a previous paper, the synthesis and characterization of macrocyclic complexes of Co(II), Ni(II), Cu(II), Zn(II) and Cd(II) derived from 1,8-diaminonaphthalene and diacetyl were reported.¹³

Prompted by these facts, in the present paper, the synthesis and characterization of Cr(III), Fe(III) and Mn(III) macrocyclic complexes derived from 1,8-diaminonaphthalene and diacetyl (2,3-butanedione) are discussed. Complexes were characterized using various physicochemical techniques, such as IR and UV/Vis spectroscopy, elemental analyses, and magnetic susceptibility and conductivity measurements.

All the synthesized macrocyclic complexes were tested for their *in vitro* antifungal activities against some fungal strains *viz.* *Aspergillus niger* (MTCC 282) and *A. fumigatus* (MTCC 870). The obtained results were compared with those for the standard antifungal drug fluconazole.

EXPERIMENTAL

Materials

All the chemicals and solvents used in this study were of Analytical grade. 1,8-Diaminonaphthalene and 2,3-butanedione were procured from Acros, New Jersey, USA, the metal salts were purchased from S.D.-fine, Mumbai, India, Merck, Ranbaxy, India, and were used as received.

Isolation of complexes

All the complexes were synthesized by the template method, *i.e.*, by condensation of 1,8-diaminonaphthalene and 2,3-butanedione in the presence of the respective trivalent metal salt. To a hot stirring methanolic solution ($\approx 50 \text{ cm}^3$) of 1,8-diaminonaphthalene (10 mmol) was added trivalent chromium, manganese or iron salt (5.0 mmol) dissolved in the minimum quantity of MeOH ($\approx 20 \text{ cm}^3$). The resulting solution was refluxed for 0.5 h. Subsequently, 2,3-butanedione (10 mmol) was added to the refluxing mixture and refluxing was continued for 8–10 h. The mixture was then concentrated to half its volume, cooled to room temperature and kept in a desiccator overnight, whereby dark-colored precipitates formed, which were filtered, washed with methanol, acetone and diethyl ether and dried *in vacuo*. The obtained yields were ≈ 60 – 70 %. The complexes were soluble in DMF and DMSO. They were thermally stable up to 265–290 °C, after which decomposition occurred.

The template condensation of 1,8-diaminonaphthalene and 2,3-butanedione in the presence of trivalent metal salts, in the molar ratio 2:2:1 is represented in Scheme 1.

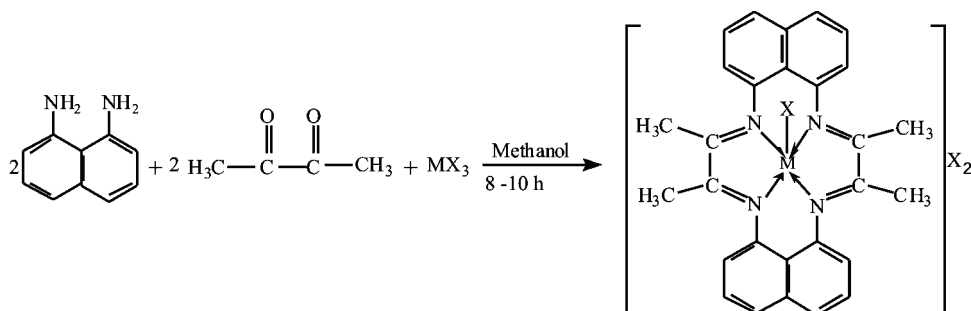
Analytical and physical measurements

The microanalysis for C, H, and N were realized using an elemental analyzer (Perkin Elmer 2400) at SAIF, Punjab University, Chandigarh, India. The magnetic susceptibility measurements were made at SAIF, IIT Roorkee, on a vibrating sample magnetometer (Model PAR 155). The metal contents in the complexes were determined by literature methods.¹⁴ The IR spectra were recorded on a FT-IR spectrophotometer (Perkin Elmer RX-I) in the range 4000 –

200 cm^{-1} using the Nujol Mull method. The electronic spectra (in DMSO) were recorded at room temperature on a Hitachi 330 spectrophotometer in the 200–850 nm range. The conductivity was measured on a digital conductivity meter (HPG system, G-3001). The melting points were determined in capillaries using a Swastika electric melting point apparatus.

In vitro antifungal activity

All the newly synthesized complexes were evaluated for their antifungal activities towards *A. niger* and *A. fumigatus* by the poison food technique.¹⁵



Scheme 1. Representation of the template condensation of 1,8-diaminonaphthalene and 2,3-butanedione in the presence of trivalent metal salts in the molar ratio 2:2:1 (M = Cr(III), Mn(III) or Fe(III) and X = Cl^- , NO_3^- or CH_3COO^-).

RESULTS AND DISCUSSION

Chemistry

The analytical data showed the suggested formula for macrocyclic complexes as: $[\text{M}(\text{C}_{28}\text{H}_{24}\text{N}_4)\text{X}]\text{X}_2$, where M = Cr(III), Fe(III) or Mn(III), X = Cl^- , NO_3^- or CH_3COO^- and $\text{C}_{28}\text{H}_{24}\text{N}_4$ corresponds to the tetradentate macrocyclic ligand. The measurements of molar conductance in DMSO showed that these chelates are 1:2 electrolytes¹⁶ (conductance 155–185 $\Omega^{-1} \text{cm}^2 \text{mol}^{-1}$). Various attempts, such as crystallization using mixtures of solvents and low temperatures, were unsuccessful for the growth of a single crystal suitable for X-ray crystallography. However, the analytical, spectroscopic and magnetic data enabled the possible structure of the synthesized complexes to be predicted. All complexes gave satisfactory elemental analyses results, as shown in Table I.

IR Spectra

It was noted that two bands present in the spectrum of 1,8-diaminonaphthalene at 3350 and 3390 cm^{-1} , corresponding to the $\nu(\text{NH}_2)$ group, were absent from the infrared spectra of all the complexes. Furthermore, no strong absorption band was observed near 1716 cm^{-1} indicating the absence of the C=O group of the 2,3-butanedione (diacetyl) moiety. The disappearance of these bands and the appearance of a new strong absorption band in the range 1590–1629 cm^{-1} confirms the condensation of the carbonyl group of 2,3-butanedione and the amino

group of diaminonaphthalene and the formation of a macrocyclic Schiff's base,¹⁷ as these bands may be assigned to $\nu(\text{C}=\text{N})$ stretching vibrations.¹⁸ The lower value of the frequency of $\nu(\text{C}=\text{N})$ vibrations may be explained by a drift of the lone pair electron density of the azo methine nitrogen towards the metal atom,¹⁹ indicating that coordination occurs through the nitrogen of the $\text{C}=\text{N}$ groups. The medium intensity bands present in the region $2830\text{--}2950\text{ cm}^{-1}$ may be assigned to the $\nu(\text{C}-\text{H})$ stretching vibrations of the methyl group of the diacetyl moiety.²⁰ The various absorption bands in the region $1400\text{--}1588\text{ cm}^{-1}$ may be assigned to $\nu(\text{C}=\text{C})$ aromatic stretching vibrations of the naphthalene ring.^{21,22} The bands in the region $740\text{--}785\text{ cm}^{-1}$ may be assigned to the $\nu(\text{C}-\text{H})$ out of plane bending of the aromatic ring.²³ The presence of the absorption bands at $1408\text{--}1440$, $1290\text{--}1320$ and $1010\text{--}1030\text{ cm}^{-1}$ in the IR spectra of all the nitrate complexes suggest that the nitrate groups are coordinated to the central metal ion in a unidentate fashion.²⁴ The IR spectra of all the acetate complexes show an absorption band in the region $1650\text{--}1680\text{ cm}^{-1}$ that is assigned to the $\nu(\text{COO}^-)_{\text{as}}$ asymmetric stretching vibrations of the acetate ion and another in the region $1258\text{--}1290\text{ cm}^{-1}$ that can be assigned to the $\nu(\text{COO}^-)_{\text{s}}$ symmetric stretching vibration of the acetate ion. The difference between ($\nu_{\text{as}} - \nu_{\text{s}}$) of around $390\text{--}370\text{ cm}^{-1}$ is greater than 144 cm^{-1} , which indicates the unidentate coordination of the acetate group with the central metal ion.²⁵

TABLE I. Analytical data of the trivalent chromium, manganese and iron complexes derived from 1,8-diaminonaphthalene and 2,3-butanedione

No.	Complex	Found (Calcd.), %			Color	Molecular weight
		M C	H	N		
1	$[\text{Cr}(\text{C}_{28}\text{H}_{24}\text{N}_4)\text{Cl}]\text{Cl}_2$ 8.96	58.52 (9.06)	4.10 (58.53) (4.18)	9.68 (9.75)	Green	574
2	$[\text{Cr}(\text{C}_{28}\text{H}_{24}\text{N}_4)(\text{NO}_3)](\text{NO}_3)_2$ 7.91	51.34 (7.95)	3.66 (51.37) (3.67)	14.94 (14.98)	Yellowish green	654
3	$[\text{Cr}(\text{C}_{28}\text{H}_{24}\text{N}_4)(\text{OAc})](\text{OAc})_2$ 8.01	63.21 (8.06)	5.10 (63.25) (5.11)	8.64 (8.68)	Dark grey	645
4	$[\text{Mn}(\text{C}_{28}\text{H}_{24}\text{N}_4)(\text{OAc})](\text{OAc})_2$ 8.47	62.92 (8.47)	5.03 (62.96) (5.09)	8.63 (8.64)	Black	648
5	$[\text{Fe}(\text{C}_{28}\text{H}_{24}\text{N}_4)\text{Cl}]\text{Cl}_2$ 9.63	58.10 (9.66)	4.10 (58.13) (4.15)	9.66 (9.69)	Black	578
6	$[\text{Fe}(\text{C}_{28}\text{H}_{24}\text{N}_4)(\text{NO}_3)](\text{NO}_3)_2$ 8.45	51.04 (8.49)	3.59 (51.06) (3.65)	14.80 (14.89)	Dark grey	658
7	$[\text{Fe}(\text{C}_{28}\text{H}_{24}\text{N}_4)(\text{OAc})](\text{OAc})_2$ 8.57	62.85 (8.60)	5.01 (62.86) (5.08)	8.61 (8.63)	Reddish brown	649

The far infrared spectra show bands in the region $420\text{--}450\text{ cm}^{-1}$ corresponding to $\nu(\text{M}-\text{N})$ vibrations.^{26–28} The bands in the spectra of all the complexes in the region $420\text{--}450\text{ cm}^{-1}$ originate from $(\text{M}-\text{N})$ azomethine vibrational modes and identify coordination of the azomethine nitrogen.²⁹ The bands present in the

range 300–320 cm^{-1} may be assigned to $\nu(\text{M}-\text{Cl})$ vibration.^{26–28} The bands present in the region 220–250 cm^{-1} in all the nitrate complexes are related to the $\nu(\text{M}-\text{O})$ stretching vibration.^{26,27}

Magnetic measurements and electronic spectra

Chromium complexes. The magnetic moments of the chromium(III) complexes at room temperature were found in the range 4.25–4.50 μ_{B} , which are close to the predicted values for three unpaired electrons in the metal ion.¹⁵ The electronic spectra of the chromium complexes show bands at ≈ 9010 –9320, 13030–13350, 17460–18320, 27420–27850 and 34810 cm^{-1} . These spectral bands cannot be interpreted in terms of either a four- or six-coordinated environment around the metal atom. However, the spectra are consistent with that of five-coordinated Cr(III) complexes, the structures of which were confirmed with the help of X-ray measurements.³⁰ Based on the analytical data, spectral studies and electrolytic nature of these complexes, a five-coordinated, square pyramidal geometry may be assigned to these complexes. Thus, assuming C_{4v} symmetry for these complexes,^{31,32} the various spectral bands may be assigned as: ${}^4\text{B}_1 \rightarrow {}^4\text{E}^{\text{a}}$, ${}^4\text{B}_1 \rightarrow {}^4\text{B}_2$, ${}^4\text{B}_1 \rightarrow {}^4\text{A}_2$ and ${}^4\text{B}_1 \rightarrow {}^4\text{E}^{\text{b}}$, respectively.

Manganese complex. The magnetic moment of the manganese(III) complex was found to be 4.89 μ_{B} , which indicates a high spin (d^4) system.¹⁵ The electronic spectra of the manganese complexes show three d–d bands, which lie in the range 12350–12590, 16050–18820 and 35420–35700 cm^{-1} . The higher energy band at 35440–35750 cm^{-1} may be assigned to charge transfer transitions. The spectra resemble those reported for five-coordinate, square pyramidal manganese complexes.^{31,32} This idea is further supported by the presence of a broad ligand field band at 20400 cm^{-1} , which is diagnostic for C_{4v} symmetry, and thus the various bands may be assigned as follows: ${}^5\text{B}_1 \rightarrow {}^5\text{A}_1$, ${}^5\text{B}_1 \rightarrow {}^5\text{B}_2$, and ${}^5\text{B}_1 \rightarrow {}^5\text{E}$, respectively. The band assignment in a single electron transition may be given as: $d_{z^2} \rightarrow d_{x^2-y^2}$, $d_{xy} \rightarrow d_{x^2-y^2}$, and d_{xz} and $d_{yz} \rightarrow d_{x^2-y^2}$, respectively, in order of increasing energy.

Iron complexes. The magnetic moments of iron complexes lie in the range 5.81–5.90 μ_{B} , corresponding to five unpaired electrons, which is close to the predicted high spin values for these metal ions.¹⁵ The electronic spectra of the iron complexes show various bands at 9820–9970, 15520–15575 and 27550–27730 cm^{-1} , which do not suggest octahedral or tetrahedral geometry around the metal atom. The spectral bands are, however, consistent with the range of spectral bands reported for five-coordinate, square pyramidal iron(III) complexes.^{32,33} Assuming C_{4v} symmetry for these complexes, the various bands can be assigned as: $d_{xy} \rightarrow d_{xz}$, and d_{yz} and $d_{xy} \rightarrow d_{z^2}$. Any attempt to make an accurate assignment is thwarted due to interactions of the metal–ligand π -bond systems, which lifts the degeneracy of the d_{xz} and d_{yz} pair.

Biological results and discussion

The antifungal activities of all the complexes were determined against two fungal strains, i.e., *A. niger* and *A. fumigatus* and then compared with the activity of the standard antifungal drug fluconazole. The antifungal activities (percentage inhibition) of the complexes and fluconazole are given in Table II. In the whole series, complex **1** showed the highest percentage inhibition against both fungal strains, whereas none of the tested compounds restricted the fungal growth excellently (Table II). However, of all the tested complexes, **2** and **7** showed nearly 50 % inhibition of mycelial growth against *A. niger*, whereas complexes **1** and **4** showed nearly 55 % inhibition of mycelial growth against *A. fumigatus* (Table II).

TABLE II. *In vitro* antifungal activities of the synthesized macrocyclic compounds determined by the poisoned food method

No. Co	Complexes	Mycelial growth inhibition, %	
		<i>A. niger</i>	<i>A. fumigatus</i>
1	[Cr(C ₂₈ H ₂₄ N ₄)Cl]Cl ₂ 54		55.5
2	[Cr(C ₂₈ H ₂₄ N ₄)(NO ₃)](NO ₃) ₂ 49.6		32.5
3	[Cr(C ₂₈ H ₂₄ N ₄)(OAc)](OAc) ₂ (–)	^a (–)	
4	[Mn(C ₂₈ H ₂₄ N ₄)(OAc)](OAc) ₂	39.3 57.5	
5	[Fe(C ₂₈ H ₂₄ N ₄)Cl]Cl ₂ (–)		(–)
6	[Fe(C ₂₈ H ₂₄ N ₄)(NO ₃)](NO ₃) ₂ 29.3		(–)
7	[Fe(C ₂₈ H ₂₄ N ₄)(OAc)](OAc) ₂ 53.3		24.2
– Fluconazole	ole ^b 75.3		80.2

^aNo activity; ^b standard antifungal drug

CONCLUSIONS

Based on various studies, such as elemental analyses, conductance measurements and magnetic susceptibilities, as well as IR, NMR and electronic spectral studies, a five-coordinate, square pyramidal geometry as shown in Scheme 1 may be proposed for all the synthesized complexes.

It has been suggested that chelation/coordination reduces the polarity of the metal ion mainly because of the partial sharing of its positive charge with the donor group within the whole chelate ring system.³⁴ Besides this, many other factors, such as solubility, dipole moment, conductivity influenced by the metal ion, may possibly explain the antifungal activities of these complexes.³⁵ It has also been observed that some moieties, such as azomethine linkage or heteroaromatic nucleus introduced into such compounds, exhibit extensive biological activities that may be a consequence of the increase in the hydrophobic character and liposolubility of the molecules in crossing the cell membrane of the microorganism and hence the enhanced biological utilization ratio and activity of the complexes.³⁶

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ИЗВОД

МАКРОЦИКЛИЧНИ КОМПЛЕКСИ: СИНТЕЗА И КАРАКТЕРИЗАЦИЈА

DHARMPAL SINGH и KRISHAN KUMAR

Department of Chemistry, National Institute of Technology, Kurukshetra – 136 119, India

Тепмплатном синтезом, полазећи од 1,8-диаминонафталена, 2,3-бутандиона и одговарајућих соли метала у метанолу као растварачу, ситетизована је серија нових комплекса типа $[M(C_{28}H_{24}N_4)X]X_2$ ($M = Cr(III)$, $Fe(III)$ и $Mn(III)$; $X = Cl^-$, NO_3^- , CH_3COO^- , док $C_{28}H_{24}N_4$ представља одговарајући макроциклични лиганд). За карактеризацију добивених комплекса, поред елементарне микроанализе, кондуктометријских и магнетних мерења, употребљена је UV/Vis, и IR спектроскопија. На основу ових мерења нађено је да су добијени пентакоординовани комплекси имају квадратно-пирамидалну геометрију. Испитивана је *in vitro* антифунгална активност синтетизованих комплекса на следећим сојевима: *Aspergillus niger* и *Aspergillus fumigatus*. Добијени резултати су поређени са резултатима за стандардни антифунгални лек флуконазол.

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