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Template synthesis and characterization of biologically active transition metal complexes comprising 14-membered tetraazamacrocyclic ligand

DHARMPAL SINGH[1]*, KRISHAN KUMAR[1], RAMESH KUMAR[1] and JITENDER SINGH[2]

[1]*Department of Chemistry, National Institute of Technology, Kurukshetra- 136 119 and*
[2]*D. M. Division, National Dairy Research Institute, Karnal-132 001, India*

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Abstract: A novel series of complexes of the type $[M(C_{28}H_{24}N_4)X_2]$, where M = Co(II), Ni(II), Cu(II), Zn(II) and Cd(II), X = Cl^-, NO_3^-, CH_3COO^- and $(C_{28}H_{24}N_4)$ corresponds to the tetradentate macrocyclic ligand, were synthesized by template condensation of 1,8-diaminonaphthalene and diacetyl in the presence of divalent metal salts in methanolic medium. The complexes were characterized by elemental analyses, conductance and magnetic measurements, as well as by UV/Vis, NMR, IR and MS spectroscopy. The low values of the molar conductance indicate non-electrolyte type of complexes. Based on these spectral data, a distorted octahedral geometry may be proposed for all of these complexes. All the synthesized macrocyclic complexes were tested for *in vitro* antibacterial activity against some pathogenic bacterial strains, *viz Bacillus cereus*, *Salmonella typhi*, *Escherichia coli* and *Staphylococcus aureus*. The *MIC* values shown by the complexes against these bacterial strains were compared with the *MIC* shown by the standard antibiotics linezolid and cefaclor.

Keywords: antibacterial activity; diaminonaphthalene; macrocyclic complexes; spectroscopic studies.

INTRODUCTION

The design and study of well-arranged metal-containing macrocycles is an interesting field of chemistry.[1] Some synthetic macrocyclic complexes (*e.g.*, Cu-complex) have been investigated for accelerating the photodegradation of hazardous pollutants.[2]

In situ one-pot template condensation reactions lie at the heart of macrocyclic chemistry.[3,4] Therefore, template reactions have been widely used for the synthesis of macrocyclic complexes, in which transition metal ions are generally used as the template agent.[5] There is continued interest in the synthesis of macro-

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* Corresponding author. E-mail: dpsinghchem@yahoo.co.in

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cyclic complexes because of their potential application in fundamental and applied sciences.[6,7] Synthetic macrocyclic complexes mimic some naturally occurring macrocycles because of their resemblance with many natural macrocycles, such as metalloproteins and metalloenzymes.[8] Macrocyclic nickel complexes find use in DNA recognition and oxidation.[9] Macrocyclic copper complexes find use in DNA binding and cleavage[10] and copper containing proteins have been identified.[11] Macrocyclic metal complexes of lanthanides, *e.g.*, Gd^{3+} are used as MRI contrast agents.[12] The macrocyclic metal chelating agent, DOTA, is useful for detecting tumour lesions.[13] The chemistry of macrocyclic complexes is also important due to their use as dyes and pigments,[14] as well as NMR shift reagents.[15] Some macrocyclic complexes have received special attention because of their mixed soft–hard donor character and versatile coordination behaviour[16] and because of their pharmacological properties, *i.e.*, toxicity against bacterial and fungal growth.[17]

Prompted by these facts, in the present paper, the synthesis and characterization of cobalt(II), nickel(II), copper(II), zinc(II), and cadmium(II) macrocyclic complexes derived from 1,8-diaminonaphthalene and diacetyl (2,3-butanedione) are discussed. The complexes were characterized using various physico-chemical techniques, such as IR, NMR, elemental analyses, magnetic susceptibility and conductivity measurements. All the synthesized macrocyclic complexes were tested for *in vitro* antibacterial activity against some bacterial strains using spot-on-lawn on Muller Hinton Agar. Four test pathogenic bacterial strains, *viz. Bacillus cereus* (MTCC 1272), *Salmonella typhi* (MTCC 733), *Escherichia coli* (MTCC 739) and *Staphylococcus aureus* (MTCC 1144) were considered for the determination of the *MIC* (minimum inhibitory concentration) values of the synthesized complexes. The *MIC* values exhibited by the complexes against these bacterial strains were compared with the *MIC* values shown by the standard antibiotics linezolid and cefaclor.

EXPERIMENTAL

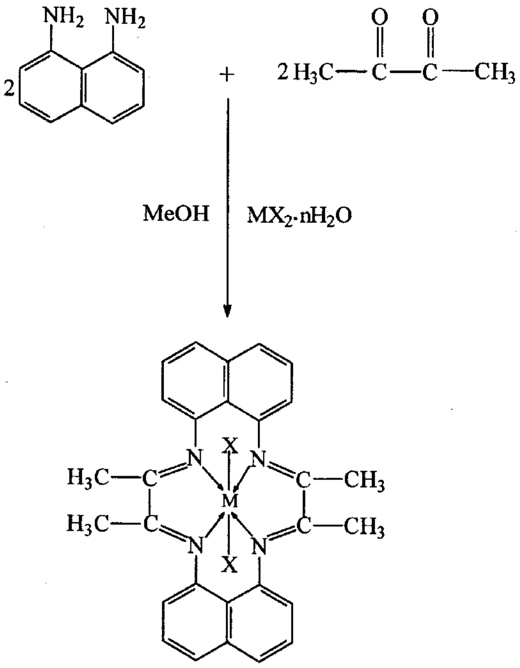
Materials

All the chemicals and solvent used in this study were of AnalaR grade. 1,8-Diaminonaphthalene and diacetyl were procured from Acros, the metal salts were purchased from s.d.-fine, Merck, Ranbaxy 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 diacetyl in the presence of the respective divalent metal salts. To a stirred hot methanolic solution (≈ 50 cm^3) of 1,8-diaminonaphthalene (10 mmol) was added a divalent cobalt, nickel, copper, zinc or cadmium salt (5 mmol) dissolved in the minimum quantity of MeOH (≈ 20 cm^3). The resulting solution was refluxed for 0.5 h, after which diacetyl (10 mmol) was added to the refluxing mixture and the refluxing was continued for 8–10 h. The mixture was concentrated to half its volume and kept in a desiccator overnight. On overnight cooling, a dark coloured precipitate formed which was filtered, washed with methanol, acetone and diethyl ether, and dried *in vacuo*. The obtained yield was ≈ 60–75 %. The complexes were soluble in DMF and DMSO. They were found to be thermally stable up to ≈ 260–280 °C, after which decomposition occurred.

The template condensation of 1,8-diaminonaphthalene and diacetyl in the presence of divalent metal salts, in the molar ratio 2:2:1, is shown in Scheme 1.



Scheme 1. Synthesis of the macrocyclic complexes, where M = Co(II), Ni(II), Cu(II), Zn(II), Cd(II); X = Cl^-, NO_3^-, CH_3COO^-; n = 2, 3, 4, 6.

Analytical and physical measurements

Microanalyses for C, H, and N were performed using an elemental analyzer (Perkin Elmer 2400) at the SAIF, Punjab University, Chandigarh. The magnetic susceptibility measurements were performed at SAIF, IIT Roorkee using a Vibrating Sample Magnetometer (Model PAR 155). The metal contents in the complexes were determined by a literature method.[18] The IR spectra were recorded on a FT-IR spectrophotometer (Perkin Elmer) in the range 4000–200 cm^{-1} using Nujol Mull. The ^{1}H-NMR spectra (at room temperature, in DMSO-d_6) were recorded on a Bruker AVANCE II 400 NMR spectrometer (400 MHz) at the SAIF, Punjab University, Chandigarh. The electronic spectra (in DMSO) were recorded on a Cary 14 spectrophotometer at room temperature. The FAB (Fast atom bombardment) mass spectra (at room temperature) were recorded on a TOF MS ES+ mass spectrometer. The conductivity was measured using a digital conductivity meter (HPG system, G-3001). The melting points were determined in capillaries using an electrical melting point apparatus.

In vitro *antibacterial activity*

All synthesized macrocyclic complexes were tested for *in vitro* antibacterial activity against some bacterial strains using spot-on-lawn on Muller Hinton Agar.[19]

Four test pathogenic bacterial strains, *viz Bacillus cereus* (MTCC 1272), *Salmonella typhi* (MTCC 733), *Escherichia coli* (MTCC 739) and *Staphylococcus aureus* (MTCC 1144) were considered for the determination of the *MIC* (minimum inhibitory concentration) of selected complexes.

The test pathogens were subcultured aerobically using Brain Heart Infusion Agar (HiMedia, Mumbai, India) at 37 °C for 24 h. Working cultures were stored at 4 °C in Brain Heart Infusion (BHI) broth while stock cultures were maintained at –70 °C in BHI broth containing 15 % (v/v) glycerol (Qualigens, Mumbai, India). The organism was grown overnight in 10 ml BHI broth, centrifuged at 5000 *g* for 10 min and the pellet was suspended in 10 ml of phosphate buffer saline (PBS, pH 7.2). The optical density at 545 nm (OD-545) was adjusted to obtain 10^8 Cfu/ml, followed by plating serial dilution onto plate count agar (HiMedia, Mumbai, India).

The minimum inhibitory concentration (*MIC*) is the lowest concentration of an antimicrobial agent that prevents the development of viable growth after overnight incubation. The antimicrobial activity of the compounds was evaluated using spot-on-lawn on Muller Hinton Agar (MHA, HiMedia, Mumbai, India). Soft agar was prepared by adding 0.75 % agar in Muller Hinton Broth. The soft agar was inoculated with 1 % of 10^8 Cfu/ml of the test pathogen and 10 ml was overlaid on MHA. From a 1000X solution of the compound (1 mg/ml of DMSO) 1, 2, 4, 8, 16, 32, 64 and 128X solutions were prepared. Dilutions of standard antibiotics (linezolid and cefaclor) were also prepared in the same manner. 5μl of the appropriate dilution was spotted onto the soft agar and incubated at 37 °C for 24 h. The zones of inhibition of the compounds were considered after subtraction of the inhibition zone of DMSO. The negative control (with no compound) was also observed.

RESULTS AND DISCUSSION

Chemistry

The analytical data show the suggested formula for the macrocyclic complexes as $[M(C_{28}H_{24}N_4)X_2]$, where M = Co(II), Ni(II), Cu(II), Zn(II) and Cd(II), and X = Cl^- NO_3^- CH_3COO^- and $(C_{28}H_{24}N_4)$ corresponds to the tetradentate macrocyclic ligand. The tests for anions were positive only after decomposing the complexes with conc. HNO_3, indicating their presence inside the coordination sphere. The low molar conductance values (10–17 Ω^{-1} cm^2 mol^{-1}) of the complexes determined in DMSO indicate their non-electrolyte nature.[20] Various attempts to obtain a single crystal suitable for X-ray crystallography, such as crystallization using mixtures of solvents and low temperature crystallization, were unsuccessful in order. However, the analytical, spectroscopic and magnetic data enabled the possible structure of the synthesized complexes to be predicted. All complexes gave satisfactory results of elemental analyses, as shown in Table I.

IR spectra

It was noted that a pair of bands were present in the spectrum of 1,8-diaminonaphthalene at 3350 and 3390 cm^{-1} corresponding to ν(NH_2), which were absent in 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

TABLE I. Analytical data of the synthesised divalent cobalt, nickel, copper, zinc and cadmium complexes derived from 1,8-diaminonaphthalene and diacetyl

Complex	Molecular weight	Found (Calcd.), %				Colour
		M	C	H	N	
$[Co(C_{28}H_{24}N_4)Cl_2]$ (**1**)	546	10.68 (10.79)	61.44 (61.53)	4.36 (4.39)	10.09 (10.26)	Black
$[Co(C_{28}H_{24}N_4)(NO_3)_2]$ (**2**)	599	9.79 (9.83)	56.00 (56.09)	3.93 (4.00)	13.96 (14.02)	Black
$[Co(C_{28}H_{24}N_4)(OAc)_2]$ (**3**)	593	9.90 (9.93)	64.59 (64.75)	4.96 (5.06)	9.37 (9.44)	Black
$[Ni(C_{28}H_{24}N_4)Cl_2]$ (**4**)	545	10.63 (10.76)	61.58 (61.65)	4.40 (4.40)	10.08 (10.27)	Grey
$[Ni(C_{28}H_{24}N_4)(NO_3)_2]$ (**5**)	598	9.70 (9.81)	56.09 (56.18)	3.91 (4.01)	14.01 (14.04)	Reddish brown
$[Ni(C_{28}H_{24}N_4)(OAc)_2]$ (**6**)	592	9.86 (9.91)	64.83 (64.86)	5.00 (5.07)	9.29 (9.45)	Dark grey
$[Cu(C_{28}H_{24}N_4)Cl_2]$ (**7**)	550	11.43 (11.55)	61.03 (61.09)	4.29 (4.36)	10.04 (10.18)	Black
$[Cu(C_{28}H_{24}N_4)(NO_3)_2]$ (**8**)	603	10.39 (10.53)	55.61 (55.72)	3.86 (3.98)	13.87 (13.93)	Black
$[Cu(C_{28}H_{24}N_4)(OAc)_2]$ (**9**)	597	10.63 (10.64)	64.22 (64.32)	4.99 (5.02)	9.20 (9.38)	Dark grey
$[Zn(C_{28}H_{24}N_4)(OAc)_2]$ (**10**)	599	10.85 (10.91)	64.03 (64.10)	4.97 (5.01)	9.19 (9.34)	Black
$[Cd(C_{28}H_{24}N_4)(OAc)_2]$ (**11**)	646	17.31 (17.40)	59.34 (59.44)	4.50 (4.64)	8.59 (8.67)	Black

group of the diacetyl moiety. The disappearance of these bands and appearance of a new strong absorption band near 1590–1629 cm^{-1} confirms the condensation of the carbonyl group of diacetyl and the amino group of diaminonaphthalene, and the formation of the macrocyclic Schiff's base,[21] as these bands may be assigned to ν(C=N) stretching vibrations.[22,23] The lower value of ν(C=N) may be explained based on a drift of the lone pair density of the azomethine nitrogen towards the metal atom,[24,25] indicating that coordination occurred through the nitrogen of the C=N groups. The medium intensity bands present in the region 2830–2950 cm^{-1} may be assigned to ν(C–H) stretching vibrations of the methyl group of the diacetyl moiety.[26] The various absorption bands in the region of 1400–1588 cm^{-1} may be assigned to ν(C=C) aromatic stretching vibrations of the naphthalene ring.[27,28] The bands in the region 740–785 cm^{-1} may be assigned to ν(C–H) out of plane bending of the aromatic ring.[29,30] The presence of the absorption bands at 1408–1440, 1290–1320 and 1010–1030 cm^{-1} in the IR spectra of all the nitrato complexes suggest that both the nitrate groups are co-ordinated to the central metal ion in a unidentate fashion.[31] The IR spectra of all the acetate complexes show an absorption band in the region 1650–1680 cm^{-1}

that is assigned to the ν(COO$^-$)$_{as}$ asymmetric stretching vibrations of the acetate ion and another in the region 1258–1290 cm^{-1} that can be assigned to the ν(COO$^-$)$_s$ symmetric stretching vibration of the acetate ion. The difference between ν_{as} and ν_s, which was around 390–370 cm^{-1}, *i.e.*, greater than 144 cm^{-1}, indicates the unidentate coordination of the acetate group with the central metal ion.[32]

The far infrared spectra show bands in the region 420–450 cm^{-1} corresponding to ν(M–N) vibrations.[33–35] The presence of bands in all complexes in the region 420–450 cm^{-1}, originating from (M–N) azomethine vibrational modes, identify coordination of the azomethine nitrogen.[36] The bands present in the range 300–320 cm^{-1} may be assigned to ν(M–Cl) vibration.[33–35] The bands present in the region 220–250 cm^{-1} in all nitrato complexes are related to ν(M–O) stretching vibration.[33,34]

^{1}H-NMR spectra

The ^{1}H-NMR spectrum of the zinc(II) complex shows multiplets at 6.65––7.32 ppm, corresponding to the aromatic ring protons (12H) of the naphthalene moiety[37]. The singlet at 2.12 ppm may be assigned to the methyl protons (12H) of diacetyl.[38]

Mass spectra

The FAB mass spectra of the Co(II), Ni(II), Cu(II), Zn(II) and Cd(II) macrocyclic complexes were recorded using an NBA (nitrobenzyl alcohol) matrix. The peaks at 136, 137, 154, 284 and 307 are due to the matrix. All the spectra exhibited parent peaks due to molecular ions [M]$^+$ and [M+2]$^+$. The proposed molecular formula of these complexes were confirmed by comparing their molecular formula weights with the *m*/*z* values. The molecular ion [M]$^+$ and [M+2]$^+$ peaks obtained for the various complexes are given in Table II. The data are in good agreement with the proposed molecular formula for these complexes, *i.e.*, [M($C_{28}H_{24}N_4$)X_2]. This confirms the formation of the macrocyclic frame. In addition to the molecular ion peaks, the spectra exhibited other peaks assignable to various fragments arising from the thermal cleavage of the complexes (Table II). The peak intensities give an idea of the stability of the fragments.

Magnetic measurements and electronic spectra

Cobalt complexes. The magnetic moment of the cobalt complexes was measured at room temperature and lay in the range of 4.90–4.99 μ_B, which corresponds to three unpaired electrons. The electronic spectra of the cobalt(II) complexes recorded in DMSO exhibits three absorption peaks in the region 1227.0––1077.6 nm (ν_1), 740.7–643.1 nm (ν_2) and 540.5–487.8 nm (ν_3). The spectra resemble those of complexes reported to be octahedral.[39] Thus, assuming the effective symmetry to be D_{4h}, the various bands may be assigned to the transitions: $^4T_{1g} \rightarrow {}^4T_{2g}$(F) ($\nu_1$); $^4T_{1g} \rightarrow {}^4A_{2g}$(F) ($\nu_2$) and $^4T_{1g} \rightarrow {}^4T_{1g}$(P) ($\nu_3$), respectively.

TABLE II. FAB mass spectral data of the synthesised divalent cobalt, nickel, copper, zinc and cadmium complexes derived from 1,8-diaminonaphthalene and diacetyl

Complex	Molecular ion peak $[M]^+$ and $[M+2]^+$ at *m*/*z*	Important peaks due to complex fragmentation
$[Co(C_{28}H_{24}N_4)Cl_2]$ (**1**)	$[M]^+ = 545.6(^{35}Cl)$, $[M+2]^+ = 547.6(^{37}Cl)$	$[Co(C_{28}H_{24}N_4)Cl]^+ = 510.1$, $[Co(C_{28}H_{24}N_4)–H]^+ = 473.6$, $[C_{28}H_{24}N_4]^+ = 414.6$, $[(C_{24}H_{12}N_4)–H]^+ = 353.6$
$[Co(C_{28}H_{24}N_4)(NO_3)_2]$ (**2**)	$[M]^+ = 598.6$	$[Co(C_{28}H_{24}N_4)(NO_3)]^+ = 536.6$, $[Co(C_{28}H_{24}N_4)–H]^+ = 473.6$, $[C_{28}H_{24}N_4]^+ = 414.6$, $[(C_{24}H_{12}N_4)–H]^+ = 353.6$
$[Co(C_{28}H_{24}N_4)(OAc)_2]$ (**3**)	$[M]^+ = 592.9$	$[Co(C_{28}H_{24}N_4)(OAc)]^+ = 533.9$, $[Co(C_{28}H_{24}N_4)–H]^+ = 473.9$, $[C_{28}H_{24}N_4]^+ = 414.9$, $[(C_{24}H_{12}N_4)–H]^+ = 353.9$
$[Ni(C_{28}H_{24}N_4)Cl_2]$ (**4**)	$[M]^+ = 544.4\ (^{35}Cl)$, $[M+2]^+ = 546.4(^{37}Cl)$	$[Ni(C_{28}H_{24}N_4)Cl]^+ = 508.9$, $[Ni(C_{28}H_{24}N_4)]^+ = 473.4$, $[(C_{28}H_{24}N_4)]^+ = 414.7$, $[C_{24}H_{12}N_4–H]^+ = 353.7$
$[Ni(C_{28}H_{24}N_4)(NO_3)_2]$ (**5**)	$[M]^+ = 597.5$	$[Ni(C_{28}H_{24}N_4)(NO_3)]^+ = 535.5$, $[Ni(C_{28}H_{24}N_4)]^+ = 473.5$, $[C_{28}H_{24}N_4]^+ = 414.8$, $[(C_{24}H_{12}N_4)–H]^+ = 353.8$
$[Ni(C_{28}H_{24}N_4)(OAc)_2]$ (**6**)	$[M]^+ = 590.9$	$[Ni(C_{28}H_{24}N_4)(OAc)]^+ = 531.9$, $[Ni(C_{28}H_{24}N_4)]^+ = 472.9$, $[C_{28}H_{24}N_4]^+ = 414.2$, $[(C_{24}H_{12}N_4)–H]^+ = 353.2$
$[Cu(C_{28}H_{24}N_4)Cl_2]$ (**7**)	$[M]^+ = 548.6\ (^{35}Cl)$, $[M+2]^+ = 550.6\ (^{37}Cl)$	$[Cu(C_{28}H_{24}N_4)Cl]^+ = 513.1$, $[Cu(C_{28}H_{24}N_4)]^+ = 477.6$, $[C_{28}H_{24}N_4]^+ = 414.1$, $[(C_{24}H_{12}N_4)–H]^+ = 353.1$
$[Cu(C_{28}H_{24}N_4)(NO_3)_2]$ (**8**)	$[M]^+ = 602.6$	$[Cu(C_{28}H_{24}N_4)(NO_3)]^+ = 540.6$, $[Cu(C_{28}H_{24}N_4)]^+ = 477.6$, $[C_{28}H_{24}N_4]^+ = 414.0$, $[(C_{24}H_{12}N_4)–H]^+ = 353.0$
$[Cu(C_{28}H_{24}N_4)(OAc)_2]$ (**9**)	$[M]^+ = 595.5$	$[Cu(C_{28}H_{24}N_4)(OAc)]^+ = 536.5$, $[Cu(C_{28}H_{24}N_4)]^+ = 477.5$, $[C_{28}H_{24}N_4]^+ = 413.9$, $[(C_{24}H_{12}N_4)–H]^+= 352.9$
$[Zn(C_{28}H_{24}N_4)(OAc)_2]$ (**10**)	$[M]^+ = 598.7$	$[Zn(C_{28}H_{24}N_4)(OAc)]^+ = 539.7$, $[Zn(C_{28}H_{24}N_4)–H]^+ = 479.7$, $[C_{28}H_{24}N_4]^+ = 414.3$, $[(C_{24}H_{12}N_4)–H]^+ = 353.3$
$[Cd(C_{28}H_{24}N_4)(OAc)_2]$ (**11**)	$[M]^+ = 645.5$	$[Cd(C_{28}H_{24}N_4)(OAc)]^+ = 586.5$, $[Cd(C_{28}H_{24}N_4)]^+ = 527.5$, $[(C_{28}H_{24}N_4)–H]^+ = 414.1$, $[(C_{28}H_{24}N_4)–H]^+ = 353.1$

It appears that the symmetry of these complexes is not idealized octahedral (O_h), but is D_{4h}. The assignment of the first spin-allowed band seems plausible since the first band appears approximately at half the energy of the visible band.[40]

Nickel complexes. The magnetic moment of the nickel complexes at room temperature was observed in the range 2.94–3.10 μ_B. These values are in tune with a high spin configuration and show the presence of an octahedral environment around the Ni(II) ion in all the complexes. The spectra of Ni(II) complexes recorded in DMSO solution exhibited a well discernable band with a shoulder on the low energy side. The other two bands generally observed in the region 606.1––581.4 nm (v_2), and 359.7–353.4 nm (v_3) were assigned to $^3A_{2g} \rightarrow {}^3T_{1g}(F)$ (v_2) and $^3A_{2g} \rightarrow {}^3T_{1g}(P)$ (v_3), respectively. The first two bands result from the splitting of one band, v_1, and are in the ranges ≈ 1036.3–980.4 and 843.9–809.7 nm, which can be assigned to $^3B_{1g} \rightarrow {}^3E_g$ and $^3B_{1g} \rightarrow {}^3B_{2g}$, respectively, assuming the effective symmetry to be D_{4h} (component of $^3T_{2g}$ in O_h symmetry).[39] The intense, higher energy bands at 289.5 nm may be due to a π–π* transition of the (C=N) group. Various bands do not follow any regular pattern and seem to be anion independent. The spectra are consistent with the distorted octahedral nature of these complexes.

Copper complexes. The magnetic moment of copper complexes is in the range 1.76–1.80 μ_B. The electronic spectra of the Cu(II) complexes exhibited bands in the region 563.4–512.8 nm, with a shoulder on the low energy side at ≈ 689.7––625.0 nm, which showed that these complexes are distorted octahedral.[38,39] Assuming tetragonal distortion in the molecule, the d-orbital energy level sequence for these complexes may be: $x^2–y^2 > z^2 > xy > xz > yz$ and the shoulder can be assigned to: $z^2 \rightarrow x^2–y^2$ ($^2B_{1g} \rightarrow {}^2B_{2g}$) and the broad band contains both the $xy \rightarrow x^2–y^2$ ($^2B_{1g} \rightarrow {}^2E_g$) and $xy, yz \rightarrow x^2–y^2$ ($^2B_{1g} \rightarrow {}^2A_{2g}$) transitions.[41] The band separation of the spectra of the complexes is of the order 4000 nm, which is consistent with proposed geometry of the complexes.[41] Therefore, it may be concluded that all the complexes formed by macrocycles with Cu(II) metal are distorted octahedral.

Biological results and discussion

The *MIC* (minimum inhibitory concentration) shown by the complexes against the studied bacterial strains was compared with the MIC exhibited by the standard antibiotics linezolid and cefaclor in Table III. Complex **6**, $[Ni(C_{28}H_{24}N_4)(OAc)_2]$, showed a minimum inhibitory concentration ranging from 8–64 µg/ml. The complex also showed a minimum inhibitory concentration of 16 µg/ml against the bacterial strain *Escherichia coli*, which is equal to the *MIC* shown by the standard antibiotic linezolid against the same bacterial strain. The *MIC* of complex **10**, $[Zn(C_{28}H_{24}N_4)(OAc)_2]$, against *E. coli* was found to be 16 µg/ml, which is equal to the minimum inhibitory concentration shown by the standard antibiotic linezolid against the same bacterial strain. For complexes **1**, **3**, **4**, **7** and **9** from Table I, a minimum inhibitory concentration of 32 μg/ml was registered against the bacterial strain *Salmonella typhi*, which is equal to *MIC* shown by the standard antibiotic linezolid against the same bacterial strain (Table III). In the whole series, based on the *MIC*, complex **6**, $[Ni(C_{28}H_{24}N_4)(OAc)_2]$, was found to be the most effective complex as it showed a *MIC* of 8 μg/ml against the bacterial strain *Staphylococcus aureus*. Complexes **4**, $[Ni(C_{28}H_{24}N_4)Cl_2]$, and **7**, $[Cu(C_{28}H_{24}N_4)Cl_2]$, showed an *MIC* of 32 μg/ml against the bacterial strain *Bacillus cereus* (Table III). Complexes **3**, **5** and **8** exhibited an *MIC* of 32 μg/ml against the bacterial strain *S. aureus*. Complexes **1**, **2**, **3** and **4** showed an *MIC* of 32 μg/ml against the bacterial strain *E. coli* (Table III).

TABLE III. Minimum inhibitory concentration (*MIC*) shown by complexes against the test bacteria using the agar dilution assay

Complex	*MIC* / μg ml^{-1}			
	Bacillus cereus	*Staphylococcus aureus*	*Escherichia coli*	*Salmonella typhi*
$[Co(C_{28}H_{24}N_4)Cl_2]$ (**1**)	64	64	32	32
$[Co(C_{28}H_{24}N_4)(NO_3)_2]$ (**2**)	64	>128	32	>128
$[Co(C_{28}H_{24}N_4)(OAc)_2]$ (**3**)	16	32	32	32
$[Ni(C_{28}H_{24}N_4)Cl_2]$ (**4**)	32	64	32	32
$[Ni(C_{28}H_{24}N_4)(NO_3)_2]$ (**5**)	64	32	>128	>128
$[Ni(C_{28}H_{24}N_4)(OAc)_2]$ (**6**)	16	8	16	64
$[Cu(C_{28}H_{24}N_4)Cl_2]$ (**7**)	32	128	128	32
$[Cu(C_{28}H_{24}N_4)(NO_3)_2]$ (**8**)	>128	32	64	64
$[Cu(C_{28}H_{24}N_4)(OAc)_2]$ (**9**)	128	64	64	32
$[Zn(C_{28}H_{24}N_4)(OAc)_2]$ (**10**)	128	16	16	64
Cefaclor[1]	8	2	8	16
Linezolid[1]	4	4	16	32

[1] Standard antibiotics

Bearing in mind the rising problems of antimicrobial resistance, these chemical compounds may be used for the formulation of novel chemotherapeutic agents. Further investigation will be necessary to identify the active component.

CONCLUSIONS

Based on various studies, such as elemental analyses, conductance measurements and magnetic susceptibilities, as well as IR, NMR, electronic and mass spectral studies, a distorted octahedral geometry may be proposed for all these complexes. The proposed structure is shown in Fig. 1.

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 a donor group within the whole chelate ring system.[42] This process of chelation thus increases the lipophilic nature of the central metal atom, which in turn, favours its permeation through the lipoid layer of the membrane, thus causing the metal complex to cross the bacterial membrane more effectively thereby increasing the activity of the complexes. In addition to this, many other factors, such as solubility, dipole moment and conductivity as well as the influence of the metal ion, may be possible reasons for the remarkable antibacterial activities of these complexes.[43]

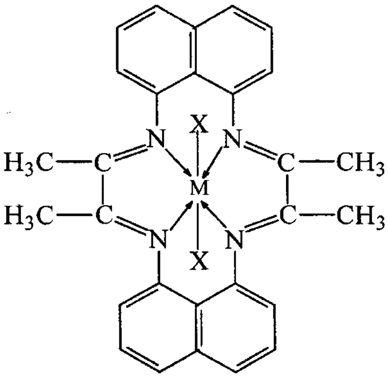


Fig. 1. Proposed structure of the complexes (M = Co(II), Ni(II), Cu(II), Zn(II), Cd(II) and X = Cl^-, NO_3^-, CH_3COO^-).

ABBREVIATIONS

MIC – Minimum inhibitory concentration
MTCC – Microbial type culture collection
MHA – Muller hinton agar
CFU – Colony forming unit
μ_B – Bohr magneton
DMF – *N*,*N*-Dimethylformamide
DMSO – Dimethyl sulphoxide
BHI – Brain heart infusion
DOTA – 1,4,7,10-Tetraazacyclododecane-1,4,7,10-tetraacetic acid
NMR – Nuclear magnetic resonance
MRI – Magnetic resonance imaging
IR – Infrared

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ИЗВОД

ТЕМПЛАТНА СИНТЕЗА И КАРАКТЕРИЗАЦИЈА БИОЛОШКИ АКТИВНИХ КОМПЛЕКСА ПРЕЛАЗНИХ МЕТАЛА КОЈИ САДРЖЕ ЧЕТРНАЕСТОЧЛАНЕ ТЕТРААЗАМАКРОЦИКЛИЧНЕ ЛИГАНДЕ

DHARMPAL SINGH[1], KRISHAN KUMAR[1], RAMESH KUMAR[1] и JITENDER SINGH[2]

[1]*Department of Chemistry, National Institute of Technology, Kurukshetra- 136 119 и*
[2]*D. M. Division, National Dairy Research Institute, Karnal-132 001, India*

Темплатном кондензацијом 1,8-диаминонафталена и диацетила у присуству двовалентних металних соли у метанолу синтетисана је нова серија комплекса типа [M($C_{28}H_{24}N_4$)X_2], где је M = Co(II), Ni(II), Cu(II), Zn(II) и Cd(II); X = Cl^-, NO_3^-, CH_3COO^-, а ($C_{28}H_{24}N_4$) одговара тетрадентатном макроцикличном лиганду. Комплекси су окарактерисани елементалном анализом, мерењем проводљивости и магнетним мерењима, UV/Vis, NMR, IR и MS спектроскопијом. Мала вредност моларне проводљивости указује на комплекс типа неелектролита. На основу спектралних података предложена је дисторгована октаедарска геометрија за све комплексе. Сви макроциклични комплекси су тестирани на *in vitro* антибактеријску активност према сојевима неких патогених бактерија, тј. *Bacillus cereus*, *Salmonella typhi*, *Escherichia coli* и *Staphylococcus aureus*. *MIC* комплекса према овим бактеријским сојевима упоређене су са *MIC* стандардних антибиотика линезолид и цефаклор.

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