

Thermal behaviour of some new complexes with decaaza bismacrocylic ligand as potential antimicrobial species

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Abstract Novel complexes of type $M_2L(CH_3COO)_4 \cdot nH_2O$ (M:Ni, $n = 4$; M:Cu, $n = 2$ and M:Zn, $n = 0$; L: ligand resulted in 1,2-phenylenediamine, 3,6-diazaoctane-1,8-diamine and formaldehyde template condensation) were synthesised and characterised. The features of complexes have been assigned from microanalytical, IR, UV–Vis, 1H NMR, EPR as well as magnetic data at room temperature. Processes as water elimination as well as oxidative degradation of both organic components (bismacrocycle and acetate) were observed. The final product of decomposition was metal (II) oxide as powder X-ray diffraction indicates.

Keywords Complexes · Bismacrocycle · One pot condensation · 1,2-Phenylenediamine · Thermal behaviour

Introduction

Having in view their interesting chemical properties as well as biological activity, design and synthesis of new types of polyaza macropolycyclic compounds have received much attention in last years. Amongst these compounds, the binuclear complexes with bis(azamacrocyclic) ligands are subject of extensive investigation concerning metal–metal interactions as well as structural and catalytic effects [1, 2]. The presence of two metal centres within a small distance each other can lead to different magnetic, redox and electrochemical properties in comparison with the corresponding mono-azamacrocyclic complex. Thus, some dimetal(II) complexes have been shown to act as a more efficient catalysts than the cyclam–metal complex for electrochemical water reduction to hydrogen [3], photochemical CO_2 reduction [4, 5], tetrahydrofuran oxidation with H_2O_2 [6–8] or the reductive dehalogenation of alkyl and aryl halide [9]. Furthermore, bis(macrocylic) complexes which directly bind to biological receptors have become increasingly interest to develop diagnostic probes and therapeutic drugs [10–13].

As result of their potential applications, several papers that cover the design and synthesis of polyaza bismacrocylic complexes have been published. Two macrocycle can be directly linked by *N,N*- or C–C bond [14] or through a variety of bridges involving an aliphatic [15–17] or aromatic [6, 7, 18–20] framework with varying lengths and many of these studies were dedicated to bis(macrocylic) based on cyclam moieties [1]. Some complexes with a polyaza bismacrocylic ligand have recently studied concerning thermal behaviour [20].

In order to gain further insight into the thermal behaviour of bismacrocylic complexes, we report here the synthesis and characterization of a new series of species prepared by the one pot condensation of aromatic linker

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1,2-phenylenediamine, formaldehyde and 3,6-diazaoctane-1,8-diamine in presence of Ni(II), Cu(II) and Zn(II). The complexes have been characterized by different analytical, spectral and magnetic methods.

The thermal behaviour of these derivatives was investigated in synthetic air by thermal analysis (TG, DTA) to evidence the modification that appear at heating and also the thermodynamic effects that accompany them.

The complexes were screened for antimicrobial activity against some Gram-negative, Gram-positive as well as fungal pathogenic strains.

Experimental

Materials

The high purity reagents were obtained commercially from Sigma-Aldrich ($\text{Ni}(\text{CH}_3\text{COO})_2 \cdot 6\text{H}_2\text{O}$, $\text{Cu}(\text{CH}_3\text{COO})_2 \cdot \text{H}_2\text{O}$, $\text{Zn}(\text{CH}_3\text{COO})_2 \cdot 2\text{H}_2\text{O}$, $\text{Na}_2\text{S} \cdot 9\text{H}_2\text{O}$), Merck (1,3-phenylenediamine, 3,6-diazaoctane-1,8-diamine, methanol) and Loba (formaldehyde, triethylamine) and were used as received without further purification.

Instruments

Chemical analysis of carbon, nitrogen and hydrogen has been performed using a Perkin Elmer PE 2400 analyzer.

Metal content was determined with AAS on a Avanta GBC spectrometer using a stock standard solution (Merck, 1,000 mg/mL) whilst the working solutions were prepared by a suitable dilution of the sample obtained after complexes calcination at 450 °C and successive treatment with HCl and HNO_3 of the residue.

IR spectra were recorded in KBr pellets with a Bruker Tensor 37 spectrometer in the range 400–4,000 cm^{-1} .

Electronic spectra by diffuse reflectance technique, with spectralon as standard, were recorded in the range 200–1,500 nm, on a Jasco V670 spectrophotometer.

Magnetic measurements were done by Faraday's method, at room temperature, using $\text{Hg}[\text{Co}(\text{NCS})_4]$ as standard. The molar magnetic susceptibilities were calculated and corrected for the atomic diamagnetism. EPR spectra were recorded on microcrystalline samples at room temperature with a MiniScope MS200 Magnetech Ltd. (Germany) that operate in X band. The field was calibrated using crystalline diphenylpicrylhydrazyl ($g = 2.0036$).

^1H NMR spectra were recorded on a Bruker spectrometer (working frequency 200 MHz) at 25 °C. Chemical shifts were measured in ppm from internal standard TMS.

The EPR measurements were performed on microcrystalline samples using a JEOL JES-ME upgrade spectrometer equipped with X-band cavity (9.5 GHz).

The heating curves (T, TG and DTA) were recorded using a Labsys 1200 SETARAM instrument, with a sample mass of 5–11 mg over the temperature range of 20–900 °C, using a heating rate of 10 °C/min. The measurements were carried out in synthetic air atmosphere (flow rate 16.66 cm^3/min) by using alumina crucibles.

The X-ray powder diffraction patterns were collected on a DRON-3 diffractometer with a nickel filtered Cu K_α radiation ($\lambda = 1.5418 \text{ \AA}$) in 2θ range of 5–70°, a step width of 0.05° and an acquisition time of 2 s per step.

Biological assays

The antimicrobial activities of the complexes were determined against ATCC reference and clinical microbial strains, i.e. Gram-positive (*Staphylococcus aureus* 0364, *Bacillus subtilis*, *Enterococcus faecalis* ATCC 2921), Gram-negative (*Klebsiella pneumoniae* 2968, *Escherichia coli* ATCC 25922, *E. coli* 714, *Enterobacter cloacae* 61R, *Pseudomonas aeruginosa* 1397) and fungus *Candida krusei* 963.

Microbial suspensions of 1.5×10^8 CFU/mL corresponding to 0.5 McFarland density obtained from 15 to 18 h bacterial cultures developed on solid media were used in our experiments. The antimicrobial activity was tested on Mueller–Hinton Agar (MHA) medium, whilst a Yeast Peptone Glucose (YPG) medium was used in case of *C. krusei*. The compounds (HDMBG and complexes) were solubilized in DMSO and the starting stock solution was of 1,000 $\mu\text{g}/\text{mL}$ concentration. The qualitative screening was performed by an adapted disc diffusion method as was previously reported [21].

The quantitative assay of the antimicrobial activity was performed by the liquid medium microdilution method, in 96 multi-well plates, in order to establish the minimal inhibitory concentration (MIC). In this purpose, serial two-fold dilutions of the compounds ranging between 1,000 and 1.95 $\mu\text{g}/\text{mL}$, were performed in a 200 μL volume of broth and each well was seeded with 50 μL microbial inoculum. Sterility control (wells containing only culture medium) and culture controls (wells containing culture medium seeded with the microbial inoculum) were used. The influence of the DMSO solvent was also quantified in a series of wells containing DMSO, diluted accordingly with the dilution scheme used for the complexes. The plates were incubated for 24 h at 37 °C, and MIC values were considered as the lowest concentration of the tested compound that inhibited the visible growth of the microbial cultures incubated overnight.

The assessment of the complexes influence on the microbial ability to colonize the plastic inert substratum was performed by the micro-titre method, following previously described protocols [21]. The absorbance at 490 nm was measured with an ELISA reader Apollo LB 911. All biological experiments were performed in triplicates.

Synthesis and spectral data of complexes and ligand

Complexes synthesis

To a suspension that contain 3,6-diazaoctane-1,8-diamine (20 mmol), hydrated metal (II) acetate (20 mmol), 2 cm³ triethylamine and 2 cm³ formaldehyde (37%) in 150 cm³ methanol was added drop wise a solution of 1,2-phenylenediamine (10 mmol) in 50 cm³ methanol. The reaction mixture was refluxed 24 h until a sparingly soluble brown coloured compound was formed. The microcrystalline products were filtered off, washed with methanol and air dried.

[Ni₂L](CH₃COO)₄·4H₂O (**1**): IR (KBr pellet), cm⁻¹: ν(OH), 3391s; ν(NH), 3242m; ν_{as}(CH₂), 2931m; ν_s(CH₂), 2820w; ν_{as}(COO), 1562vs, ν(C=C), 1531s, 1455s; ν_s(COO), 1404m; ¹H NMR (250 MHz, DMSO-*d*₆) δ (ppm): 1.12 (s, 8H, NH), 2.51 [sb, 24H, (CH₂)₂], 2.82 (sb, 12H, CH₃), 4.30 (s, 8H, CH₂), 7.26 (m, 2H, Ar-H), 7.67 (m, 2H, Ar-H).

[Cu₂L](CH₃COO)₄·2H₂O (**2**): IR (KBr pellet), cm⁻¹: ν(OH), 3440vs; ν(NH), 3266m; ν_{as}(CH₂), 2924w; ν_s(CH₂), 2853w; ν_{as}(COO), 1561vs, ν(C=C), 1469vs; ν_s(COO), 1400m; [Zn₂L(CH₃COO)₄] (**3**): IR (KBr pellet), cm⁻¹: ν(NH), 3280m; ν_{as}(CH₂), 2972w; ν_s(CH₂), 2875w; ν_{as}(COO), 1585vs, ν(C=C), 1468vs; ν_s(COO), 1405s.

The ligand [1,2-bis(*N,N*-1,3,6,9,12-pentaazacyclotridecane)-benzene] synthesis

To a suspension of complex [Cu₂L](CH₃COO)₄·2H₂O in water an excess of sodium sulphide nonahydrate was added and the reaction mixture was magnetically stirred at 50 °C until a black precipitate was formed. The suspension was

filtered off and the filtrate was treated with HCl 2 N until the cessation of effervescence. After solvent evaporation, the solid product was treated several times with tetrahydrofuran. The combined extracts were then concentrated to dryness and the yellow product formed was recrystallized from DMSO. IR (KBr pellet), cm⁻¹: ν(NH), 3322vs; ν_{as}(CH₂), 2921m; ν_s(CH₂), 2844w; ν(C=C), 1636m, 1445s, 1406vs; ¹H NMR (250 MHz, DMSO-*d*₆) δ (ppm): 2.11 (s, 8H, NH), 2.53 [*t*, *J* = 1.8Hz, 24H, (CH₂)₂], 4.85 (s, 8H, CH₂), 7.24 (m, 2H, Ar-H), 7.64 (m, 2H, Ar-H).

Results and discussions

Synthesis and physico-chemical characterisation of complexes and ligand

The one-pot reactions of excess formaldehyde with 2:2:1 molar ratio of nickel (II), copper(II) or zinc (II) acetate, 3,6-diazaoctane-1,8-diamine and 1,2-phenylenediamine in an alkaline medium produced the species M₂L(CH₃COO)₄·*n*H₂O (**1**) M:Ni, *n* = 4; (**2**) M:Cu, *n* = 2 and (**3**) M:Zn, *n* = 0; L: 1,2-bis(*N,N*-1,3,6,9,12-pentaazacyclotridecane)-benzene] (Scheme 1).

The free ligand 1,2-bis(*N,N*-1,3,6,9,12-pentaazacyclotridecane)-benzene was synthesized by Cu(II) complex treatment with sodium sulphide, followed by extraction from dryness reaction mass with tetrahydrofuran and DMSO recrystallization. The ¹H NMR spectrum of ligand reveals the characteristic pattern of protons from both ethylene and methylene groups, that generate signals at 2.56 and 4.85 ppm, respectively. The secondary amine group was identified by signal located at 2.11 ppm.

Scheme 1 The complexes synthesis route

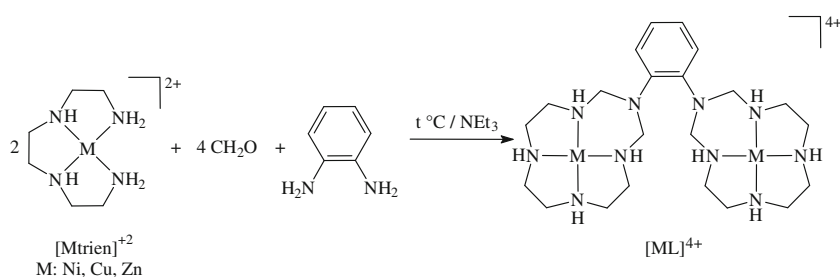


Table 1 Analytical data of complexes

Compound	Chemical formula	MW/g mol ⁻¹	% Found (calcd.)			
			M	C	H	N
L	C ₂₂ H ₄₄ N ₁₀	448.65	–	58.81 (58.90)	9.71 (9.89)	31.34 (31.22)
(1)	Ni ₂ C ₃₀ H ₆₄ N ₁₀ O ₁₂	874.28	13.35 (13.43)	41.11 (41.21)	7.18 (7.38)	16.23 (16.02)
(2)	Cu ₂ C ₃₀ H ₆₀ N ₁₀ O ₁₀	847.95	14.68 (14.99)	42.31 (42.49)	6.97 (7.13)	16.63 (16.52)
(3)	Zn ₂ C ₃₀ H ₅₆ N ₁₀ O ₈	815.65	15.87 (16.04)	44.01 (44.18)	6.69 (6.92)	17.29 (17.17)

The chemical analyses are in accord with the formulas proposed for complexes (Table 1).

The IR spectra of complexes (experimental part) indicate the presence of absorptions assigned to some fragments provided both by 3,6-diazaoctane-1,8-diamine and 1,2-phenylenediamine, such as that associated with the CH_2 and $\text{C}=\text{C}$ (aromatic) groups [22, 23]. The IR spectra showed also a sharp absorption around $3,300\text{ cm}^{-1}$ assigned to secondary amine stretching vibration [7, 24]. This band is shifted by $40\text{--}80\text{ cm}^{-1}$ to lower wavenumbers in comparison with metal-free ligand as an indicative of secondary amine coordination [7]. For carboxyl group two bands can be noticed for all complexes in the $1,560\text{--}1,585$ and $1,400\text{--}1,405\text{ cm}^{-1}$ ranges respectively, assigned to $\nu_{\text{as}}(\text{COO})$ and $\nu_{\text{s}}(\text{COO})$ vibration modes. The difference between these bands of about 160 cm^{-1} for complexes (1) and (2) indicates the acetate as free ion in these compounds. A value of 180 cm^{-1} for this difference in the case of complex (3) is in agreement with unidentate nature of acetate in this case [25].

A broad band in the range $3,390\text{--}3,450\text{ cm}^{-1}$ can be assigned to $\nu(\text{OH})$ stretching vibration for water molecule, except for complex (3) [26].

The amine group coordination as well as the acetate presence for complex (1) was further supported by ^1H NMR spectrum. Thus, additional resonance arises from the methyl group of acetate appears at 2.82 ppm, whilst that assigned to NH group is upfield-shifted relative to the signal of the free ligand. The low solubility of Zn(II) complex do not allowed their characterisation through this technique.

The electronic spectrum of compound (1) displays a broad band with maxima at $20,830$, $16,950$ and $15,040\text{ cm}^{-1}$, pattern characteristic for the distorted square-planar stereochemistry, these components can be thus assigned to $^1A_{1g} \rightarrow ^1E_g$, $^1A_{1g} \rightarrow ^1B_{1g}$ and $^1A_{1g} \rightarrow ^1A_{2g}$ transitions, respectively [27]. The broad band with maximum at $20,410\text{ cm}^{-1}$ and a shoulder at $17,240\text{ cm}^{-1}$ indicates for complex (2) the same stereochemistry [27, 28]. It was assumed that the Zn(II) complex adopts an octahedral stereochemistry considering that square-planar species are found less frequently for this ion, e.g. when one of ligands is macrocyclic [2].

As expected, the square-planar Ni(II) complex and the octahedral Zn(II) species are diamagnetic. Instead for Cu(II) complex, a value of 1.87 B.M. per metallic ion lies in the normal range for Cu(II) compounds with $S = 1/2$.

The powder EPR spectrum of (2) in X-band displays an asymmetric line with $g_{\parallel} = 2.154$, $g_{\perp} = 2.069$, $A_{\parallel} = 16.8\text{ mT}$ and $A_{\perp} \leq 7.2\text{ mT}$, respectively (Fig. 1). This pattern is consistent with an axial symmetry having all axes parallel aligned as observed for other square-planar Cu(II) complexes with ligands having nitrogen donors [29].

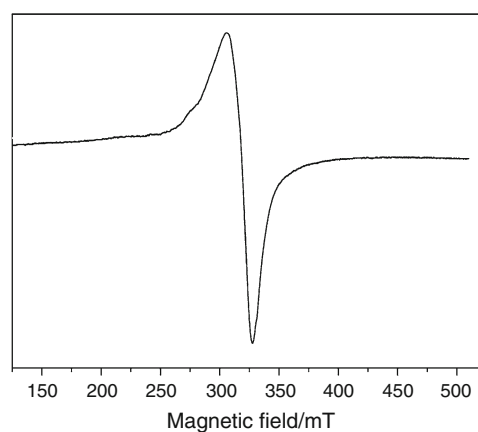


Fig. 1 X-band EPR spectrum of $[\text{Cu}_2\text{L}](\text{CH}_3\text{COO})_4 \cdot 2\text{H}_2\text{O}$ (2)

Thermal behaviour of complexes

The TG and DTA curves corresponding to the complex (1) heated in the $20\text{--}900\text{ }^\circ\text{C}$ temperature range indicate that decomposition follows three steps (Fig. 2).

The first step consists in an endothermic elimination of water molecules up to $110\text{ }^\circ\text{C}$ (Table 2), behaviour observed as well as for other complexes with crystallisation water [30]. This species is stable over a $66\text{ }^\circ\text{C}$ temperature range. The second step, weak exothermic, corresponds to acetate into carbonate transformation. The third step is not a single one, being an overlap of at least two processes according to DTA curve profile. This step corresponds to carbonate decomposition and oxidative degradation of bismacrocyclic ligand leading finally to the non-stoichiometric nickel (II) oxide (found/calcd. overall mass loss: $82.1/82.9\%$). The nature of final product was confirmed by IR and powder X-ray diffraction data (ASTM 78-0429). This species loses continuously oxygen from the lattice as indicate both the slightly decrease of the mass according to TG curve and the endothermic effect noticed on DTA curve.

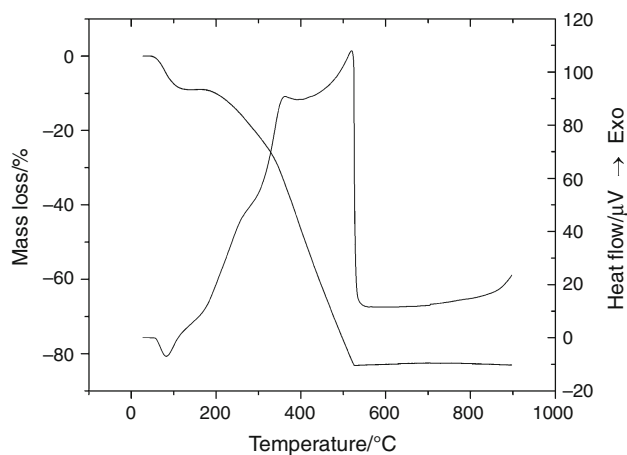
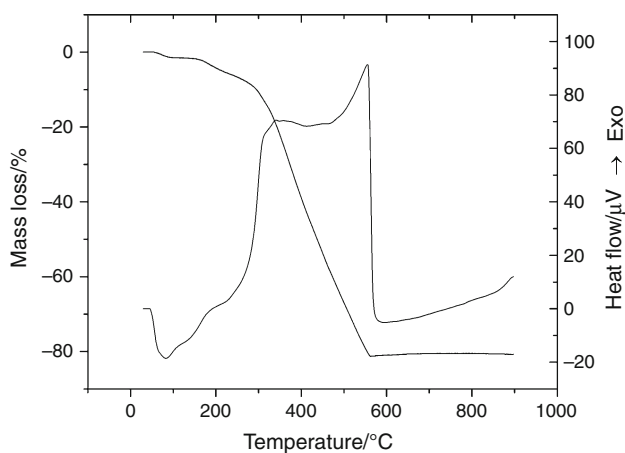
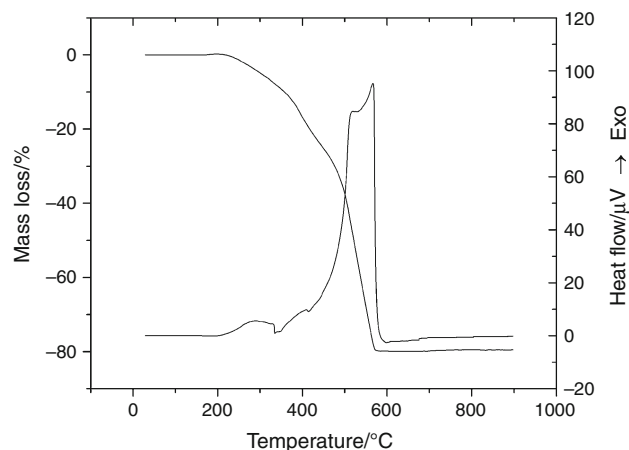


Fig. 2 TG and DTA curves for $[\text{Ni}_2\text{L}](\text{CH}_3\text{COO})_4 \cdot 2\text{H}_2\text{O}$ (1)

Table 2 Thermal behaviour data (in air atmosphere) for complexes

Compound	Step	Thermal effect	Temperature range/°C	$\Delta m_{\text{exp}}/\%$	$\Delta m_{\text{calcd}}/\%$
[Ni ₂ L](CH ₃ COO) ₄ ·4H ₂ O (1)	1	Endothermic	54–110	8.1	8.2
	2	Exothermic	176–308	13.4	13.3
	3	Exothermic	308–550	60.6	61.4
[Cu ₂ L](CH ₃ COO) ₄ ·2H ₂ O (2)	1	Endothermic	54–130	1.8	2.1
	2	Endothermic	130–186	1.9	2.1
	3	Exothermic	186–280	6.2	6.8
	4	Exothermic	280–580	70.5	70.2
[Zn ₂ L(CH ₃ COO) ₄] (3)	1	Exothermic	210–387	14.3	14.2
	2	Exothermic	387–590	65.9	65.8

The water molecules are lost in two well definite, endothermic steps as it can see in the thermogram of compound (2) (Fig. 3). These steps occurred in the temperature ranges 54–130 and 130–186 °C, respectively, as an indicative of water molecules involving in different interactions. Considering that the electronic spectrum indicate a square-planar geometry of Cu(II) and the fact that coordinative bonds are realised with macrocyclic ligand, it results that water molecules are not involved in coordination. Consequently, some water molecules are evolved at higher temperatures, being involved in hydrogen bonds in the lattice [31]. Next exothermic step corresponds to half content of acetate into carbonate transformation. Third step is not a single one, being an overlap of at least three processes according to DTA curve profile and corresponds to carbonate decomposition and oxidative degradation of both residual acetate and bismacrocyclic ligand. All these transformations generate finally the CuO as powder X-ray diffraction indicates (ASTM 5-661) (found/calcd. overall mass loss: 80.4/81.2%). This displays the same behaviour with NiO and loses oxygen from lattice according with both TG and DTA curves.

**Fig. 3** TG and DTA curves for [Cu₂L](CH₃COO)₄·2H₂O (2)**Fig. 4** TG and DTA curves for [Zn₂L(CH₃COO)₄] (3)

Complex (3) is an anhydrous species and as result their thermal degradation starts at 210 °C (Fig. 4). First step is exothermic and according to the mass loss corresponds to acetate anions into carbonate transformations. The second step, exothermic and complex, results from overlapping of at least three processes as DTA curve profile indicates. According to mass loss, this step corresponds to carbonate decomposition and bismacrocyclic pyrolyse. All these processes are finished with zinc (II) oxide generation at 590 °C (ASTM 00-036-1451) (found/calcd. overall mass loss: 80.2/80.0%).

Having in view all above data, the complexes were formulated as [Ni₂L](CH₃COO)₄·2H₂O (1), [Cu₂L](CH₃COO)₄·2H₂O (2) and [Zn₂L(CH₃COO)₄] (3), respectively. The coordination proposed for the new complexes is presented in Fig. 5.

Biological activity

The antimicrobial activity of the new compounds was assayed against Gram-positive (*S. aureus*, *B. subtilis*, *E. faecalis*), Gram-negative (*K. pneumoniae*, *E. coli*, *E. cloacae*, *P. aeruginosa*) pathogenic bacteria as well as

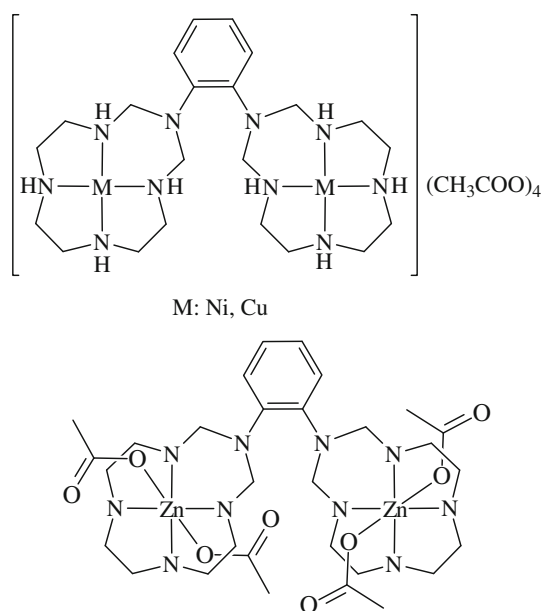


Fig. 5 The coordination proposed for complexes (water molecules are omitted)

against *C. krusei* fungal stain. The tests revealed a good antimicrobial activity only in the case of complex (3) with a MIC value 125 $\mu\text{g}/\text{mL}$ in the case of *E. coli*.

Having in view, the differences in physiology and susceptibility to antibiotics of biofilm-embedded microorganism, the complexes were investigated concerning their efficiency against the adherent cells grown in biofilms developed in plastic wells. From this point of view, it was observed that the complexes interact differently with the biofilm of microbial strains, the effect being either inhibitory or stimulatory depending on strains and concentration. The complex (3) exhibited the most evident inhibitory effect upon adherence ability of *E. coli* on the entire range concentrations (1,000–1.95 $\mu\text{g}/\text{mL}$), whilst in the case of *B. subtilis*, *K. pneumoniae* and *E. cloacae* the anti-biofilm activity was expressed only at higher concentrations of 31.25 $\mu\text{g}/\text{mL}$. This aspect is important considering that genetic resistance of different microbial strains to antimicrobials is amplified when pathogenic microorganism is developing in biofilm.

The increased activity of Zn(II) complex (3) could be explained considering its non-electrolyte nature resulted from both bismacrocycle and acetate coordination. This increases the compound lipophilicity, allowing an easier carriage across the lipid membrane of the pathogenic microorganism.

Conclusions

The Ni(II), Cu(II) and Zn(II) complexes with bismacrocycle ligand resulted in one-pot condensation of

3,6-diazaoctane-1,8-diamine, formaldehyde and 1,2-phenylenediamine have been synthesised. The new ligand 1,2-bis(*N,N*-1,3,6,9,12-pentaazacyclotridecane)-benzene was also isolated and characterised.

The compounds were characterised by means of IR, ^1H NMR, EPR, electronic spectroscopy as well as magnetic measurements at room temperature. Spectral and magnetic data indicate for Ni(II) and Cu(II) complexes a square-planar stereochemistry.

Thermal decomposition of complexes allowed the establishing of number and nature of water molecule, the composition of complexes and also the intervals of thermal stability. After water elimination up to 186 $^\circ\text{C}$, the complexes decompose in two steps leading to metal (II) oxide as residue.

From the tested compounds, only the Zn(II) complex (3) showed antimicrobial activity both against isolated and biofilm-embedded strains.

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