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Zinc, copper and nickel complexes of a macrocycle synthesized from pyridinedicarboxylic acid: A spectroscopic, thermal and theoretical study

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Abstract: The metal(II) ion complexes of a pentadentate macrocycle **1**, namely 3,12-dioxa-6,9,18-triazabicyclo[12.3.1]octadeca-1(18),14,16-triene-2,13-dione are synthesized. This macrocycle is prepared from the reaction of dipotassium salt of 2,6-pyridinedicarboxylic acid with ethylenediamine and 1,2-dibromoethane. The reaction of **1** (L) in methanol with $MCl_2.xH_2O$ gave complexes with the general formula $[M(L)Cl_2]$ (where M= Ni(II) **2**, Cu(II) **3** and Zn(II) **4**, respectively). The analysis of IR, ^{1}H- and ^{13}C-NMR spectral data of all complexes propose that **1** is bonded to metal(II) ions through a nitrogen atom of pyridine ring, two nitrogen atoms of amine groups and two oxygen atoms of ester moieties. The thermal analysis indicated that there are no water molecules of hydration or coordinated in the structure of the complexes. Among these complexes, the Cu(II) **3** complex demonstrated good antibacterial and antifungal activities. The molecular geometry, AIM atomic charge and frontier molecular orbitals of the compounds are investigated theoretically using DFT method. Based on the theoretical data of these complexes represented, a bipyramidal pentagonal arrangement can be envisaged in such a way that the N_3O_2 pentadentate donor sites form the planar pentagonal base of the bipyramid and the two Cl atoms occupy the vertexes.

Keywords: macrocycle ligand; pyridinedicarboxylic acid; thermal analysis; molecular modeling; DFT calculation; antimicrobial studies.

INTRODUCTION

Macrocycles can be defined as cyclic organic framework with several potential donor atoms which surround a central metallic ion as a coordination center. Macrocycles have received a continuous and prolonged attention due to their wide applications as catalysts, optic and magnetic materials.[1–3]

The various roles performed by the naturally occurring macrocycles in biological systems are well known. The synthesis of macrocycle complexes is very

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important due to their application as dyes, pigments, and MRI contrast agents.[4,5] Some macrocycle complexes have been reported to display antifungal, antibacterial and anti-inflammatory activities.[6,7]

A series of macrocycle complexes of Cd(II), Zn(II), Cu(II), Ni(II) and Co(II) obtained from the condensation reaction of 2,6-diaminopyridine and isatin has been investigated.[8] These complexes displayed significant antibacterial activity against some selected bacterial strains.

Abdallah and co-workers synthesized tetradentate macrocycle ligand and its complexes of N_2O_2 donor atoms with Fe(III) and Cr(III) ions.[9] Their studies cover the thermal and antimicrobial behaviour of the complexes. Thermal analysis indicated that all complexes have low stability due to the hydration water. All compounds demonstrated an outstanding biological activity against some bacteria (*S. aureus* and *E. coli*) and fungi (*C. albicans* and *A. flavus*).

Some other macrocycle complexes of Co(II), Ni(II), Cu(II) and Zn(II) have been synthesized from condensation of glyoxal and L-leucine in ethanol.[10] The fluorescence and absorption spectroscopic studies indicated that all the complexes display a significant binding to calf thymus DNA.

Mohamed and co-workers prepared tridentate macrocycle and its Mn(II), Fe(III), Co(II), Ni(II), Cu(II) and Zn(II) complexes from triazine ligand with NNO donation sites towards metal ions.[11] The coordination sites of triazine ligand namely the two nitrogen atoms and oxygen atom are useful as they will form a cavity to bind the metal ions. Therefore they can be used as analytical reagents for determination of metal ions. The triazine ligand and all its complexes are found to have biological activity against the desert locust *Schistocerca gregaria* (Orthoptera, Acrididae). The thermal analysis showed neither water molecules of coordination nor hydration in the structure of these complexes.

The macrocycle complexes of Co(II), Ni(II), Cu(II) and Zn(II) prepared from the condensation of carbohydrazide and isatin has been investigated .[12] These complexes displayed excellent antibacterial behaviour against some pathogenic bacteria.

The synthesis and characterization of a new series of macrocycle complexes have also been reported through template condensation reaction of 1,8-diaminonaphthalene and dimedone in presence of divalent transition metal ions.[13] The *in vitro* antimicrobial tests of these complexes showed some notable antibacterial activity against the Gram-positive (*S. aureus* and *B. subtilis*) bacteria and yeast (*C. albicans*).

Pyridinedicarboxylate can be an important starting material for producing macrocycle ligand owing to its ability to form strong covalent bonds. The non--adjacent positions of the two carboxylic acid groups on the aromatic ring in pyridinedicarboxylate leads to either an oligomer or a polymeric chain structure. The nitrogen atom of the pyridine may also act as a potential site for coordination.[14] An excellent feature of these macrocycles is their multifarious biological activity.[15] They are present in many natural products, as an oxidative degradation product of vitamins, coenzymes and alkaloids, and are also an important component of fulvic acids. Pyridinedicarboxylate complexes of iron are well known electron carriers in various biological models and are diagnosed as specific molecular tools for DNA splitting.[16]

In continuation of our previous work,[17,18] and due to versatile biological and chemical properties of macrocycle complexes derived from 2,6-pyridinedicarboxylate, we are reporting the synthesis and characterization of a new macrocycle derived from the reaction of this dicarboxylate with 1,2-dibromoethane and ethylenediamine, together with its complexes of three metal(II) ions. These complexes were also screened for their antimicrobial activity against some bacteria and fungi.

The thermal analyses were carried out in an inert atmosphere of nitrogen gas. Thermo-gravimetric studies of macrocycle and its complexes were performed to obtain information about their thermal stability, and to decide about the presence of the water molecules and the decomposition steps of their structures. Moreover, the thermal analysis technique that provides extremely sensitive measurements of heat changes can be applied widely in pharmaceutical development.

The theoretical studies of molecular and electronic structures of the macrocycle and its metal complexes have also been carried out. Molecular orbital calculations were conducted by density functional theory (DFT) at B3LYP level with standard 6-31G(d,p) and LANL2DZ basis sets. The calculations were performed to obtain the optimized molecular geometry, charge density distribution, highest occupied molecular orbital (HOMO) and lowest unoccupied molecular orbital (LUMO) of the macrocyclic ligand and its complexes.

EXPERIMENTAL

Phosphorus pentoxide (Aldrich), DMSO (Aldrich), $NiCl_2\cdot6H_2O$, $CuCl_2\cdot2H_2O$ and $ZnCl_2\cdot2H_2O$ (Merck), methanol (Merck), 2,6-pyridinedicarboxylic acid (Aldrich), 1,2-dibromoethane (Merck), ethylene diamine (Merck) and potassium were used as received.

Physical and spectral measurements

The ^1H- and ^{13}C-NMR spectra were recorded in DMSO on a Brucker AV300 NMR spectrometer with the TMS as an internal reference. The elemental analyses were performed on a Heraeus Carlo Erba 1108 elemental analyzer. The electronic spectra (10^{-3} mol dm^{-3} in DMSO) were obtained with a Shimadzu UV-160 spectrophotometer. The IR spectra (4000–400 cm^{-1}) were recorded on a Perkin-Elmer model 377 spectrometer using KBr pellets. Magnetic susceptibility measurements were done with a 155 Allied Research vibrating sample magnetometer at room temperature. Molar conductivities (10^{-3} mol dm^{-3} in DMSO) were measured with CMD 8500 laboratory conductometer. Melting points were measured using an electrothermal Buchi 512 melting point apparatus. The metals were determined by spectrophotometric method using an AA-670 Shimadzu atomic absorption flame emission spectrophotometer. Thermal analyses (TG and DTG) were carried out on a SDT Q 600/V8.3 build 101 thermal analyzer with a heating rate of 10 °C/min using N_2 atmosphere (20 mL/min). The samples were heated up at atmospheric pressure in a temperature range of 25–800 °C.

Physical and spectral data of the compound are given in Supplementary material to this paper.

*Synthesis of macrocycle **1***

Methanolic solution of potassium (0.276 g, 12 mmol; 5 mL) was added to the solution of 2,6-pyridinedicarboxylic acid (1.060 g, 6 mmol; 30 mL). The solution was refluxed for 2 h until a pale yellow solution was obtained. Then a solution of 1,2-dibromoethane (2.256 g, 12 mmol; 10 mL methanol) was added slowly to this solution. A white precipitate forms immediately which dissolves and gives a clear solution on further refluxing for 4 h. Ethylenediamine (0.360 g, 6 mmol) was added, and was further refluxed for 6 h to ensure the completion of the reaction. On cooling the solution, a white precipitate was obtained. It was filtered, washed with methanol and dried over P_4O_{10} *in vacuo* to give (1.473 g, 88 %) of macrocycle **1**. Elemental analysis, found % (calculated %): C 56.07 (55.91), H 5.88 (6.09), N 15.27 (15.05). The molecular formula compatible with this analysis is ($C_{13}H_{17}N_3O_4$). The compound was decomposed at 234 °C.

*Synthesis of the Ni(II) complex **2***

The macrocycle (L) **1** (530 mg, 2 mmol) was dissolved in 15 mL of hot methanol. A solution of $NiCl_2\cdot 6H_2O$ (475 mg, 2 mmol) in the same solvent (20 ml) was then gradually added to the solution of **1** with stirring to obtain an immediate precipitation accompanied by a visible color change. The mixture was then refluxed for a further 8 h on a hot plate to ensure the completion of the reaction. The green precipitate was then filtered off, washed with methanol and dried over P_4O_{10} *in vacuo* to give (695 mg, 85 %) of complex **2**. Elemental analysis, found % (calculated %): C 38.33 (38.17), H 4.04 (4.16), N 10.12 (10.27), Ni 14.14 (14.36). Its molecular formula was suggested to be ($C_{13}H_{17}Cl_2NiN_3O_4$), and was decomposed at 261 °C.

*Synthesis of the Cu(II) **3** and Zn(II) **4** complexes*

The same procedure as explained above, was used for the synthesis of the Cu(II) **3** and Zn(II) **4** complexes.

The Cu(II) complex **3** was obtained as a blue precipitate with a yield of 86 %. Elemental analysis, found % (calculated %): C 37.93 (37.73), H 4.02 (4.11), N 10.02 (10.16), Cu 15.19 (15.37). Its molecular formula was suggested to be $C_{13}H_{17}Cl_2CuN_3O_4$, and was decomposed at 251 °C.

The Zn(II) complex **4** was obtained as a yellow pale precipitate with a yield of 80 %. Elemental analysis, found % (calculated %): C 37.93 (37.59), H 4.02 (4.09), N 10.02 (10.12), Zn 15.19 (15.66). Its molecular formula was suggested to be $C_{13}H_{17}Cl_2ZnN_3O_4$, and was decomposed at 297 °C.

Biological activity monitoring

The antifungal and antibacterial activities of **1** and its complexes were examined *in vitro* against two fungi (*S. cerevisiae* and *C. albicans*) and two Gram positive (*B. subtilis* and *S. aureus*) and two Gram-negative (*E. coli* and *P. aeruginosa*) bacteria by the disc diffusion method. Nystatin and ofloxacin were used as standards for comparison of the antifungal and antibacterial activities, respectively.

The test organisms were grown on nutrient agar for antibacterial and potato dextrose agar medium for antifungal in Petri dishes. The compounds were prepared in DMSO and soaked in a filter paper disc of 5 mm diameter and 1.0 mm thickness. The discs were placed on the previously seeded plates and incubated at 37 °C and the diameter of inhibition zone around each disc was measured after 72 h for antifungal and 24 h for antibacterial activities. All experiments were performed as triplicate.

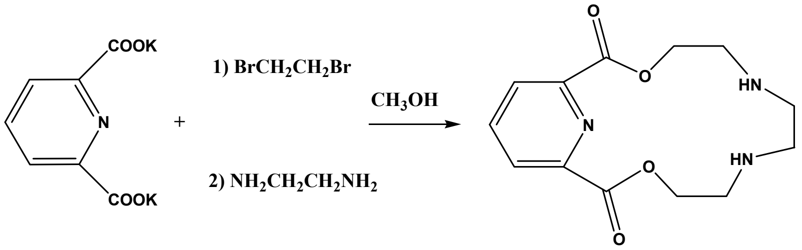
Computational details

Full-unconstrained geometry optimizations of **1** and its complexes were carried out at gradient corrected DFT using Becke's three parameter hybrid method and the Lee–Yang–Parr correlation functional (B3LYP) combined with 6-31G(d,p) and LANL2DZ basis sets using GAUSSIAN 03W in gas phase.[19–21] The studied complexes are characterized as minima (no imaginary frequency) in their potential energy surface.

Molecular frontier orbitals: HOMO and LUMO, and the optimized structures were projected with Gaussian view.[22] Using HOMO and LUMO orbital energies, the ionization energy and electron affinity can be expressed as: $IE = -E_{\mathrm{HOMO}}$, $EA = -E_{\mathrm{LUMO}}$, respectively. The hardness, η and chemical potential, μ were described by the following relations: $\eta = (IE-EA)/2$ and $\mu = -(IE+EA)/2$, respectively.[23] Electronegativity can be expressed as: $\chi = -\mu$.

RESULTE AND DISCUSSION

The macrocycle **1**, namely, 3,12-dioxa-6,9,18-triazabicyclo[12.3.1]octadeca-1(18),14,16-triene-2,13-dione, was synthesized by the method described in our previous works.[17,18] First, the dipotassium salt of 2,6-pyridinedicarboxylic acid was produced from its reaction with potassium methoxide. The interaction of this dipotassium salt with 1,2-dibromoethane in methanolic solution, subsequently produces bis(2-bromoethyl)-2,6-pyridinedicarboxylate intermediate which reacts further with ethylenediamine to give the macrocycle **1** (Scheme 1).

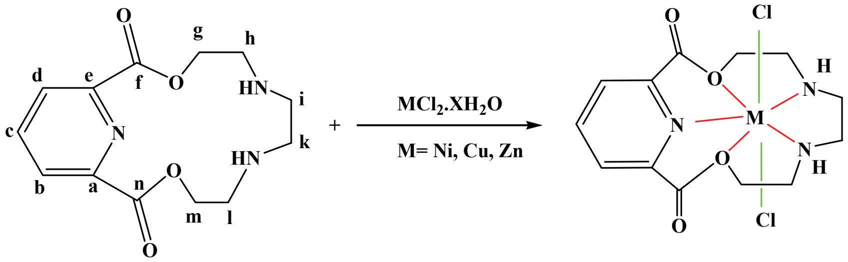


Scheme 1. Reaction for preparation of the macrocycle **1**.

Secondly, the complexes were synthesized from the reaction of **1** (L) with $MCl_2.xH_2O$ in MeOH, giving the compounds that have the general formula $[M(L)Cl_2]$ (where M = Ni(II) **2**, Cu(II) **3** and Zn(II) **4**, respectively, Scheme 2).

Unfortunately, our attempts to obtain single crystals of all the complexes have not been successful. Therefore **1** and its complexes were characterized on the basis of magnetic susceptibility measurement, electronic spectra data, ^{1}H and ^{13}C-NMR, and IR spectra, elemental and thermal analyses.

The molar conductance of complexes **2**–**4** were obtained to be 27, 35 and 23 Ω^{-1} cm^2 mol^{-1}, respectively. This revealed that all of the three complexes are non-electrolyte.[24] So based on elemental analysis and molar conductance data, all complexes have [M(L)Cl_2] formula in which two chloride ions are placed on coordination layer.



Scheme 2. Reaction for preparation of the complexes [M(L)Cl_2], and its formula structure.

A single sharp band was observed at 3245 cm^{-1} in IR spectrum of **1** that can be assigned to stretching of ν(N–H) secondary amine vibration,[25] although its position was found to be lower by 20–30 cm^{-1} in its complexes. This behavior suggests that nitrogen atom of the secondary amines coordinated to the metal(II) ions.[26] A medium band was observed at 1598 cm^{-1} which was attributed to stretching of ν(C=N) of the pyridine ring. This band was shifted to lower frequencies at 1582, 1580 and 1583 cm^{-1} in complexes **2**–**4**, respectively. This observation means that nitrogen atom of the pyridine ring takes part in coordination.[27,28] The band at 1275 cm^{-1} due to ν(C–O) of the ester group of **1** that was shifted to lower frequencies at 1258, 1260 and 1262 cm^{-1} in complexes **2**–**4**, respectively. This suggests that the oxygen atom of the ester groups are also coordinated to metal(II) ions.[29] These facts are further supported by the appearance of new bands at around 475 and 459 cm^{-1} in all complexes, which were attributed to the ν(M–O) and ν(M–N) stretching vibrations, respectively.[28]

The two strong bands at 1720 and 1685 cm^{-1} due to asymmetric and symmetric frequencies of ν(C=O) in **1**, were observed to shift to 1715–1725 and 1678–1685 cm^{-1} in the spectra of the complexes **2**–**4**, respectively.[30] Since no considerable change were observed for ν(C=O) of **1** and its complexes, it was concluded that the oxygen atoms of the carbonyl in the carboxylic group were not involved in the coordination to the metal ions.

The ^{1}H-NMR spectrum of **1** displayed a triplet (1H, H^c) and a doublet (2H, H^b, H^d) of relative intensities 1:2 centered at 8.18 and 7.86 ppm, which is in good agreement with the protons of the pyridine ring.[31]

Two sets of peaks were observed as triplets at 3.82 ppm (4H, H^h, H^l) and 2.64 ppm (4H, H^g, H^m) which correspond to CH_2 protons adjacent to the nitrogen atoms (–CH_2N) and the oxygen atoms (–CH_2O) in the macrocycle ring, respectively. The singlet peak at 3.41 ppm (4H, H^i, H^k) is due to the –NCH_2–CH_2N– moiety of **1**.[32] These peaks were all changed slightly in **4** which indicates that the oxygen and nitrogen atoms attached to CH_2 participate in coordination with the metal ions. A broad signal obtained at 4.82 ppm (2H) is due to the N–H proton of secondary amine group of **1** which shifts in coordination with Zn(II) ion.[33]

These are confirmed by the ^{13}C-NMR spectra, which show seven signals for the 13 carbon atoms of **1** skeleton. The ^{13}C-NMR spectrum of **1** displayed two resonances due to two different carbons of the methylene groups at 75.66 ppm (C^g, C^m) adjacent to the oxygen (O–CH_2) and at 63.83 ppm (C^h, C^l) adjacent to the nitrogen atom (N–CH_2).[34] These resonances were shifted up-field to 71.24 and 58.76 ppm in **4**, respectively, which indicates coordination of oxygen and nitrogen donor atoms to the M(II) ions. The resonances of the two equivalent methylenes of the ethylenediamine moiety of **1** appear at 48.72 ppm (C^i, C^k).[35] This peak is shifted to 45.25 ppm in **4**. The shielding effects on this signal in **4** suggest coordination of nitrogen donor atoms of the macrocycle ring to M(II) ions.

The peaks obtained at 124.68 ppm (C^c), 136.26 ppm (C^b, C^d) and 155.12 ppm (C^a, C^e) of **1** were attributed to three types of carbons of pyridine ring,[36,37] and also the peak at 176.38 ppm (C^f, C^n) is due to carbon of the carbonyl of the ester groups.[38] Carbon signal adjacent to the nitrogen atom of pyridine ring (C^a, C^e) changed slightly in its position in the spectrum of **4**. Therefore, this may be attributed to participation of the nitrogen atom of the pyridine ring in the coordination.

The electronic spectra of **1** and its complexes show an absorption band in the region 255–265 nm that can be attributed to $\pi\rightarrow\pi^*$ intra-ligand transfer of the pyridine ring incorporated in the skeleton of **1**.[39,40] In addition to the above band, two other bands were also observed for complexes **2** and **3**. These two bands were at 778 nm (12853 cm^{-1}) and 470 nm (21276 cm^{-1}) for **2** that can be attributed to ν_1: $^1A'_1\rightarrow{}^1E'_2$ and ν_2: $^1A'_1\rightarrow{}^1E''_1$ transitions in a pentagonal bipyramidal geometry around Ni(II) ion, respectively.[41] Since **2** is diamagnetic, so ground state configuration is $(e''_1)^4(e'_2)^4$ and partial term of the electronic ground state is $^1A'_1$. The two bands at 655 nm (15267 cm^{-1}) and 522 nm (19157 cm^{-1}) for **3** were assigned to the $^2A'_1\rightarrow{}^2E'_2$ and $^2A'_1\rightarrow{}^2E''_1$ transitions in a pentagonal bipyramidal geometry around Cu(II) ion, respectively.[41]

The complex **4** is diamagnetic. As it is expected due to the d^{10} electronic configuration of Zn(II) ion, electronic spectra of **4** did not show any d–d transition. By analogy to those described for the complexes **2** and **3** containing N_3O_2 donor atoms in **1** and two chloride ions, one can suggest pentagonal bipyramidal geometry for **4**.

Thermal analysis

Thermal gravimetric analysis offers information about the thermal stability of the complex as well as whether the water molecules are in the inner or outer coordination sphere of the central metal ion.[42] The TG and DTG data for macrocycle **1** and complexes **2**–**4** which were recorded under a nitrogen atmosphere are given in Table I.

TABLE I. The thermogravimetric data (TG and DTG) of macrocycle **1** and its complexes

Compound	TG range, °C	$\mathrm{DTG}_{\mathrm{max}}$, °C	Mass loss (Calcd.), %	Assignments
$(C_{13}H_{17}N_3O_4)$	198–280	234	41.5 (40.8)	– $C_6H_{14}N_2$
(**1**)	281–335	308	58.5 (59.1)	– $C_7H_3O_4$
$[Ni(C_{13}H_{17}N_3O_4)Cl_2]$	262–340	282	18.5 (17.8)	– 2 HCl
(**2**)	341–534	415	63.5 (63.2)	– macrocycle moiety, $C_{13}H_{15}N_3O_3$
			18.0 (18.3)	residue: NiO
$[Cu(C_{13}H_{17}N_3O_4)Cl_2]$	268–325	292	19.0 (17.6)	– 2 HCl
(**3**)	326–404	358	63.5 (63.1)	– macrocycle moiety, $C_{13}H_{15}N_3O_3$
			17.5 (19.3)	residue: CuO
$[Zn(C_{13}H_{17}N_3O_4)Cl_2]$	285–355	310	18.5 (17.6)	– 2 HCl
(**4**)	356–495	472	63.0 (62.9)	– macrocycle moiety, $C_{13}H_{15}N_3O_3$
			18.5 (19.5)	residue: ZnO

The macrocycle **1** and its complexes decomposed in two stages. The first step decomposition of **1** occurred at the temperature range 198–280 °C which is associated with a DTG peak at 234 °C. This corresponds to the loss of organic moiety ($C_6H_{14}N_2$) with a mass loss of 41.5 % (calcd. 40.8 %). The second step of the decomposition happened in the range of 281–335 °C relating to a DTG peak at 308 °C. This correlates with the loss of pyridine-2,6-dicarboxylate moiety ($C_7H_3NO_4$) with a mass loss of 58.5 % (calcd. 59.1 %).

It can be noticed that TG curve of complexes displays no mass loss up to 262 °C, indicating the absence of water molecules in the coordination sphere,[42] and also confirms the stability of the complexes up to 262 °C.

The thermogram of **3** represents two decomposition steps. The first step of the decomposition at the temperature range 268–325 °C is associated with a DTG peak at 292 °C corresponding to the loss of two chloride ions as HCl with a mass loss of 19.0 % (calcd. 17.6 %). The second decomposition step occurred in the range of 326–404 °C and showed a DTG peak at 358 °C which corresponds to the loss of **1** moiety with a mass loss of 63.5 % (calcd. 63.1 %). At the end of decomposition process, the resulting residue is CuO with a mass of 17.5 % (calcd. 19.3 %).

The thermograms of complexes **2** and **4**, which are similar to **3**, display two decomposition steps. Complexes **2** and **4** were stable up to 262 and 285 °C, respectively. The first step of the decomposition in the range 262–340 °C for **2** and 285–355 °C for **4** is associated with DTG peaks at 282, and 310 °C. This shows the loss of two HCl with a mass loss of 18.5 and 18.5 % (calcd. 17.8, and 17.6 %), respectively.

The second step of the decomposition occurred in the range of 341–534 °C for **2** and 356–495 °C for **4** relating to DTG peaks at 415 and 472 °C. This can be attributed to the loss of **1** moiety with a mass loss of 63.5 and 63.0 % (calcd. 63.2 and 62.9 %), respectively. After these decomposition steps, what is left is NiO and ZnO with a mass of 18.0 and 18.5 % (calcd. 18.3 and 19.5 %), respectively.

The thermal properties (TG and DTG curves) of complexes **2**–**4** exhibited the absence of hydrated or coordinated water molecules. Therefore the results of thermal analyses of complexes showed good agreement with the molecular formula $[M(L)Cl_2]$ as suggested from the elemental analyses.

The macrocycle **1** and its complexes have been screened for both antibacterial and antifungal activities. The results of the microbial screening of **1** and its complexes are given in Table II.

TABLE II. Antimicrobial activity of macrocycle **1** and its complexes; diameter of growth of inhibition zone, mm

Compound	Microbe					
	S. aureus	*B. subtilis*	*E. coli*	*P. aeruginosa*	*S. cerevisiae*	*C. albicans*
Macrocycle **(1)**	4	5	4	4	–	–
$[Ni(L)Cl_2]$ **(2)**	14	13	12	16	–	–
$[Cu(L)Cl_2]$ **(3)**	30	27	31	30	25	18
$[Zn(L)Cl_2]$ **(4)**	–	–	18	15	8	14
Ofloxacin	36	34	38	36	–	–
Nystatin	–	–	–	–	19	24

The antimicrobial monitoring data displayed that macrocycle **1** does not exhibit any activity. The complex **2** represented antibacterial activities against Gram positive bacteria (*B. subtilis* and *S. aureus*) and Gram negative bacteria (*E. coli* and *P. aeruginosa*), while complex **4** demonstrated antibacterial activity towards Gram negative bacteria (*E. coli* and *P. aeruginosa*), and antifungal activity against fungi (*S. cerevisiae* and C. *albicans*). The complex **3** also exhibits good activities against Gram-positive and Gram-negative bacteria and fungi, albeit it has lower antimicrobial activity compared to standard antibiotic ofloxacin and antifungal drug nystatin.

The results from this investigation have also demonstrated that coordination of metals to macrocycle serves to amend the antimicrobial activity of the ligand. The increased activity of the metal complexes can be described based on chelating theory. The other factors such as conductivity, solubility and bond distance between the metal and ligand also increase the activity.[43]

Molecular modeling

Molecular orbital geometry optimization permits a quantitative discussion about not only the geometry, but also the ground electronic properties of the ligands and their complexes. Electronic and geometric structures of the investigated macrocycle and its complexes were computed by the optimization of their bond angles, dihedral angles and bond lengths. The optimized molecular structures with minimum energies and its atom numbering obtained from the quantum chemical calculations for **1** and its complex **3** are shown in Figs. 1 and 2, respectively. The selected bond lengths and bond angles of **1** and its complexes are listed in Table S-I of the Supplementary material.

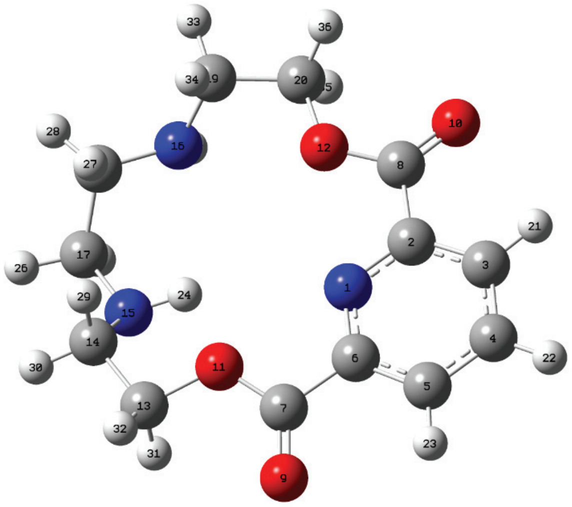


Fig. 1. The optimized geometry of the macrocycle **1**.

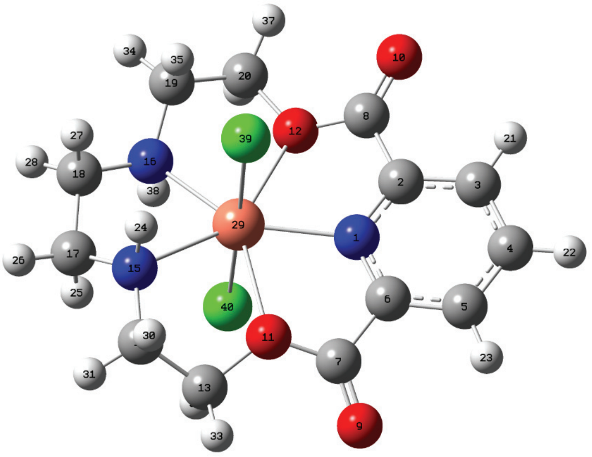


Fig. 2. The optimized geometry of complex **3**.

As can be seen, based on the coordination number seven, and the bond angles close to 72° in equatorial plane, all complexes have distorted pentagonal bipyramidal geometry. The two axial positions are occupied by chloride ions, while the pyridine nitrogen atom, the two nitrogen atoms of amino groups and the two oxygen atoms of ester moieties of 1, occupy the equatorial positions.

The N1–Cu–O11, N1–Cu–O12, N15–Cu–O11, N16–Cu–O12 and N15–Cu––N16 bond angles in **3** have values of 71.48, 71.48, 71.27, 72.40 and 73.30°, respectively. The bond angle Cl39–Cu–Cl40 is found to be 177.26°. These results indicated that **3** has distorted pentagonal bipyramidal geometry.

The bond lengths of the adjacent atoms attached to the central atom are slightly increased. These behaviors are caused by macrocycle **1** atoms participating in the coordination process of the metal ions. For example the N1–C2, O12–C8, N16–C19, N15–C17 and O11–C13 bonds in **3** are slightly increased to be 1.357, 1.384, 1.482, 1.486 and 1.462 Å, respectively. The other bond distances in **1** are either affected slightly or not affected at all by the coordination to the metal ion. The bond distances of the coordinating atoms with the central metal atom in **3** are found Cu–N1 = 2.160, Cu–O1 = 2.424, Cu–O12 = 2.428, Cu–N15 = 2.340, Cu–N16 = 2.340 Å in equatorial, and Cu–Cl39 = 2.512, Cu–Cl40 = = 2.514 Å in axial positions.

The two Cu–N_{amine} bond distances (Cu–N15 = 2.340 and Cu–N16 = 2.340 Å) are longer than the Cu–N_{py} distance (Cu–N1 = 2.160 Å). It seems pyridine nitrogen atom is a stronger donor than nitrogen of amine group. These values are in good agreement with the observed X-ray data for Cu(II) complexes with N3O2 macrocycle including pyridine moiety and chloride ion.[44–46]

The calculations showed that **2** and **4** have similar geometry to that of **3**. The N1–M–O11, N1–M–O12, N15–M–O11, N16–M–O12 and N15–M–N16 bond angles in **2** and **4** have values 70.77–73.71, 70.13–76.08, 71.20–72.25, 72.21––78.25 and 71.70–74.87°, respectively. The bond angles Cl39–M–Cl40 are also found to be 178.90 and 176.38° for **2** and **4**, respectively. Therefore, these results indicate that the complexes **2** and **4** have distorted pentagonal bipyramidal geometry.

Energy of some bonding molecular orbital for macrocycle ligand **1** and its complexes are shown in Table S-II of the Supplementary material.

Binding energy is more stable in complexes compared to macrocycle ligand **1**. For example energy of N1–C2 bond in macrocycle **1** is found to be –0.848 a.u., and for its complexes **2**–**4** to be –0.880, –0.874 and –0.848 a.u., respectively. Also it can be seen that the energy of all bonds is more stable for complexes. So it demonstrates that complexes are more stable than macrocycle **1**.

The most important orbitals in a molecule are the frontier molecular orbitals (FMOs), called HOMO and LUMO. The determination of energies of the HOMO (π-donor) and LUMO (π-acceptor) are significant parameters in quantum chemical calculations. The HOMO is the orbital that primarily acts as an electron donor and the LUMO is the orbital that largely acts as the electron acceptor.

The calculated energies (eV) of important molecular orbitals containing HOMO and LUMO, electronegativity (χ), chemical potential (μ), global hardness (η) for **1** and its complexes are listed in Table S-III of the Supplementary material.

The HOMO and LUMO orbitals for macrocycle **1** and its complexes are also shown in Figs. S-1 and S-2 of the Supplementary material, respectively.

The E_{HOMO} and E_{LUMO} and their neighboring orbitals are all negative, which demonstrate that the prepared complexes are stable.[47,48] The HOMO–LUMO energy gap of **1** is small, which means that the charge transfer occurs easily. The lower HOMO energy values show that the ability of the molecules donating electrons is weaker. On the other hand, the higher HOMO energy implies that the molecule is a good electron donor. LUMO energy presents the ability of a molecule to receive an electron.[48,49] The orbital energy level analysis for complexes **2**–**4** display that E_{HOMO} values are –6.232, –6.125 and –5.558 eV, respectively, while E_{LUMO} values are –2.820, –3.225 and –2.80 eV, respectively. As a result, **4** is a better electron donor, while **3** is a better electron acceptor.

The HOMO of **1** is concentrated on two nitrogen atoms of amine groups, while LUMO is concentrated on pyridine ring atoms and carboxyl groups. Calculations showed that contribution of the central atomic orbitals in the formation of HOMO (18 % Cu) and LUMO (58 % Cu) for **3** is greater than HOMO (7 % Ni and 4 % Zn) and LUMO (2 % Ni and 1 % Zn) for complexes **2** and **4**. The contribution of the chloride ion in the formation of HOMO for **4** (94 % Zn) is greater than HOMO for complexes **2** (3 % Ni) and **3** (12 % Ni). This behavior can be attributed to the stronger interaction of the hard base chloride ion with harder acid Zn^{2+} than Ni^{2+} and Cu^{2+}.

AIM atomic charge calculation has a significant role in the application of quantum chemical calculations of molecular systems; this is due to the fact that the atomic charges affect some properties of molecular systems including dipole moment, and molecular polarizability.[50,51] The selected net charges at the atomic sites of **1** and its complexes are given in Table S-IV of the Supplementary material.

The charges on two of the hydrogen atoms (H24 and H38) are greater than other hydrogen atoms in the compounds. This is because they are connected to nitrogen atoms (N15 and N16) of amine groups.

All carbon atoms of **1** have negative charges, except the carbon atoms of carboxyl groups (C7 and C8) that have highly positive charges. These carbon atoms of the carboxyl group (C7 and C8) together with the carbon atoms attached to the pyridine nitrogen (C2 and C6) are positively charged in the complexes, but the other carbon atoms have still negative charges.

The negative charges of the oxygen atoms (O11 and O12) of the carboxyl groups and the nitrogen atoms (N15 and N16) of amine groups increased in coordination with the metal ion. The charges on O11, O12, N15 and N16 atoms for **1** are –0.816, –0.825, –0.718 and –0.712, respectively, while the charges for the atoms in **3** are –0.928, –0.937, –0.948 and –0.947, respectively.

The charge of the Ni^{2+} in the free state is 2.0. It is seen that the positive charge of the metal ion decreases to 1.027 in **2**, which indicates that the transfer of electrons from **1** to the metal ion has occurred, and the coordination bonds have formed. Our calculations show that a total of 0.580 is transferred to Cu(II) during the coordination process, and the net charge on the Cu(II) reduces to 1.420. Similar behaviour in charge transfer is noted in case of **4**. The charge on central metal ion reduces to 1.405 after coordination.

The charge of the chloride ion in the free state is –1.0. It is seen that the negative charge of the chloride ion decreases to –0.679 in **2**, which indicates that the transfer of electrons from chloride ion to the metal ion has occurred, and the coordination bonds have formed. Our calculations show that a charge equal to –0.350 from chloride ion is transferred to Cu(II) during the coordination process, and the net charge on chloride ion reduces to –0.650. Similar behavior of charge transfer is noted in the case of **4**. The charge on the chloride ion after coordination reduces to –0.606.

Thus it can be concluded from the distribution of electric charges on the atoms of the complexes that much electron transfer occurs from the macrocycle to the metal ions, and therefore a strong interaction occurs between **1** with metal(II) ions.

CONCLUSIONS

The macrocycle **1,** namely, 3,12-dioxa-6,9,18-triazabicyclo[12.3.1]octadeca-1(18),14,16-triene-2,13-dione, was prepared via the reaction of dipotassium salt of 2,6-pyridinedicarboxylic acid with ethylenediamine and 1,2-dibromoethane. The complexes of **1** were prepared from its reaction with $MCl_2 \cdot xH_2O$. The complexes have the general formula $[M(L)Cl_2]$ (where M = Ni(II) **2**, Cu(II) **3** and Zn (II) **4,** respectively).

Analyses of the NMR and IR spectral data and molar conductivity measurements propose that **1** is bonded to metal(II) ions through a nitrogen atom of pyridine ring, the two nitrogen atoms of amine groups and the two oxygen atoms of ester moieties. Thermal gravimetric analyses displayed that these complexes can be stable up to 262 °C.

The complex **2** exhibited antibacterial activities against Gram-positive bacteria (*B. subtilis* and *S. aureus*) and Gram-negative bacteria (*E. coli* and *P. aeruginosa*), while **4** showed antibacterial activity against Gram-negative bacteria (*E. coli* and *P. aeruginosa*), and antifungal activity against fungi (*S. cerevisiae* and *C. albicans*). The complex **3** demonstrated good activities towards tested bacteria and fungi.

The optimized structures of **1** and its complexes were computed by theoretical DFT method, and all the complexes have distorted pentagonal bipyramidal geometry. The HOMO and LUMO energies were also determined. The charges on the atoms of compounds have also been calculated, and it has been found that much electron transfer occurs from **1** to the central atoms in the complexes. This behaviour confirms strong interaction of **1** with metal(II) ions.

SUPPLEMENTARY MATERIAL

Physical and spectral data of the compound are available at the pages of journal website: http://www.shd.org.rs/JSCS/, or from the corresponding author on request.

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ИЗВОД

КОМПЛЕКСИ ЦИНКА, БАКРА И НИКЛА СА МАКРОЦИКЛИЧНИМ ЛИГАНДОМ КОЈИ ЈЕ СИНТЕТИСАН ИЗ ПИРИДИНДИКАРБОКСИЛНЕ КИСЕЛИНЕ: СПЕКТРОСКОПСКА, ТЕРМАЛНА И ТЕОРИЈСКА ИСПИТИВАЊА

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Синтетисани су метал(II) комплекси са макроцикличним пентадентатним лигандом 3,12-диокса-6,9,18-триазабицикло[12.3.1]октадека-1(18),14,16-триен-2,13-дионом (L, **1**). Овај макроциклични лиганд је добијен у реакцији калијумове соли 2,6-пиридиндикарбоксилне киселине са етилендиамином и 1,2-диброметаном. У реакцији **1** (L) са $MCl_2\cdot xH_2O$ у метанолу настају комплекси опште формуле $[M(L)Cl_2]$ (M = Ni(II) **2**, Cu(II) **3** и Zn(II) **4**). На основу IR и NMR (^{1}H и ^{13}C) спектроскопских мерења нађено је да је у свим комплексима лиганд **1** координован за испитиване јоне метала преко атома азота из пиридина, два атома азота аминских група и два атома кисеоника из естарске групе. На основу термалне анализе нађено је да у структури испитиваних комплекса не постоје координовани или хидратисани молекули воде. Од свих синтетисаних комплекса, само је комплекс бакра(II) **3** показао добру антибактеријску и антифунгалну активност. Геометрија комплекса, Маликеново (Mulliken) наелектрисање атома и молекулске орбитале $[M(L)Cl_2]$ комплекса испитивани су применом DFT методе. На основу теоријских израчунавања за испитиване комплексе претпостављена је пентагонална бипирамидална геометрија са N_3O_2 хромофором у планарној пентагоналној основи бипирамиде са два хлоридо лиганда у њеном аксијалном положају.

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