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Syntheses, characterization and antimicrobial activity of the first complexes of Zn(II), Cd(II) and Co(II) with *N*-benzyloxycarbonylglycine X-ray crystal structure of the polymeric Cd(II) complex

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Abstract

For the first time, complexes of Zn(II), Cd(II) and Co(II) (**1**–**3**) with *N*-benzyloxycarbonylglycine have been synthesized and characterized. The complexes adopt tetrahedral, pentagonal-bipyramidal and octahedral geometry, respectively. The structure of the polymeric cadmium complex was resolved by single crystal X-ray analysis. The cadmium ion has a distorted pentagonal-bipyramidal coordination formed by two water molecules and two *N*-benzyloxycarbonylglycinato ligands (*N*-Boc) coordinated in different fashions, one as bidentate and the second connecting three cadmium atoms. In a rather complicated 2D supramolecular structure, the phenyl rings interact mutually exclusively by the CH$\cdots\pi$ interactions.

Investigation of the antimicrobial activity of the obtained complexes and *N*-benzyloxycarbonylglycine revealed that the ligand does not inhibit the growth of *Candida albicans*, whereas the newly synthesized complexes suppress the growth of this human fungal pathogen.

Keywords: Zinc(II), Cadmium(II) and Cobalt(II) complexes; *N*-Boc-glycine; X-ray; DFT; Microbiological assay

1. Introduction

Metal complexes with aromatic amino acids have proved to be simple model systems for studying weak, non-covalent π-interactions in which the aromatic rings participate [1–6]. It was shown that these interactions are very important for many biological molecules [7–10]. In our previous articles, the metal complexes containing aromatic amino acids were described [11–15]. As a continuation, in this study, new metal complexes having *N*-benzyloxycarbonyl protected amino acids as ligands were examined. The presence of a phenyl ring, as a part of a group attached to the primary amino group of an amino acid enabled investigations on non-covalent π-interactions to be continued. It is interesting to note that the *N*-benzyloxycarbonyl-protected amino acids and their derivatives were reported as anti-convulsant, anti-inflammatory and anti-neoplastic agents [16–21]. The investigated ligand, *N*-benzyloxycarbonylglycine (*N*-Boc-glyH), having optimal distribution properties for the penetration of the blood–brain barrier, exhibits better anti-convulsant activity than glycine itself [16–18,21].

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Hitherto, only one crystal structure of a complex compound with a coordinated *N*-Boc-gly anion is described in the literature. In the binuclear complex, each Cu(II) ion shows a slightly distorted square-pyramidal geometry, formed by the bidentate 2,2′-bipyridine and two monodentate *N*-Boc-gly ligands in the equatorial plane, with a propan-2-ol molecule in the apical position [22]. The authors pointed out that the crystal packing is mainly determined by the intermolecular stacking interactions between the bipy ligands and by the intermolecular hydrophobic interactions between the phenyl groups of the *N*-Boc-gly moieties.

In this article, the first syntheses of Zn(II), Cd(II) and Co(II) complexes with *N*-Boc-glycinato ligand are described. The very interesting polymeric structure of the Cd(II) complex was resolved by a single crystal X-ray diffraction analysis. In this complex, non-covalent interactions in which the aromatic rings participate are discussed. The modes of coordination of the ligand in the three complexes are compared. As *N*-Boc-glycine itself has favorable membrane penetration properties, it was supposed that in neutral complexes, the ligand could facilitate the migration of the metal ions through the biological membranes. Thus, the antibacterial and antifungal activities of the synthesized neutral complexes were investigated.

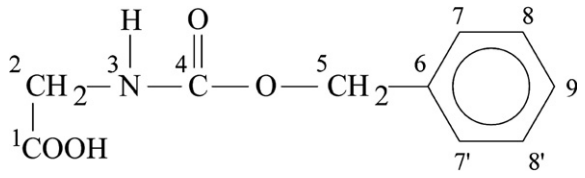
2. Experimental

2.1. General remarks

All the employed reagents and solvents were of analytical grade. *N*-Boc-glycine and the metal salts were obtained from Aldrich and were used without further purification. Elemental analyses for C, H, N were performed on a Vario III CHNOS Elemental analyzer, Elementar Analysensysteme GmbH. The solid state IR spectra (KBr pellets) were measured on a Perkin–Elmer FT-IR 1726X spectrometer.

The ^{1}H NMR (200 MHz) spectra were recoded using a Varian Gemini 2000 spectrometer at room temperature in the DMSO-d_6 solution. *N*-Boc-glycine (Scheme 1). δ: H1 12.5 (s), H3 7.60 (t), H (7,7′,8,8′,9) 7.36 (m), H5 5.07 (s), H2 3.73 (d).

The ^{13}C NMR (50.3 MHz) spectra were obtained in the DMSO-d_6 solution. The solvent peak at 39.7 ppm was used to calibrate the scale of the chemical shifts. *N*-Boc-glycine δ: C1 172.2, C4 157.1, C6 137.5, C8,8′ 128.9, C9 128.4, C7,7′ 128.3, C5 66.0, C2 42.6.



Scheme 1. *N*-benzyloxycarbonylglycine (*N*-Boc-glyH) with labeled atoms.

The magnetic momentum at room temperature (293 K) of the new Co(II) complex with *N*-Boc-gly was determined using a magnetic susceptibility balance (MSB-MK 1), the Sherwood Scientific Ltd. The susceptibility was corrected for the diamagnetic contribution per Pascal's rule.

The electronic absorption spectrum of the synthesized Co(II) complex in DMSO solution was recorded on a GBC Cintra 40 UV–Vis spectrophotometer.

Thermal behavior of Zn(II) complex was investigated from the room temperature to 1273 K using a SDT Q600 simultaneous DTA–TGA instrument (TA Instruments) with a heating rate of 5 K min^{-1} under dynamic (100 cm^3 min^{-1}) N_2 atmosphere.

2.2. Syntheses

2.2.1. Synthesis of [Zn(*N*-Boc-gly)$_2$] (**1**)

To a 50 mL flask containing 0.2 g (1 mmol) of *N*-benzyloxycarbonylglycine in 5 mL of ethanol–water mixture (1:1) was added 0.07 g (0.5 mmol) of $ZnCl_2$ dissolved in a minimal volume of water. The flask was placed on a water bath at 50 °C and its content stirred with a magnetic stirrer. The pH value of the system was then adjusted to 5–6 with a sodium hydroxide solution. The obtained suspension was heated for one hour under constant stirring. The reaction mixture was then filtered to remove the precipitate and the obtained filtrate was left to stand at room temperature. After a few days, colorless crystals were obtained from the filtrate. The crystals of the Zn(II)-complex were separated by filtration and left standing at room temperature. The colorless crystals, obtained in 45.7% (220 mg) yield, were soluble in DMSO, and insoluble in water, methanol, ethanol and chloroform. *Anal.* Calc. for $ZnC_{20}H_{20}N_2O_8$ or [Zn(*N*-Boc-gly)$_2$]: C, 49.86; H, 4.15; N, 5.82. Found: C, 49.48; H, 4.17; N, 5.81%. Selected IR bands (KBr pellets, cm^{-1}): 3314 (ν(N–H)), 1695 (ν(C=O)), 1571 (ν(COO$_{asym}$)), 1400 (ν(COO$_{sym}$)). ^{1}H NMR, δ: H3 7.28 (t), H(7,7′,8,8′,9) 7.34 (m), H5 5.02 (s), H2 3.55 (d). ^{13}C NMR, δ: C1 175.2, C4 156.7, C6 137.6, C8,8′ 128.7, C9 128.1, C7,7′ 128.0, C5 65.5, C2 43.7 (Scheme 1).

2.2.2. Synthesis of [Cd(*N*-Boc-gly)$_2$(H_2O)$_2$]$_n$ (**2**)

The colorless crystals of the cadmium(II) complex were obtained in the same manner as the Zn(II)-complex, using $CdCl_2 \cdot 2.5H_2O$ as the cadmium source. Yield: 79.7% (319 mg). The complex is soluble in DMSO and methanol, and insoluble in water, ethanol and chloroform. *Anal.* Calc. for $CdC_{20}H_{24}N_2O_{10}$ or [Cd(*N*-Boc-gly)$_2$(H_2O)$_2$]: C, 41.86; H, 4.29; N, 4.96. Found: C, 41.71; H, 4.17; N, 4.88%. Selected IR bands (KBr pellets, cm^{-1}) 3690–3125 (ν(H_2O) + ν(N–H)), 1704 (ν(C=O)), 1588 (ν(COO$_{asym}$)), 1403 (ν(COO$_{sym}$)).

^{1}H NMR, δ: H3 7.24 (t), H (7,7′,8,8′,9) 7.30 (m), H5 5.02 (s), H2 3.58 (d). ^{13}C NMR, δ: C1 176.1, C4 156.6, C6 137.5, C8,8′ 128.7, C9 128.0, C7,7′ 128.0, C5 65.5, C2 43.6.

2.2.3. Synthesis of $[Co(N\text{-Boc-gly})_2(H_2O)_4]\cdot 2H_2O$ (3)

To a 50 mL flask, containing 0.35 g (1.7 mmol) of *N*-benzyloxycarbonylglycine in 7 mL of ethanol–water mixture (1:1) was added 0.20 g (0.84 mmol) of $CoCl_2\cdot 6H_2O$ dissolved in a minimal volume of water. The flask was placed on a water bath at 50 °C and its content stirred with a magnetic stirrer. The pH value of the obtained solution was then adjusted to 6 by the addition of a sodium hydroxide solution. The obtained pink suspension was heated for 1 h under constant stirring. During the reaction, a small volume (5 mL) of ethanol was added to dissolve the formed pink precipitate. The reaction mixture was then filtered and after a few days, pink crystals were obtained from the filtrate. The crystals of Co(II)-complex was separated by filtering and left standing at room temperature. The pink crystals, obtained in 59.3% (288 mg) yield, were soluble in DMSO, and insoluble in water, methanol, ethanol and chloroform.

Anal. Calc. for $CoC_{20}H_{32}N_2O_{14}$ or $[Co(N\text{-Boc-gly})_2(H_2O)_4]\ 2H_2O$: C, 41.17; H, 5.49; N, 4.80. Found: C, 41.20; H, 5.99; N, 4.44%. Selected IR bands (KBr pellets, cm^{-1}) 3650–2920 ($\nu(H_2O)$), 3414 (ν(N–H)), 1700 (ν(C=O)), 1633 ($\nu(COO_{asym})$), 1397 ($\nu(COO_{sym})$).

2.3. X-ray measurements

The single crystal X-ray data for the $\{[Cd(N\text{-Boc-gly})_2(H_2O)_2]\}_n$ complex were collected on an Enraf-Nonius CAD-4 diffractometer [23] using Mo Kα radiation ($\lambda = 0.71073$ Å) and $\omega/2\theta$ scans in the 1.77–26.00° θ range. The cell constants and an orientation matrix for the data collection, obtained from 23 centered reflections in the θ range 11.16–13.71°, corresponded to a monoclinic cell. (The unit cell dimensions and other crystallographic data are given in Table 1). The data were corrected for Lorentz and polarization effects [24].

The crystal structure was solved by the direct methods [25] and the difference Fourier methods and refined on F^2 by the full-matrix least-square method [26]. All H atoms were included in the refinement at their geometrically calculated positions but the H atoms from the water molecules were taken from the ΔF map and refined isotropically with the O–H distance fixed at 0.85 Å. The anisotropic displacement parameters were refined for all non-hydrogen atoms. The software used for the preparation of the crystallographic materials for publication were PLATON [27,28], WINGX [29], PARST [30] and ORTEPIII [31].

2.4. Density functional method calculation

The studied compounds (**1** and **3**) were subjected to geometry optimization using the density functional theory (DFT) with the Becke three-parameter exchange functional (B3) [32] and the Lee–Yang–Parr (LYP) correlation functional [33]. The DFT method was used as it gives good results for all first row transition metal complexes [34–36]. These B3LYP calculations were performed with the GAUSSIAN03 program [37]. Various rotamers of compound **1** were computed, but they reveal a single most stable structure. The optimized geometry of complex **1** is given in Fig. 1.

Table 1
Crystallographic data for $\{[Cd(N\text{-Boc-gly})_2(H_2O)_2]\}_n$ complex

Empirical formula	$C_{20}H_{24}CdN_2O_{10}$
Formula weight	564.81
Crystal size (mm^3)	$0.42\times0.36\times0.24$
Temperature (K)	293(2)
Wavelength (Å)	0.71073
Crystal system	monoclinic
Space group	$P21/a$
Unit cell dimensions	
a (Å)	9.549(3)
b (Å)	9.998(2)
c (Å)	23.201(6)
α (°)	90
β (°)	96.01(2)
γ (°)	90
V ($Å^3$)	2202.8(10)
Z	4
D_{calc} ($Mg\ m^{-3}$)	1.703
Absorption coefficient (mm^{-1})	1.051
Theta range for data collection (°)	1.77–26.00
Index ranges	$0\leqslant h\leqslant 11, 0\leqslant k\leqslant 12, -27\leqslant l\leqslant 27$
Reflections collected	4580
Independent reflections [R_{int}]	4301 [0.0561]
Data/parameters	4301/298
Goodness-of-fit on F^2	0.910
Final R indices [$I>2\sigma(I)$]	$R_1 = 0.0678$, $wR_2 = 0.1609$

The computational study of the $[Co(N\text{-Boc-gly})_2(H_2O)_4]\cdot 2H_2O$ complex (**3**) was particularly challenging because of existence of the conformational and geometrical isomers of it. The geometries of all conformers of the complex were fully optimized using LANL2DZ basis set. The optimized geometries and energies of the geometrical isomers of the $[Co(N\text{-Boc-gly})_2(H_2O)_4]\cdot 2H_2O$ complex (**3**) were obtained, too.

As the starting point for the calculation, the conformation of the *N*-Boc-residue obtained by the single crystal

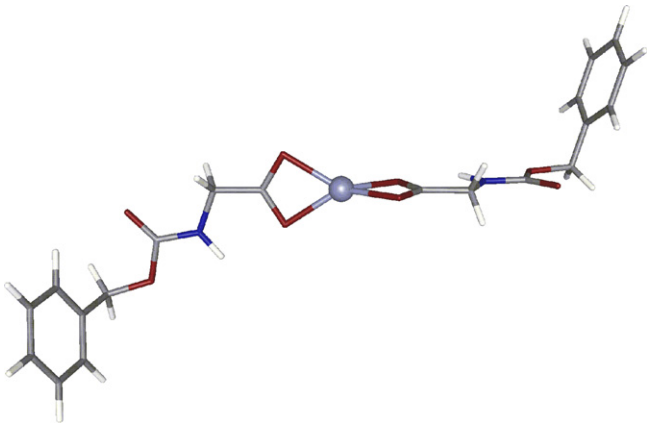


Fig. 1. Proposed tetrahedral geometry of $[Zn(N\text{-Boc-gly})_2]$ complex (structure optimized using B3LYP//LANL2DZ).

X-ray method [22,38] was used. The arrangement of the ligands in the cobalt(II) complex was initially estimated by analogy to the measured glycine [39] and/or *N*-acetyl-DL-phenylglycinato complexes [40].

2.5. Microbiological assay

N-benzyloxycarbonylglycine and its Zn(II), Cd(II) and Co(II) complexes were screened for their in vitro antifungal activity against *Candida albicans* (ATCC 24433) and *Aspergillus niger* and their antibacterial activity against: *Escherichia coli* (ATCC 25922, Gram negative), *Staphylococcus aureus* (ATCC 25923, Gram positive) and *Micrococcus lysodeicticus* (ATCC 4698, Gram positive); (''Collection of Microorganisms'', Department of Chemistry, Institute of Chemistry, Technology and Metallurgy, University of Belgrade). The screening on the antifungal and antibacterial activity was performed by determining the minimal inhibitory concentration (MIC) [41].

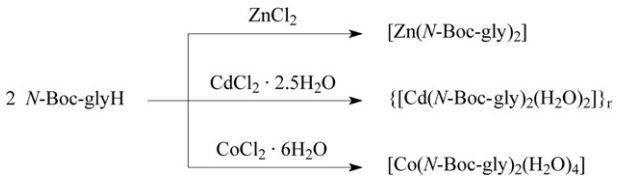
3. Results and discussion

3.1. Syntheses of the Zn(II), Cd(II) and Co(II) complexes (1–3)

The new complexes (**1**–**3**) were synthesized via a simple reaction between $ZnCl_2$, $CdCl_2 \cdot 2.5H_2O$, or $CoCl_2 \cdot 6H_2O$ and *N*-benzyloxycarbonylglycine in a 1:2 molar ratio in an ethanol–water mixture at pH 5–6 (Scheme 2).

3.2. IR spectroscopy of complexes 1–3

The IR spectra of complexes **1**–**3** are different, especially in the 3500–3000 cm^{-1} and 1600–1350 cm^{-1} region. In the 3500–3000 cm^{-1} region in the IR spectrum of complex **1**, a sharp band of ν(N–H) is observed, which indicates that the complex crystallizes without water molecules (in agreement with the elemental analysis and thermogravimetric analysis – the first decomposition step of complex **1** occurs in the temperature region from 178 to 264 °C with 48.3% mass loss). On the contrary, in the IR spectrum of complex **3**, broad bands in this region can be attributed to the $\nu(H_2O)$ vibration associated with both the coordinated and crystal water molecules (ν(N–H) at 3281 cm^{-1}) [42,43]. In the IR spectrum of complex **2**, one broad band is observed.



Scheme 2. Reaction of the simple metal salts with *N*-benzyloxycarbonylglycine.

On the basis of the differences in the frequencies (1600–1350 cm^{-1} region) of the asymmetric and symmetric skeletal vibration of the carboxylic group ($\Delta\nu$), it has been proposed that the mode of coordination of the carboxylic group in complexes **1**–**3** is different [44]. Namely, it was proposed that in the case of complex **3** ($\Delta\nu = 236\ cm^{-1}$), monodentate coordination of the carboxylic group occurs, while in the case of complex **1** ($\Delta\nu = 171\ cm^{-1}$), chelate bidentate coordination of the carboxylic group and a tetrahedral geometry around the Zn(II) ion was proposed (structure optimized using B3LYP//LANL2DZ, Fig. 1). In the case of complex **2** ($\Delta\nu = 185\ cm^{-1}$), the $\Delta\nu$ value is close to that of the *N*-Boc-gly anion ($\Delta\nu = 198\ cm^{-1}$), which could possibly indicate that the carboxylic group is in the bridging mode. However, in comparison with the corresponding bands in the IR spectra of complexes **1** and **3**, the bands assigned to $\nu(COO_{asym})$ and $\nu(COO_{sym})$ in the IR spectrum of complex **2** are broad. The broadening of these bands is explained by the solving of the crystal structure of complex **2**.

3.3. Description of the crystal structure of the polymeric $\{[Cd(N\text{-}Boc\text{-}gly)_2(H_2O)_2]\}_n$ complex (2)

The solid state structure of complex **2**, determined by the single crystal X-ray experiment, together with the atom labeling scheme is illustrated in Fig. 2.

Initially, when analysing the coordination around the Cd(II) ion, two different coordination behaviors of the *N*-Boc-glycinato ligands must be recognized, in Fig. 2 labeled as ligands A and B, respectively. Namely, ligand B coordinates to only one metal atom as a bidentate ligand, forming the O1b–Cd–O2b–C1b four-membered chelate ring (Fig. 2). Its M–O1b and M–O2b bond lengths differ by 0.45 Å, which is not rare for the coordinated COO groups [45]. However, ligand A coordinates three cadmium atoms, playing the role of a bridging ligand (Fig. 2). The O1a atom is directly bonded to two Cd-atoms with Cd–O1a and Cd–$O1a^i$ bond lengths of 2.286(6) and 2.422(6) Å, respectively. As a consequence of the different coordination behavior, the C–O bond lengths in the COO groups of two ligands are different (Table 2). Of the O1a, O2a, O1b and O2b atoms, the O2b forms the weakest M–O bond (2.75 Å) and, consequently, its C–O bond is the shortest one (1.22 Å). The other bond lengths in ligands A and B are more or less similar. The Cd(II)-ions with two *N*-Boc-gly ligands and two coordinated water molecules per one metal atom (Fig. 2a) form a rather complicated 2D supramolecular structure. The building unit in this 2D polymer structure is the binuclear structure presented in Fig. 2b. These binuclear units are further mutually interconnected using ligand A as a bridging ligand. In this way, 2D supramolecular layers are formed, the structure of which will be explained in the text below.

The cadmium ion has a distorted pentagonal-bipyramidal coordination (Fig. 2c), formed by two water molecules,

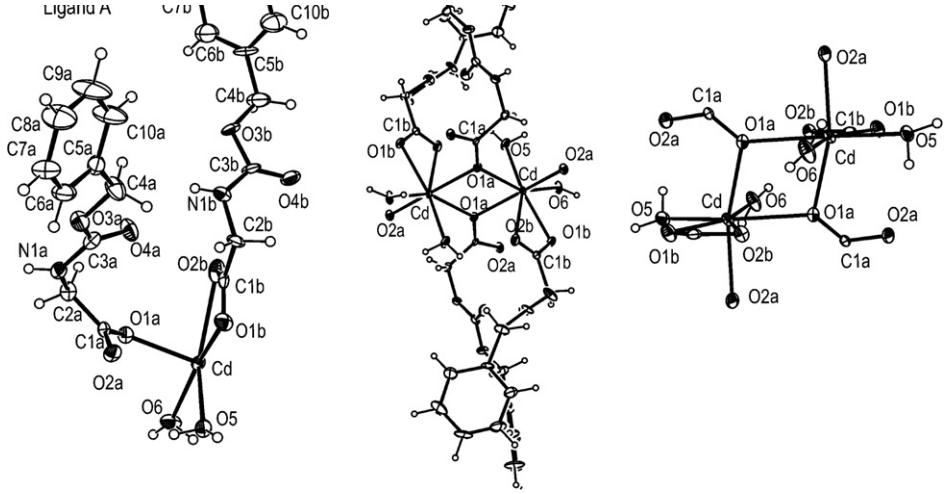


Fig. 2. (a) Asymmetric unit of the polymeric $\{[Cd(N\text{-Boc-gly})_2(H_2O)_2]\}_n$ complex showing atom-numbering scheme. (Displacement ellipsoids are drawn at 40% level.) (b) Binuclear building unit in the 2D supramolecular structure of the $\{[Cd(N\text{-Boc-gly})_2(H_2O)_2]\}_n$ complex; (c) Coordination geometry of the cadmium atom. (The $–CH_2–NH–C(=O)–O–CH_2–C_6H_5$ residuals bonded to the C1 atoms are omitted for clarity.)

Table 2
Selected bond lengths and angles (Å, °) for $\{[Cd(N\text{-Boc-gly})_2(H_2O)_2]\}_n$ complex (symmetry codes (i) $-x, -y, -z+1$; (ii) $-x+1/2, y+1/2, -z+1$)

Cd–O5	2.370(6)	O6–Cd–O1a	88.0(2)
Cd–O6	2.276(6)	O6–Cd–O2a^{ii}	101.7(3)
Cd–O1a	2.286(6)	O1a–Cd–O2a^{ii}	159.7(2)
Cd–O1a^{i}	2.422(6)	O6–Cd–O1b	156.8(2)
Cd–O2a^{ii}	2.292(7)	O1a–Cd–O1b	93.8(2)
Cd–O1b	2.300(6)	O2a^{ii}–Cd–O1b	84.3(2)
Cd–O2b	2.750(7)	O6–Cd–O5	75.2(2)
O1a–C1a	1.253(10)	O1a–Cd–O5	107.2(2)
O2a–C1a	1.251(10)	O2a^{ii}–Cd–O5	92.5(2)
O3a–C3a	1.347(12)	O1b–Cd–O5	82.2(2)
O3a–C4a	1.396(12)	O6–Cd–O1a^{i}	75.7(2)
O4a–C3a	1.227(13)	O1aCd–O1a^{i}	74.9(2)
N1a–C3a	1.326(13)	O2a^{ii}–Cd–O1a^{i}	90.2(2)
N1a–C2a	1.455(11)	O1b–Cd–O1a^{i}	127.1(2)
O1b–C1b	1.272(11)	O5–Cd–O1a^{i}	150.7(2)
O2b–C1b	1.218(11)		
O3b–C3b	1.345(10)		
O3b–C4b	1.459(13)		
O4b–C3b	1.210(12)		
N1b–C3b	1.317(12)		
N1b–C2b	1.445(11)		

one molecule of ligand B and even three molecules of ligand A. The equatorial coordination plain consists of the O1a, O1b, O2b, O5 and O6 oxygen atoms, which are almost coplanar (including the metal atom). The mean displacement of these atoms from the least-square plain defined by the same atoms is 0.058 Å. Contrary to this regularity of the planarity of equatorial coordination plane, the coordination angles within the plane and the Cd–O bonds lengths are mutually rather different (Table 2). Thus, the shortest Cd–O bond length is Cd–O6 of 2.276(6) Å, while the longest one is Cd–O2b of 2.750(7) Å. The O5–Cd–O6 and O6–Cd–O1a coordination angles are very similar (75.2(2)° and 75.7(2)°, respectively) and are the largest ones in the equatorial plane and are significantly larger than the O1b–Cd–O2b coordination angle of 50.6(2)°. The axially coordinated atoms are the O1a and O2a oxygen atoms, which form O1a–Cd–O2a of 159.7(2)°, that significantly deviates from 180°. Probably all the above quoted distortions could be explained by the formation of a 2D polymer structure, which influences the coordination geometry of the cadmium atom.

As mentioned above, ligand A plays a crucial role in the formation of the 2D supramolecular structure. Binuclear units are mutually connected by –C1a–O2a– groups, as shown in Fig. 3a and b. In this way each unit is bonded to another four units forming a 2D supramolecular layer in the crystal packing. In addition to the Cd–O1a–Cd–O1a four-membered rings, the layers are composed of 16-membered rings with four Cd–O1a–C1a–O2a repeating fragments, $(Cd–O1a–C1a–O2a)_4$ (see Fig. 3).

In the crystal packing, the 2D supramolecular layers are (mutually) parallel and stacked along the *z*-axis with an interlayer distance equal to the c unit cell dimension (23.20 Å). The space between the layers is occupied by the residual parts of the *N*-Boc-gly ligands $–CH_2–NH–C(=O)–O–CH_2–C_6H_5$. Although ligands A and B possess terminally bonded phenyl rings capable of rotating around the C4–C5 bonds, a $\pi\cdots\pi$ interaction does not exist between them. However, the phenyl rings mutually interact exclusively by the $CH\cdots\pi$ interactions (Table 3). The same type of non-covalent interactions stabilize the structure of a dimeric copper(II) complex previously described in the literature [22]. The middle part of the ligands ($–CH_2–NH–C(=O)–O–CH_2–$) participates in the formation of hydrogen bonds. The most important H bonds are: O5–H...O1b, O5–H···O2b, O6–H···O4b, O6–H···O2b, N1a–H···O4b and N1b–H···O4a.

Taking in account all the mentioned inter-ligand interactions and H-bonds, it can be concluded that the $\{[Cd(N\text{-Boc-gly})_2(H_2O)_2]\}_n$ complex forms a very compact 2D supramolecular structure with two non-polar surfaces com-

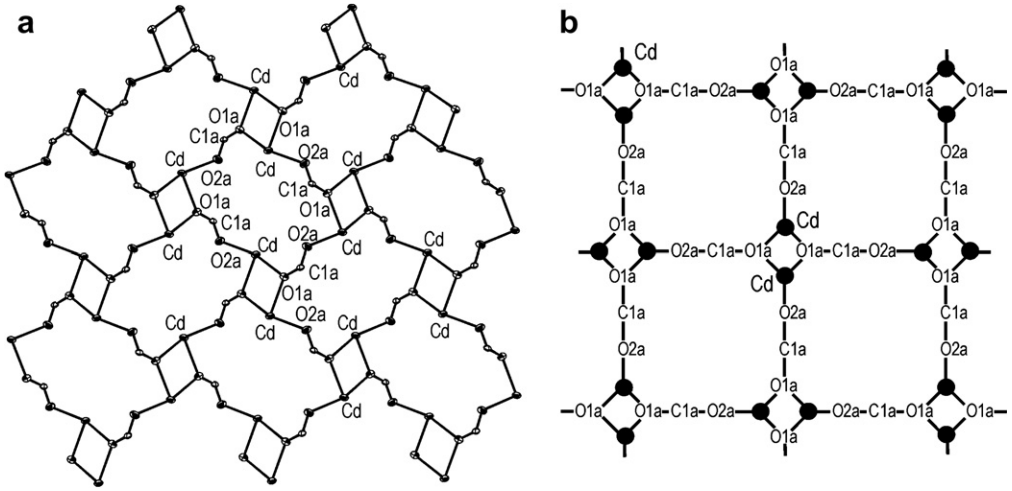


Fig. 3. (a) Crystal lattice fragment showing how the binuclear units are interconnected; (b) schematic representation of one 2D supramolecular layer with bonding mode of binuclear polymer units.

Table 3
Geometrical parameters for C–H···π interactions in crystal structure of $\{[Cd(N\text{-Boc-gly})_2(H_2O)_2]\}_n$ complex

C–H group	Phenyl ring	d (Å)	β (°)	C–H···Ω (°)
C4a–H	ring A	2.98	22.8	147.3
C10a–H	ring A	3.07	10.9	135.5
C10b–H	ring B	2.83	7.6	169.3

Ω is the midpoint of the phenyl ring; d is the shortest distance between H atom and mean plane of phenyl ring; β is angle between H···Ω vector and normal to plane of phenyl ring.

posed of phenyl rings interconnected by CH···π interactions [46]. Similarly, as in our previous work, where CH···π, NH···N and other intramolecular interactions played a decisive role in the conformation of a very flexible tetradentate ligand [47], the same type of weak interactions in the present crystal structure of $\{[Cd(N\text{-Boc-gly})_2(H_2O)_2]\}_n$ complex are of crucial importance, but in this case for the formation of the 2D supramolecular structure.

3.4. ^1H and ^{13}C NMR spectroscopy of complexes **1** and **2**

The complexes of Zn(II) and Cd(II) were also characterized by ^1H and ^{13}C NMR spectroscopy. The ^1H NMR spectra of the investigated complexes are in accordance with coordination through the carboxylic group (disappearance of the –COOH proton signal). In both the complexes, the N–H proton is more shielded than the N–H proton in non-coordinated *N*-Boc-glycinato ligand, which indicates that the nitrogen atom does not participate in the coordination. The supposition that coordination through the nitrogen atom does not occur (except in the complexes of Pb(II), Cd(II) and Cu(II) with *N*-sulfonilamino acids) is in accordance with the data concerning the coordination abilities of other *N*-substituted amino acids [48–50].

The ^{13}C NMR signal of the C1 atom shifted the most toward higher ppm values upon coordination. This is an additional indication that coordination through the carboxylic group occurs. The signal of the C4 atom was slightly shifted toward lower ppm value upon coordination, which indicates that the nitrogen atom does not participate in the coordination to the metal ion, as confirmed by the single crystal X-ray analysis of the cadmium complex.

3.5. Cobalt(II) complex (complex **3**)

On the basis of the results of the elemental analysis, it is supposed that an octahedral complex of composition $[Co(N\text{-Boc-gly})_2(H_2O)_4]\cdot 2H_2O$ was obtained. The presumption that the *N*-Boc-glycinato anions are monodentate coordinated in this complex is supported by the IR data (the $\Delta\nu$ value is significantly higher than that of the free ligand). The IR spectrum exhibited a broad band at 3560–3325 cm^{-1}, which is attributed to ν(OH) of the associated water molecules, while the band observed at 843 cm^{-1} is assigned to the coordinated water molecules [42].

Electronic absorption spectrum of the Co(II)-complex is in accordance with an octahedral $Co^{II}O_6$ chromophore; in the visible region one asymmetric maximum at $\lambda_{max} =$ 556 nm ($^4A_{2g} \leftarrow {}^4T_{1g}(F)$ and $^4T_{1g}(P) \leftarrow {}^4T_{1g}(F)$ transitions) [51].

The magnetic susceptibility value for the solid Co(II) complex is indicative of three unpaired electrons per Co(II) ion ($\mu_{eff} = 4.38$ BM), which is consistent with their octahedral environment [52].

The two monodentate *N*-Boc-glycinato ligands could be in the *cis* or *trans* position. To determine which geometry is more stable, DFT calculations were applied. The DFT calculations were performed for the two geometrical isomers and several conformations of the $–CH_2–NH–C(=O)–O–CH_2–C_6H_5$ residuals.

The conformational search was performed by variation of the Co–O torsion angle. Each starting geometry was allowed to fully optimize its geometry.

The DFT calculations revealed that two *trans*-isomers, with a C_2 axis and center of symmetry (Figs. 4 and 5, respectively), are the most stable. These two conformations differ by less than 0.1 kcal/mol. For the corresponding *cis*-isomer, two low-energy conformations were found, differing by 1.13 kcal/mol in energy. The most stable *trans*-form is approximately 4.6 kcal/mol more stable than the most stable *cis*-isomer.

Thus, the two monodentate *N*-Boc-glycinato ligands should be in the *trans*-position. This finding is in agreement with the X-ray crystal structure of the $[Co(glyH)_2(H_2O)_4]^{2+}$ ion [39], in which two monodentate glycine ligands are in the *trans*-position.

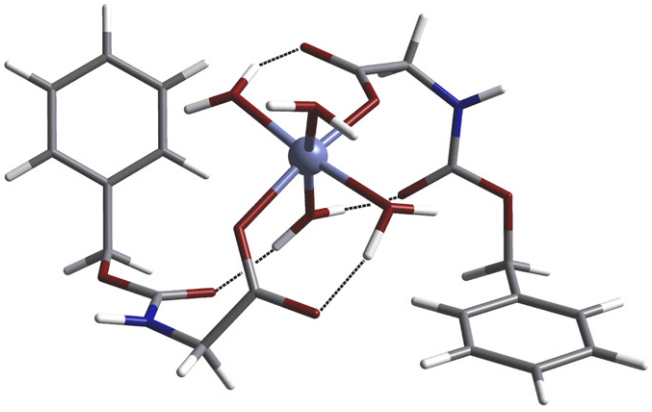


Fig. 4. *trans*-Isomer of $[Co(N\text{-Boc-gly})_2(H_2O)_4]$ complex with C_2 axis (intramolecular H-bonds are presented by dashed lines).

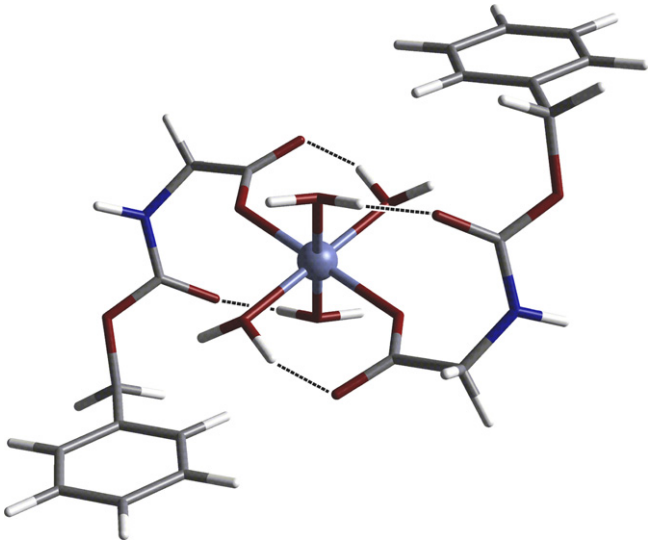


Fig. 5. *trans*-Isomer of $[Co(N\text{-Boc-gly})_2(H_2O)_4]$ complex with center of symmetry (intramolecular H-bonds are presented by dashed lines).

Table 4
Antimicrobial activities of *N*-benzyloxycarbonylglycine and complexes **1**–**3** evaluated by minimum inhibitory concentration (MIC; mg/mL)

Microorganism	*N*-Boc-glyH	**1**	**2**	**3**
Candida albicans	>10	0.625	0.625	0.568
Aspergillus niger	>10	>10	0.078	>10
Escherichia coli	>10	>10	0.039	>10
Staphylococcus aureus	>10	>10	>10	>10
Micrococcus lysodeicticus	>10	>10	0.0195	>10

3.6. Microbiological assay

The complexes **1**–**3** and *N*-benzyloxycarbonylglycine were screened for their in vitro antifungal and antibacterial activity against the representative strains. The minimal inhibitory concentrations are presented in Table 4, which shows that all the investigated complexes exhibited inhibitory activity against the human fungal pathogen *C. albicans*. *N*-Boc-glycine was inactive against this pathogen, as well as against all the other investigated strains. The Zn(II) and Co(II) complexes (**1** and **3**) were selective and acted only on *C. albicans*. However, the MIC values for the newly synthesized complexes **1** and **3** are higher in comparison to those obtained for example for the Ag(I)-complex with *N*-acetylglycine, but the latter is unselective and acts on all the investigated bacterial and fungal strains [53]. The cadmium complex (**2**) inhibited the growth of the fungi *C. albicans* and *A. niger*, as well as the bacteria *E. coli* and *M. lysodeicticus*, but was inactive against *S. aureus*.

As mentioned above, the ligand itself does not inhibit the growth of the investigated fungal and bacterial strains. The process of chelation of the *N*-benzyloxycarbonylglycinato anions to a metal ion reduces the polarity and increases the liphophilic nature of the central metal ion, which in turn favors its permeation through the lipid layer of the cell membrane of a microorganism [54]. This could be the reason for the higher inhibitory activities of the newly synthesized complexes in comparison with the ligand.

4. Conclusion

In this study, the first Zn(II), Cd(II) and Co(II) complexes with *N*-benzyloxycarbonylglycine were synthesized and characterized. On the basis of different techniques, it is proposed that the complexes have different geometries and that the *N*-benzyloxycarbonylglycinato ligand is coordinated through its carboxylic group in several different ways. In the case of the zinc(II) complex, tetrahedral geometry with two *N*-benzyloxycarbonylglycinato ligands coordinated as O,O bidentate is proposed. Octahedral geometry was obtained in the case of the cobalt(II) complex with the two *N*-Boc-gly ligands in the *trans*-position coordinated in a monodentate fashion. The structure of the polymeric cadmium(II)-complex was resolved using the single crystal X-ray diffraction method. The cadmium ion has a distorted pentagonal-bipyramidal coordination formed by the two

water molecules and two *N*-Boc-gly ligands coordinated in different fashions (one as a bidentate and the second connecting three cadmium atoms), forming a rather complicated 2D supramolecular structure.

The new complexes were screened for their in vitro antifungal and antibacterial activity against representative fungal and bacterial strains. It was shown that all the complexes inhibited the growth of the human fungal pathogen *C. albicans*. *N*-benzyloxycarbonylglycine itself does not suppress the growth of this pathogen. The zinc(II) and cobalt(II) complexes were selective and acted only on *C. albicans*. The polymeric cadmium complex inhibited the growth of the fungi *C. albicans* and *A. niger*, as well as of the bacteria *E. coli* and *M. lysodeicticus*, but was inactive against *S. aureus*.

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Appendix A. Supplementary material

CCDC 627139 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via http://www.ccdc.cam.ac.uk/conts/retrieving.html, or from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: (+44) 1223-336-033; or e-mail: deposit@ccdc.cam.ac.uk. Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.ica.2007.06.041.

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