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Synthesis, NMR, DFT and antimicrobial studies of Zn(II) complexes with *N*-benzyloxycarbonyl-*S*-alanine

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Abstract: In this study, the first complexes of Zn(II) with the *N*-benzyloxycarbonyl-*S*-alaninato ligand (*N*-Boc-*S*-ala) were synthesized. The new complexes were characterized by elemental analysis, conductometric measurements, IR, ^{1}H-NMR, ^{13}C-NMR and 2D-NMR spectroscopy. On the basis of the experimental data, tetrahedral geometry of the Zn(II) complexes was proposed. A very good agreement between the NMR and DFT calculated data was obtained. Investigation of antimicrobial activity of the newly synthesized complexes was also performed. It was established that [Zn(*N*-Boc-*S*-ala)$_2$] was selective and acts only on *Candida albicans*.

Keywords: antimicrobial activity; DFT; *N*-benzyloxycarbonyl-*S*-alanine; NMR; Zn(II) complexes.

INTRODUCTION

It is well known that metal complexes with aromatic amino acids can serve as model systems for the study of various interactions in which aromatic amino acids residues participate.[1–3] In our previous articles, metal complexes containing aromatic amino acids were described.[4–6] As a continuation, new metal complexes with *N*-benzyloxycarbonyl (*N*-Boc) protected amino acids were examined.[7] It is interesting to note that the *N*-benzyloxycarbonyl amino acids and their derivates were reported as anti-convulsant, anti-inflammatory and anti-neoplastic agents.[8–11] *N*-Protected amino acids have abilities to function as cholecystokinin receptor antagonists[12] and derivates of *N*-Boc amino acids also show a good degree of inhibition of the gastric proton pump.[13]

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In spite of interesting biological activities, only a few complexes with *N*-Boc amino acids have hitherto been described.[14–18] As *N*-benzyloxycarbonylglycine has favorable membrane penetration properties,[19,20] neutral complexes of it with various metal ions were prepared in a previous study.[7] Since in the literature there are no data concerning the antimicrobial activities of these compounds, the antimicrobial activities of the obtained metal complexes were also determined. It was established that among the investigated strains, the Zn(II) and Co(II) complexes were selective, acting only against the fungus *Candida albicans*.

The elaboration of new types of antifungal agents is presently a very urgent task.[21] As a result of this, the aim of this work was to synthesize new neutral zinc(II) complexes with the *N*-benzyloxycarbonyl-*S*-alaninato ligand (*N*-Boc-*S*--ala), with or without bipyridine as an additional ligand, and to investigate and compare the antimicrobial activity of the Zn(II) complexes with *N*-Boc-*S*-ala and *N*-Boc-gly ligands with mixed complexes containing 2,2'-bipyridine.

EXPERIMENTAL

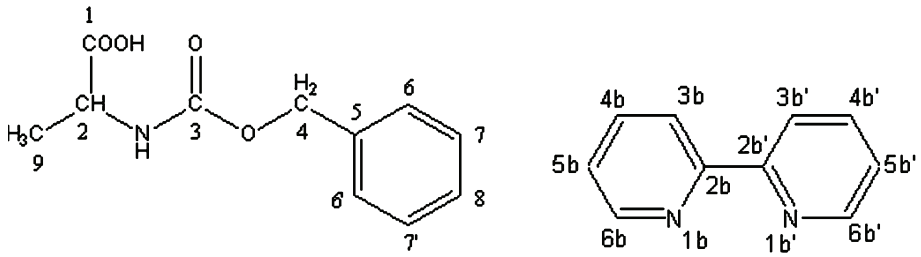
Materials and measurements

All the employed reagents and solvents were of analytical grade. *N*-Boc-Glycine, *N*-Boc--*S*-alanine, 2,2'-bipyridine and the metal salts were obtained from Aldrich and 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 performed on a Perkin-Elmer FT-IR 1726X spectrometer.

The molar conductivity of a methanolic solution of the complexes (c = 10^{-3} mol dm^{-3}) was measured at room temperature on a Jenway-4009 digital conductivity meter.

The ^{1}H-NMR (200 MHz) spectra were recorded using a Varian Gemini 2000 spectrometer at room temperature in DMSO-d_6 solution. The ^{13}C-NMR (50.3 MHz) spectra were recorded using the same instrument in DMSO-d_6 solution. The solvent peak at 39.7 ppm was used to calibrate the scale of chemical shifts. 2D-NMR spectra: DQF–COSY, TOCSY (mixing time 40 ms), ROESY (mixing time 80 ms) and {^{1}H-^{13}C}-HSQC, were recorded on a Bruker 700 MHz instrument.

N-*Boc*-S-*Alanine (Scheme 1)*. ^{1}H-NMR (δ, ppm): 12.3 (1H, *bs*, H(1)), 7.62 (1H, *d*, J = = 7.4 Hz, H(NH)), 7.36 (5H, *m*, H (6,6',7,7',8)), 5.03 (2H, *s*, H(4)), 4.02 (1H, *quintet*, J = 7.4 Hz, H(2)), 1.27 (3H, *d*, J = 7.4 Hz, H(9)); ^{13}C-NMR (δ, ppm): 174.8 (C1), 156.2 (C3), 137.3 (C5), 128.7 (C7,C7'), 128.1 (C8), 128.1 (C6,C6'), 65.7 (C4), 49.5 (C2), 17.3 (C9).



Scheme 1. Numbering of the C atoms in *N*-benzyloxycarbonyl-*S*-alanine and in 2,2'-bipyridine.

*Synthesis of [Zn(*N-*Boc*-S-*ala)$_2$]·1.5H$_2$O (**1**)*

To a solution of *N*-benzyloxycarbonyl-*S*-alanine (0.20 g, 0.90 mmol) in ethanol–water (1:1) mixture (5.0 cm^3), $ZnCl_2$ (0.060 g, 0.44 mmol) dissolved in a minimal volume of water was added. The resulting solution was allowed to reflux for 30 min, with constant stirring. The pH value of the obtained system was then adjusted to 6.0 using NaOH solution (0.20 mol dm^{-3}).

The resulting suspension was stirred for one hour at room temperature. The reaction mixture was then filtered and the obtained filtrate left at room temperature. After a few days, the obtained white crystals were separated by suction and then air-dried. Yield: 0.90 g (40 %).

*Synthesis of [Zn(*N-*Boc*-S-*ala)$_2$(bipy)]·2H$_2$O (**2**)*

To a 50-cm^3 flask, containing 0.18 g (0.34 mmol) of [Zn(*N*-Boc-*S*-ala)$_2$]·1.5H$_2$O in 2.5 cm^3 of acetonitrile, 0.060 g (0.38 mmol) of 2,2'-bipyridine in 2.0 cm^3 of acetonitrile was added. The obtained suspension was stirred for one hour without heating. The transparent reaction mixture was filtered by suction and the filtrate was left at room temperature. After a few days, white-yellow crystals were obtained. Yield: 0.19 g (81 %).

*Synthesis of [Zn(*N-*Boc-gly)$_2$(bipy)]·H$_2$O (**3**)*

To a solution of [Zn(*N*-Boc-gly)$_2$][7] (0.10 g, 0.21 mmol) dissolved in chloroform (15 cm^3), 0.032 g (0.20 mmol) of 2,2'-bipyridine dissolved in chloroform (2.5 cm^3) was added dropwise during 60 min with stirring at room temperature. The mixture was then continuously stirred for about 120 min. The filtrate was concentrated in a vacuum evaporator and left in a refrigerator. White crystals were obtained two days later. Yield: 0.80 g (61 %).

Density functional method calculation

The studied compounds **1** and **2** were subjected to geometry optimization using the density functional theory (DFT) with the Becke three-parameter exchange functional (B3)[22] and the Lee–Yang–Parr (LYP) correlation functional.[23] The DFT method was used as it gives good results for all 3d-metal complexes.[24-26] These B3LYP calculations were performed with the Gaussian03 program.[27] Various rotamers of compounds **1** and **2** were computed. As the starting point for the calculation, the conformation of the *N*-Boc residue obtained by the single crystal X-ray method was used.[15,18] The DFT calculation was performed for several conformations of the *N*-Boc-*S*-ala residuals. The conformation search was performed by variation of the Zn–O–C–N torsion angles. The geometries of conformers of the complexes were fully optimized using the LANL2DZ basis set. The optimized geometry of the most stable conformers of complexes **1** and **2** are given in Figs. 1 and 2, respectively.

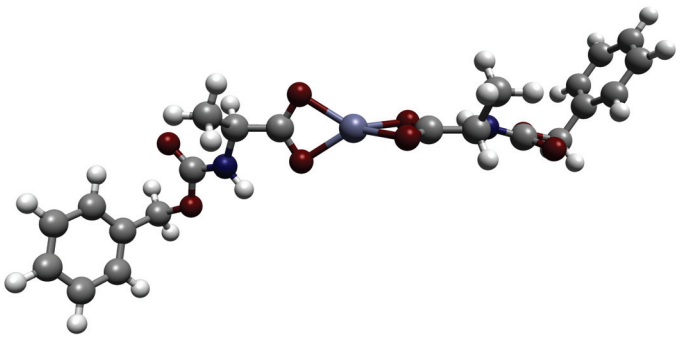


Fig. 1. Proposed tetrahedral geometry of the [Zn(*N*-Boc-*S*-ala)$_2$] complex (**1**) (structure optimized using B3LYP//LANL2DZ).

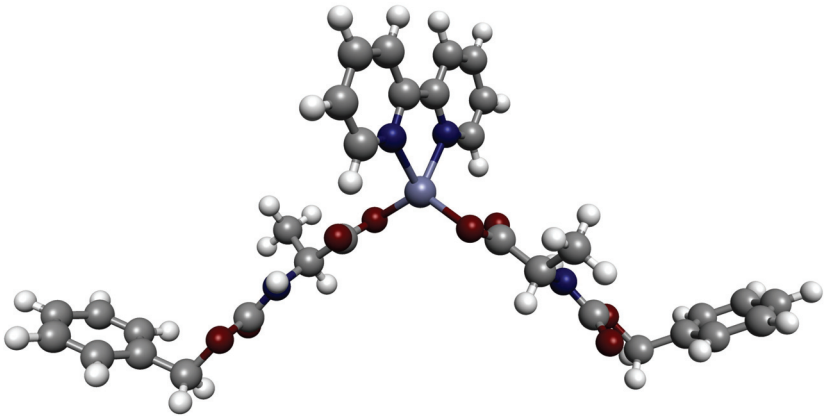


Fig. 2. Proposed tetrahedral geometry of the [Zn(*N*-Boc-*S*-ala)$_2$bipy] complex (**2**) (structure optimized using B3LYP//LANL2DZ).

Microbiological assay

N-Benzyloxycarbonyl-*S*-alanine and its Zn(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 lysodeikticus* (ATCC 4698, Gram positive). The antifungal and antibacterial activity of these complexes was determined using the minimal inhibitory concentration (MIC) test.[28] The MIC test was performed by making serial dilutions in the appropriate medium with the investigated substances dissolved in DMSO in a predetermined range of concentration (5000–625 μg ml^{-1}). After plating, the bacteria were incubated at 37 °C and the growth was observed after 24 h, while fungi were incubated at 27 °C and growth was observed after 72 h. The media for the growth of the bacteria and fungi were Mueller-Hinton agar and Sabouraud dextrose agar, respectively. The experiments were performed in triplicate. The control was DMSO.

RESULTS AND DISCUSSION

Synthesis

One of the goals of this work was the synthesis of neutral (because of facilitated transport through cell membranes) complexes of zinc(II) ion with the *N*-benzyloxycarbonyl-*S*-alaninato ligand with or without 2,2'-bipyridine as an additional ligand. Compound **1** was obtained by direct synthesis by the reaction of $ZnCl_2$ with the *N*-Boc-*S*-ala ligand in the mole ratio 1:2. Complex **2** was obtained by reaction of compound **1** with 2,2'-bipyridine in the mole ratio 1:1. Compound **3** was obtained by the reaction of the previously synthesized [Zn(*N*-Boc-gly)$_2$] complex[7] with 2,2'-bipyridine. This complex was synthesized to compare the antimicrobial activities of the mixed complexes **2** and **3**. The values of the molar conductivity of the synthesized complexes in methanol (c = 10^{-3} mol dm^{-3}), *i.e.*, Λ_M = 49.15, 42.24 and 43.5 Ω^{-1} cm^2 mol^{-1} for complexes **1**, **2** and **3**, respectively, confirmed their non-electrolyte type.

Analytic and spectroscopic characterization

*[Zn(*N-*Boc*-S-*ala)$_2$]·1.5H$_2$O* (***1***). Anal. Calcd. for $C_{22}H_{25}O_{9.5}N_2Zn$: C, 49.22; H, 5.03; N, 5.22. Found: C, 49.40; H, 4.79; N, 5.43. ^{1}H-NMR (δ, ppm): 3.96 (1H, *quintet*, J = 7.4 Hz, H(2)), 7.12 (1H, *d*, J = 7.8 Hz, H(NH)), 5.01 (2H, *s*, H(4)), 7.35 (5H, *m*, H (6,6',7,7',8)), 1.25 (3H, *d*, J = 7.2 Hz, H(9)). ^{13}C-NMR (δ, ppm): 178.1 (C1); 155.9 (C3); 137.5 (C5); 128.6 (C7,C7'); 128.6 (C8); 128.0 (C6,C6'); 65.4 (C4); 50.5 (C2); 18.8 (C9).

*Zn(*N-*Boc*-S-*ala)$_2$(bipy)]·2H$_2$O* (***2***). Anal. Calcd. for $C_{32}H_{36}O_{10}N_4Zn$: C, 54.74; H, 5.13; N, 7.98. Found: C, 54.63; H, 5.03; N, 8.14. ^{1}H-NMR (δ, ppm): 8.75 (2H, *d*, J = 4.6 Hz, H(6b,6b')), 8.55 (2H, *d*, J = 8 Hz, H(3b,3b')), 8.16 (2H, *t*, J = 7.6 Hz, H(4b,4b')), 7.65 (2H, *t*, J = 5.9 Hz, H(5b,5b')), 7.34 (5H, *m*, H (6,6',7,7',8)), 6.97 (1H, *d*, J = 7.6 Hz, H(NH)), 4.98 (2H, *s*, H(4)), 3.89 (1H, *quintet*, J = 7.4 Hz, H(2)), 3.49 (H_2O), 1.19 (3H, *d*, J = 6 Hz, H(9)). ^{13}C-NMR (δ, ppm): 177.6 (C1), 155.7 (C3), 151.0 (C2b,2b'), 149.3 (C6b,6b'), 140.0 (C4b,4b'), 137.5 (C5), 128.5 (C7,C7'), 128.6 (C8), 127.8 (C6,C6'), 126.0 (C5b,5b'), 121.6 (C3b,3b'), 65.2 (C4), 50.8 (C2), 19.0 (C9).

*[Zn(*N-*Boc-gly)$_2$(bipy)]·H$_2$O* (***3***). Anal. Calcd. for $C_{30}H_{30}O_9N_4Zn$: C, 54.93; H, 4.58; N, 8.54. Found: C, 54.63; H, 4.52; N, 8.50. ^{1}H-NMR (δ, ppm): 8.68 (2H, *d*, J = 8 Hz, H(6b,6b')), 8.58 (2H, *d*, J = 4.4 Hz, H(3b,3b')), 8.19 (2H, *t*, J = 7.6 Hz, H (4b,4b')), 7.68 (2H, *t*, J = 6.1 Hz, H(5b,5b')), 7.33 (5H, *s*, H (6,6',7,7',8)), 7.13 (1H, *t*, J = 5.5 Hz, H(NH)), 4.99 (2H, *s*, H(4)), 3.51 (2H, *d*, J = 6 Hz, H(2)). ^{13}C-NMR (δ, ppm): 174.8 (C1), 156.5 (C3), 151.0 (C2b,C2b'), 149.3 (C6b,C6b'), 140.3 (C4b, C4b'), 137.5 (C5), 128.6 (C7,C7'), 128.6 (C8), 127.9 (C6,C6'), 126.2 (C5b, C5b'), 121.8 (C3b,C3b'), 65.4 (C4), 43.8 (C2).

*IR spectroscopy of complexes **1**–**3***

On the basis of the differences in the frequencies of the asymmetric and symmetric skeletal vibration of the carboxylic group (1600–1350 cm^{-1} region) in free ($\Delta\nu$ = 182 cm^{-1}) and coordinated *N*-Boc-*S*-ala it can be concluded that the modes of coordination of the carboxylic group in the complexes of zinc(II) with *N*-Boc-*S*-ala (**1** and **2**) are different.[29] Namely, in the case of complex **1** ($\Delta\nu$ = = 146 cm^{-1}), chelate bidentate coordination of the carboxylic group occurs. These findings are in agreement with the coordination mode of the carboxylic group in the previously described [Zn(*N*-Boc-gly)$_2$] complex.[7] In the case of the mixed complex **2** ($\Delta\nu$= 208 cm^{-1}), monodentate coordination of the carboxylic group seems likely, *i.e.*, the introduction of 2,2'-bipyridine into the coordination sphere of the metal ion changes the coordination mode of carboxylic group from bidentate to monodentate.

The complexes **1**–**3** crystallize with 1–2 water molecules. Since in the IR spectra of the new compounds, bands that could be assigned to vibration of coordinated water are missing,[29] tetrahedral geometry around the Zn(II) ion in all complexes was proposed.

DFT calculation

Since all attempts to obtain a single crystal suitable for X-ray crystallography failed, DFT calculation was applied to check the hypothesis that the new zinc(II) complexes with *N*-benzyloxycarbonyl-*S*-alaninato ligands adopt tetrahedral geometry (Figs. 1 and 2).

Another goal was to determine which geometry of the complex of stoichiometric composition [Zn(*N*-Boc-*S*-ala)$_2$bipy] (**2**) is more stable, the tetrahedral one with monodentate coordination of the carboxylic groups (as assumed) or the octahedral one with bidentate coordination of the carboxylic group. DFT calculation was performed for several conformations of the *N*-Boc-*S*-ala residuals. The conformation search was performed by variation of the Zn–O–C–N torsion angle. Each starting geometry was allowed to be fully optimized. The DFT calculation revealed that the most stable geometry is tetrahedral with monodentate coordination of carboxylic groups (Fig. 2). The most stable octahedral geometry is higher in energy by 2.6877 kJ mol^{-1} than the most stable tetrahedral geometry. The results of the DFT calculations confirmed the assumption based on IR spectroscopy that coordination of 2,2'-bipyridine caused a change in the coordination mode of the carboxylic groups of the *N*-Boc-*S*-ala ligands, from bidentate to monodentate. Monodentate coordination of *N*-Boc-*S*-ala through carboxylate oxygen atom is also in accordance with monodentate coordination of *N*-benzoylalaninato and DL-alaninato ligands in mixed Zn(II)-complexes, the structures of which were determined by single crystal X-ray analysis.[30,31]

In the case of complex **3** ($\Delta\nu$ = 211 cm^{-1}), coordination of 2,2'-bipy causes a change in the coordination mode of the carboxylic group from bidentate (in the previously synthesized [Zn(*N*-Boc-gly)$_2$] complex)[7] to monodentate. Tetrahedral geometry is proposed for this complex, as in the case of complex **2**.

*NMR spectroscopy of complexes **1**–**3***

Assignment of ^{1}H- and ^{13}C-NMR chemical shifts was obtained from analysis of DQF–COSY, TOCSY and {^{1}H-^{13}C}-HSQC spectra.

In the ^{1}H-NMR spectra of complexes **1**–**3**, a signal assignable to carboxylic group protons was absent, indicating that deprotonation of carboxylic group occurred and that coordination through this group took place.

The complexes **1**–**3** were also characterized by means of ^{13}C-NMR spectroscopy. The higher values of the chemical shift of C(1), C(2) and C(9) atom signals in complexes **1**–**3** in comparison with those of the signals in the respective non-coordinated ligands,[7] strongly suggest that coordination through the carboxylate groups had occurred. On the other hand, the absence of a change of the chemical shift of the carbamate carbon C(3) indicates that the carbamate group does not participate in the coordination. The assumption that coordination through nitrogen atom does not occur (except in complexes of Pb(II), Cd(II) and Cu(II) with

N-sulfonylamino acids) is in accordance with the data concerning the coordination abilities of other *N*-acylated amino acids.[15,18,32–34] The NMR spectra of the 2,2'-bipyridine complexes show that both pyridine nitrogen atoms participate in the coordination.

The most direct evidence for the DFT calculated geometry is the close contacts between the protons seen in the 2D-ROESY spectrum of **2** (Fig. 3). Thus, the proton at position 6b of the 2,2'-bipyridine ligand is close in space to the methyl protons at position 9 of the *N*-benzyloxycarbonyl-*S*-alaninato ligand. The data presented in Fig. 3 give a good example of how theoretical and experimental data can fit.

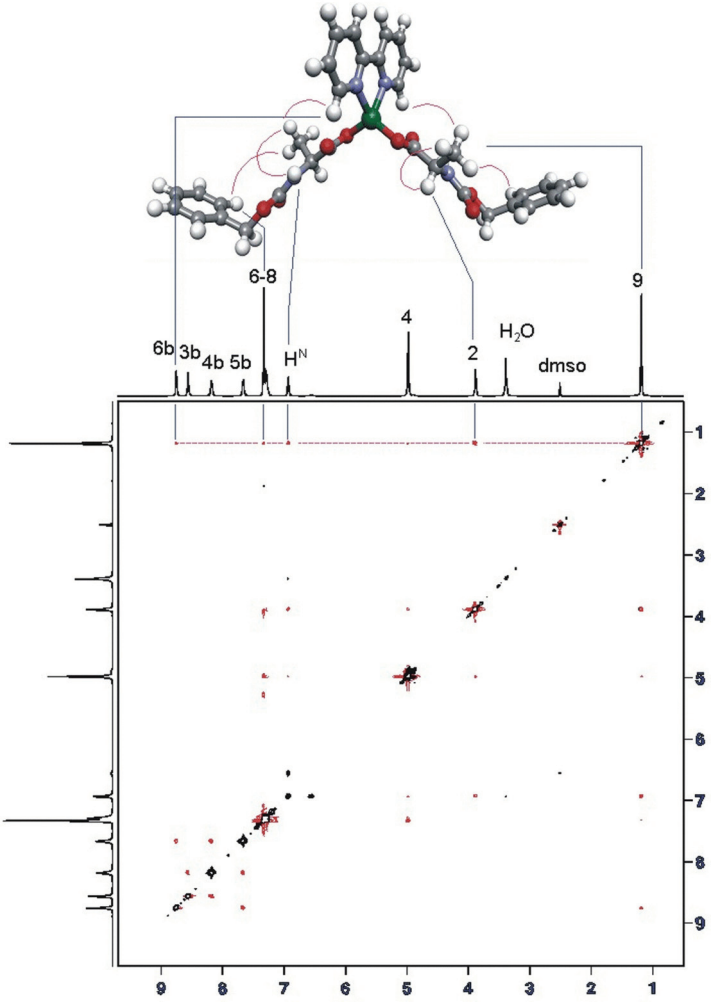


Fig. 3. ROESY spectrum of [Zn(*N*-Boc-*S*-ala)$_2$bipy] complex (**2**) exhibits inter-proton close contacts in agreement with the DFT calculated structure. ^{1}H spectral axis is in ppm relative to TMS.

Microbiological assay

The complexes **1**–**3** and *N*-benzyloxycarbonyl-*S*-alanine were screened for their *in vitro* antifungal and antibacterial activity against representative strains. The investigated complex **1** was inactive against bacterial and fungal strains, except against *Candida albicans*. The complex was more efficient in suppressing the growth of this pathogen than both the ligand and a simple zinc salt. The MIC value (625 μg ml^{-1}) was the same as that obtained for the analogue complex with the *N*-Boc-gly ligand.[7] The small increase in lipophilicity caused by the introduction of a methyl group did not change the MIC value.

Mixed complexes **2** and **3** suppressed the growth of neither *C. albicans* nor of any other investigated strains. These results are in agreement with those of recently *in vitro* performed antimicrobial studies of Cu(II) and Mn(II) complexes with 2,2'-bipy, which also did not suppress the growth of clinical isolates of *Candida* species, although their complexes with 1,10-phenanthroline were extremely toxic to the cells.[35–37] Although the MIC values for the present complexes were higher in comparison to those obtained, for example, for the Ag(I) complex with *N*-acetylglycine,[38] complexes of Zn(II) with *N*-Boc-gly and *N*-Boc-*S*-ala ligands were selective in suppressing the growth of *C. albicans*. Only the established selectivity of zinc(II) complexes with *N*-benzyloxycarbonylamino acids against one of the investigated strains may be of interest for further studies on antimicrobial activities of similar compounds.

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ИЗВОД

СИНТЕЗА, NMR И DFT ПРОРАЧУНАВАЊА И ИСПИТИВАЊЕ АНТИМИКРОБНЕ АКТИВНОСТИ Zn(II) КОМПЛЕКСА СА *N*-БЕНЗИЛОКСИКАРБОНИЛ-*S*-АЛАНИНОМ

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У овом раду су синтетизовани први комплекси Zn(II) са *N*-бензилоксикарбонил-*S*-аланинато лигандом (*N*-Boc-*S*-ala). Комплекси су окарактерисани елементалном анализом, кондуктометријским мерењем, IR, ^{1}H-NMR, ^{13}C-NMR и 2D-NMR спектроскопијом. Тетраедарска геометрија Zn(II) комплекса претпостављена је на основу експерименталних података. Добијено је веома добро слагање између NMR и DFT података. Испитивана је антимикробна активност новосинтетизованих комплекса. Установљено је да је [Zn(*N*-Boc-*S*-ala)$_2$] комплекс селективан и да делује само на гљиву *Candida albicans*.

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