Hindawi
Journal of Chemistry
Volume 2018, Article ID 8910242, 9 pages
https://doi.org/10.1155/2018/8910242

Research Article

Synthesis and Crystalline Structure of Zinc Complexes with Antihypertensive Drug Lisinopril

Márcia C. de Souza,[1] Luan F. Diniz,[1] Chris H. J. Franco,[1] and Renata Diniz[1,2]

[1]*Department of Chemistry, Federal University of Juiz de Fora, Juiz de Fora, Minas Gerais 36036-900, Brazil*
[2]*Department of Chemistry, Federal University of Minas Gerais, Belo Horizonte, Minas Gerais 31270-901, Brazil*

Correspondence should be addressed to Renata Diniz; dinizr@ufmg.br

Received 29 May 2018; Accepted 10 September 2018; Published 18 October 2018

Academic Editor: Henryk Kozlowski

The structural investigation of Zn^{2+} complexes with the ligand lisinopril (LIS), an inhibitor of angiotensin-converting enzyme (ACE), was performed. The main objective is to compare if Zn-LIS coordination *in vitro* is similar to that observed *in vivo*. Two zinc complexes were obtained from different synthetic routes. The synthesis of LISZn1 used stirring, while for LISZn2 involved solvothermal conditions, which favoured the full deprotonation of lisinopril ligand. In this sense, the different synthetic routes resulted in the formation of complexes with notorious chemical and structural differences. The crystal structure of LISZn2 showed that the ligand is coordinated to Zn^{2+} ion by oxygen and nitrogen atoms which is different from that observed *in vivo*. *In vitro*, the coordination of lisinopril occurs only by an oxygen atom of the central carboxylate group. LISZn2 forms a one-dimensional (1D) coordination polymer and presents disorder atoms in its unit cell.

1. Introduction

Hypertension is a disease that affects millions of people around the world. This disease is identified if the blood pressure levels maintain above the reference values [1]. Angiotensin-converting enzyme (ACE) inhibitors are considered the most effective drugs used to treat the arterial hypertension. ACE is a zinc-containing metallopeptidase that catalyzes the conversion of the angiotensin I-inactive decapeptide to angiotensin II-potent vasopressor octapeptide. This reaction promotes vasoconstriction and hydrolysis of the vasodilator bradykinin [2–4]. It plays an essential role in blood pressure regulation, and its interaction with an ACE inhibitor (ACEI) sets an important research topic for treatment of hypertension [2]. Some synthetic ACEIs are useful in various cardiovascular pathologies, acting in both reduction of blood pressure and also in the treatment for postmyocardial infarction [3, 5].

Lisinopril, (*S*)-1-[N^2-(1-carboxy-3-phenylpropyl)-L-lysyl]-L-proline, (Figure 1), is an angiotensin-converting enzyme (ACE) inhibitor, widely used in the treatment of hypertension, congestive heart failure, acute myocardial infarction, and diabetic nephropathy [3, 6–8]. The mechanism of action of the lisinopril is known to be related to its ability to interact with ACE forming a (*in vivo*) compound with the Zn^{2+} ion present in ACE. The Zn-ACEI occurs through the central carboxylate group of lisinopril molecule [9]. Electrostatic interactions, hydrogen bonds, and aromatic stacking appear to be sufficient to act as a backstop, positioning the substrate molecule [2, 9]. There are some studies investigating the nature of the interaction between lisinopril and ACE or metal ions by crystal structure analyses [9, 10]. A dihydrate phase of lisinopril is recognized as the most stable crystalline form, and it is extensively used within medicine [6, 11].

This work consists of structural characterization of zinc complexes with ACE inhibitor lisinopril. The LISZn structures are described to evaluate whether the interaction between lisinopril and Zn^{2+} ion *in vitro* resembles that proposed *in vivo*. The molecular and structural details reported in this study may be useful for the development of novel and more effective ACEI to combat high blood pressure.

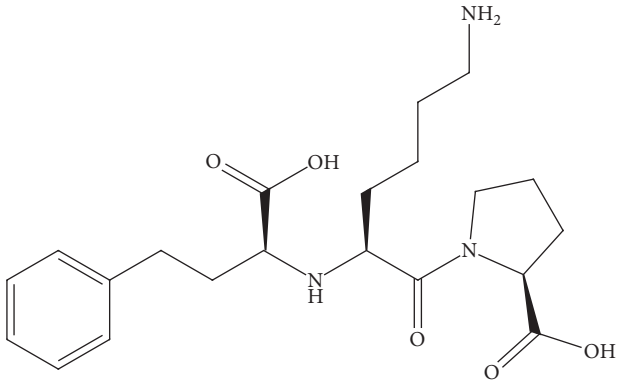


Figure 1: Molecular structure of the lisinopril.

2. Materials and Methods

All products used in the syntheses and analysis present analytical grade, and they were used without purifying. Elemental analyzes (C, H, and N) were performed on a Perkin-Elmer 2400 analyzer. Spectroscopic data in the infrared region were recorded on the Alpha Bruker FT-IR spectrophotometer in the 4000–400 cm^{-1} range with 64 scans and a 4 cm^{-1} resolution for samples using KBr pellets. The Raman spectra were obtained on a Bruker FRS 100 spectrometer using Nd3 +/YAG laser radiation (1064 nm) and a CCD detector. The measures were obtained with 256 scans, 4 cm^{-1} of spectral resolution, and 100 mW laser power.

2.1. Synthesis and Chemical Characterization of the LISZn1. A methanolic solution (2 mL) of $Zn(ClO_4)_2{\cdot}6H_2O$ (1.13 mmol) was added dropwise to a mixture of lisinopril dihydrate (1.13 mmol) and triethylamine (1.09 mmol) in methanol (15 mL) under stirring [10]. The resulting solution was maintained at room temperature. After few hours was observed the formation of a colourless material that visually looked to be single crystals with a yield of 52%. Elemental analysis points to $C_{27}H_{50}Cl_2N_4O_{15}Zn$: calcd. C 40.18, H 6.24, N 6.94; found C 41.03, H 6.13, N 6.88.

2.2. Synthesis and Chemical Characterization of the LISZn2. A methanolic solution of $Zn(ClO_4)_2{\cdot}6H_2O$ (0.89 mmol), 8 mL, was mixed with another aqueous solution, 10 mL, of lisinopril dihydrate (3.40 mmol) and triethylamine (3.26 mmol). This mixture was transferred to a 23 mL Teflon-line Parr acid digestion bomb. The reaction vessel was heated at 353 K for 38 h and, after this time, was slowly cooled to 298 K. At the end of this process, colourless crystals appropriate for single crystal X-ray diffraction analysis were obtained with a yield of 60%. Elemental analysis to $C_{21}H_{37}N_3O_9Zn$: calcd. C 46.63, H 6.89, N 7.77; found C 46.37, H 6.41, N 7.62.

Caution! Perchlorate salts with organic solvents are potentially explosive. Only small amounts of material should be prepared, and they should be handled with care.

2.3. Thermal Analyses (TGA/DTA). Thermal analyses (TGA/DTA) measurements were carried out on a Shimadzu TG-60 with a heating rate of 10 $K{\cdot}min^{-1}$ from room temperature to 874 K and in an air atmosphere (rate flow of 50 $mL{\cdot}min^{-1}$).

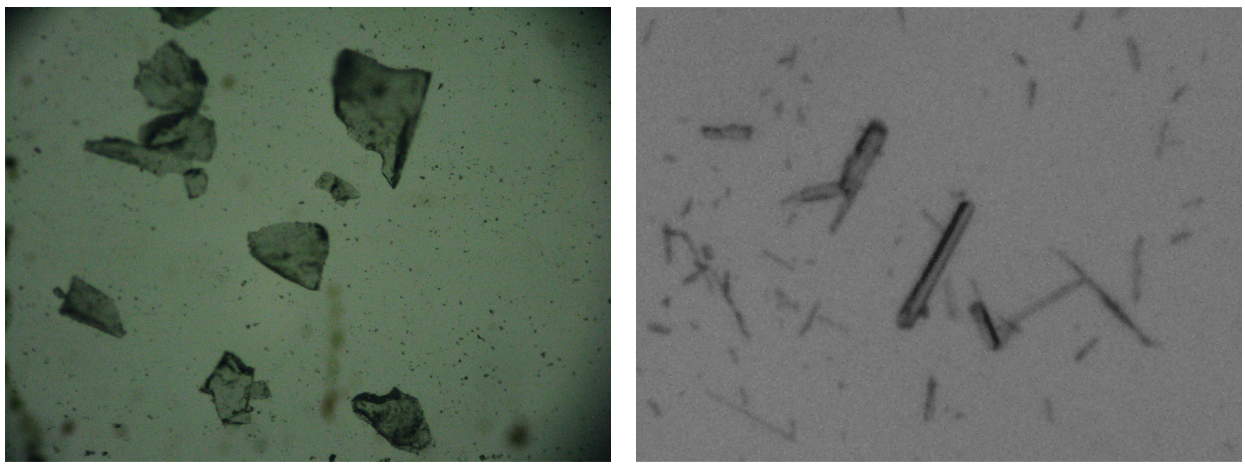
2.4. Single Crystal X-Ray Diffraction. Single crystal X-ray diffraction data were collected using a SuperNova diffraction system from Agilent/Rigaku Technologies with CuKα (λ = 1.54056 Å) at 120 K. Data collection, reduction, and cell refinement were performed with the CrysAlisPro [12]. A multiscan absorption correction was applied [13]. The structure was solved and refined by means of SHELXL-2014/7 program package [14]. Anisotropic displacement parameters were assigned to all nonhydrogen atoms. H atoms were located in different Fourier maps and subsequently geometrically optimized and allowed as riding atoms, with C-H = 0.93 Å for aromatic CH groups and 0.97 Å for secondary CH_2 groups with $U_{iso}(H) = 1.2\ U_{eq}$ (for secondary CH_2 groups). The positions of other H atoms were refined freely. The structures were drawn by the programs ORTEP-3 for Windows [15] and Mercury [16].

2.5. Powder Crystal X-Ray Diffraction. X-ray powder diffraction data were collected using a Bruker D8 Advance DaVinci diffractometer, equipped with CuKα (λ = 1.5418 Å) radiation, Ni-filter, LynxEye Detector, and Bragg–Brentano geometry. Data were collected between 5 and 50° in 2θ with a step size of 0.01° and the count time of 0.1 s per step for LISZn2 and with a step size of 0.02° and the count time of 0.05 s per step for LISZn1. Soller slit with a 0.02 mm divergent slit and a 0.6 mm sample slit were used. For all analyses, a voltage of 40 kV and current of 40 mA were applied to generate the incident radiation, and the measurements were performed at room temperature (298 K).

3. Results and Discussion

The combination of zinc perchlorate salt with the lisinopril drug has produced two new complexes (LISZn1 and LISZn2) with 1 : 1 metal:ligand stoichiometric ratio and lattice water, whereas the LISZn1 complex also contains lattice perchlorate ions and triethylamine, suggested by elemental analysis. The synthesis of LISZn2 involved solvothermal conditions, which favoured the full deprotonation of lisinopril ligand, while the synthesis of LISZn1 used only stirring. These two distinct synthetic methodologies employed led to the formation of compounds with chemical and structural differences that can be seen by their distinct solid habits (Figure 2).

3.1. Thermal Analyses (TGA/DTA). Thermogravimetric analysis (TGA) and differential thermal analysis (DTA) curves for the LISZn1 and LISZn2 complexes are depicted in Figures 3 and 4, respectively. It can be observed that the curves are quite different indicating that there are chemical differences between these compounds. Thermogravimetric



(a) (b)

Figure 2: Pictures taken at the polarized light microscope of (a) LISZn1 and (b) LISZn2 showing their distinct solid habits.

curve for LISZn1 displays four weight losses. The first one occurs between 298 and 377 K and corresponds to the weight loss of two moles of water that is in the crystalline lattice and 0.5 mol of triethylamine (obsd. 10.93%, calcd. 10.73%) per mol of the complex. Afterwards, three consecutive steps of weight losses above 500 K can be associated to the loss of 0.5 mol of the remained triethylamine, two moles of perchlorate ion and thermal decomposition of lisinopril drug (obsd. 74.34%, calcd. 74.71%). Finally, at 874 K, the residual percentage weight agrees with ZnO (obsd. 14.73%, calcd. 14.51%). For the LISZn2 complex, the curve shows three weight losses. The first one observed between 308 and 411 K is assigned to the loss of four moles of the lattice water (obsd. 12.10%, calcd. 13.33%) per mol of the complex. The second and third weight losses together refer to the thermal decomposition of lisinopril drug (obsd. 72.83%, calcd. 71.67%). The final residue at 874 K is in good agreement with one mol of ZnO (obsd. 15.07%, calcd. 15.00%). In the DTA curves of these complexes, one endothermic event at 334 K and 378 K for LISZn1 and LISZn2, respectively, can be noticed corresponding to the dehydration process. The other events in DTA curves for LISZn1 and LISZn2 are exothermic and can be associated with the thermal decomposition of both compounds. Thermal analysis results of LISZn2 complex are consistent with the X-ray crystallographic data.

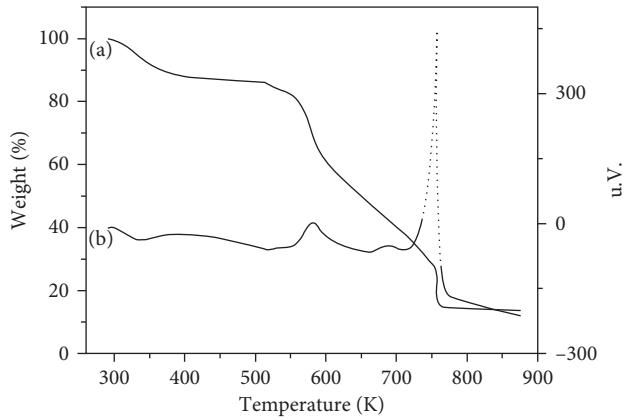


Figure 3: (a) TGA and (b) DTA plot of LISZn1 complex.

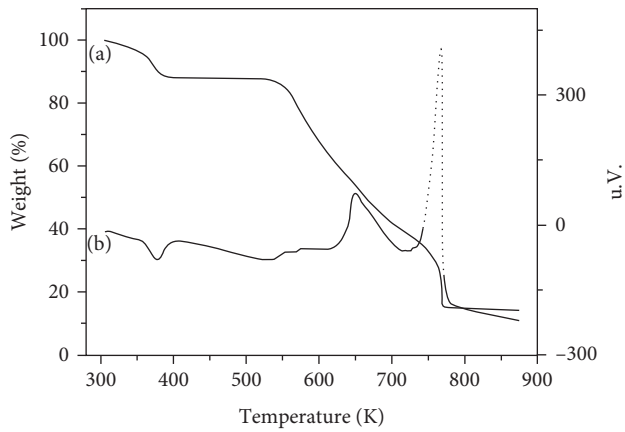


Figure 4: (a) TGA and (b) DTA plot of LISZn2 complex.

3.2. Spectroscopic Analyses. The spectroscopic data and vibrational assignments for lisinopril, LISZn1, and LISZn2 are shown in Table 1. The IR and Raman vibrational spectra are shown in the supplementary material (Figures S1 and S2, respectively). In the solid state, the main significant characteristic of the lisinopril structure is its double zwitterionic character. Both nitrogen atoms of amine groups are protonated, while the two carboxylic acid groups exist as carboxylate anions [6]. This behaviour directly influences the appearance of its vibrational spectra. The IR spectrum of the free lisinopril ligand shows one band with weak intensity at 3556 cm^{-1} related to the O-H stretching vibration of water molecules and some broad bands in the range of 3400 and 3200 cm^{-1} regarding to ν(N-H) of protonated amines. The decrease in the 3290 cm^{-1} absorption to 3247 cm^{-1} in LISZn1 and 3241 cm^{-1} in LISZn2 is associated with the coordination of amine nitrogen atom to the metal centre. The vibrational spectra (infrared and Raman) of the LISZn1

Table 1: Principal IR and Raman bands (cm^{-1}) for lisinopril, LISZn1, and LISZn2 compounds.

Lisinopril		LISZn1		LISZn2		Assignment[a]
IR[b]	Raman[b]	IR	Raman	IR	Raman	
3556w		3450m		3452m		ν(OH)
3397w				3315vw		ν(NH)
3290vw		3247vw		3241vw		$\nu(NH_2)$
3027vw	3058m	3024vw	3058m	3027vw	3056m	ν(CH)
2966w	2982m	2952w	2979m	2955w	2983w	ν(CH), $\nu_a(CH_3)$
2925vw	2934s		2927s		2935w	$\nu_a(CH_2)$
2877vw	2878w	2874vw	2881m	2885vw	2865w	$\nu_s(CH_2)$, $\nu_s(CH_3)$
1657s	1654w	1602vs	1604m	1603vs	1604vs	$\nu(CO)_{amide}$
1578m	1585m		1585m		1585m	$\nu_a(COO)$
1391m	1398vw	1392m	1398vw	1396m	1400vw	$\nu_s(COO)$
		1088m	933vs			$\nu(ClO)$

[a]Tentative assignment according to [6, 18–20]. ν = stretching; a = antisymmetric; s = symmetric; d = deformation. [b]s = strong; m = medium; w = weak; v = very.

and LISZn2 display characteristic bands of aliphatic and aromatic moiety of the structure of lisinopril, such as ν(CH), $\nu_a(CH_3)$, $\nu_s(CH_3)$, $\nu_a(CH_2)$, and $\nu_s(CH_2)$. The band at 1657 cm^{-1} and 1654 cm^{-1} observed in the IR and Raman spectra of lisinopril attributed to ν(CO)amide shifted to 1602 cm^{-1} in IR and 1604 cm^{-1} in Raman for LISZn1 and 1603 cm^{-1} in IR and 1604 cm^{-1} in Raman for LISZn2. These results suggest that the oxygen atom of the amide group is also coordinated to Zn(II) ion.

The lisinopril Raman spectrum exhibits bands related to ν_a(COO) (at 1585 cm^{-1}) and ν_s(COO) (at 1398 cm^{-1}) that agree with the complete dissociation of the drug in the solid state. These bands are observed in spectra of LISZn1 and LISZn2 at 1585 cm^{-1} (ν_a(COO) for both complexes) and at 1398 and 1400 cm^{-1} (ν_s(COO) for LISZn1 and LISZn2, respectively). Some information about the coordination mode can be obtained by the difference between the wave numbers of these modes, thus indicating whether the compound is in its ionic or coordinate form or on the type of coordination of the ligand with the metal site [17]. Differences determined from the Raman spectra are 187 cm^{-1}, 185 cm^{-1}, and 187 cm^{-1} for LISZn1, LISZn2, and ionic compound, respectively [6] These values very close are inconclusive regarding the lisinopril's coordination mode to the metal site in the LISZn1 and LISZn2 complexes. Additionally, spectroscopic data of LISZn1 display a medium intensity band at 1088 cm^{-1} (in IR) and a strong intensity band at 933 cm^{-1} (in Raman) assigned to the presence of noncoordinated perchlorate ion. IR spectra of the LISZn1 and LISZn2 complexes show a broad band centred at 3450 cm^{-1} and 3452 cm^{-1}, respectively, that are attributed to the O-H stretching vibration of water molecules. Spectroscopic data suggest similar coordination mode for both complexes. The vibrational results are in agreement with the X-ray diffraction data for LISZn2.

3.3. Powder Crystal X-Ray Diffraction. The simulated diffractogram generated from the crystal structure of LISZn2 crystal structure is in excellent agreement with the experimental diffractogram on the bulk sample of LISZn2 (Figures 5(a) and 5(b)). Qualitative analysis of the experimental and simulated diffraction patterns show that the Bragg peaks are in the same position. This proved that all further experimental results obtained for the complex LISZn2 could be interpreted based on the crystallographic model established in this study, i.e., the crystal structure is representative of the whole sample. In order to analyse the crystallinity of the solid LISZn1, powder X-ray diffraction measurement was realized (Figure 5(c)). No crystallinity was found in the diffraction pattern confirming its amorphous nature.

3.4. Crystallographic Analysis. The LISZn2 complex asymmetric unit is shown in Figure 6 in which can be seen four lisinopril drug molecules, four crystallographically independent zinc (II) ions, and sixteen water molecules. The complex is neutralized through full deprotonation of lisinopril ligand molecules and crystallizes in a noncentrosymmetric space group, $P3_2$ (Table 2), building a coordination polymer. In Figure S3 (Supplementary Material), it is possible to see a section of the polymeric structure of LISZn2.

The refinement was not satisfactory using default methods. The first problem was to determine the space group. There were systematic absences for a 3_1 or a 3_2 axis. It was possible to obtain the crystal structure of LISZn2 in the space group $P3_1$ with relatively low R values (R and wR indices for $[F_{obs} > 4\sigma(F_{obs})]$ equal to 0.066 and 0.1731, respectively). However, in crystals that crystalize in a noncentrosymmetric space groups is important the determination of absolute structure analyzing the Flack parameter. The Flack parameter obtained for this complex was 0.71(2) [21], which means that the absolute structure is wrong and the space group $P3_2$ is the correct one instead of $P3_1$. The refinement using the space group $P3_2$ presented the Flack parameter equal to 0.023(11) indicating that $P3_2$ is the correct space group [22]. All necessary changes have been made, and the refinement became satisfactory (Table 2).

The refinement of the LISZn2 complex shows some atoms (derived from lisinopril ligand and water molecules) with disordered effect in the unit cell. The O31A, O35A, and O36A oxygen atoms of water molecules; the C47A, C48A, and C64A carbon atoms; and the N3A nitrogen atom of the lisinopril ligand exhibited these disorder effects (Figure 7).

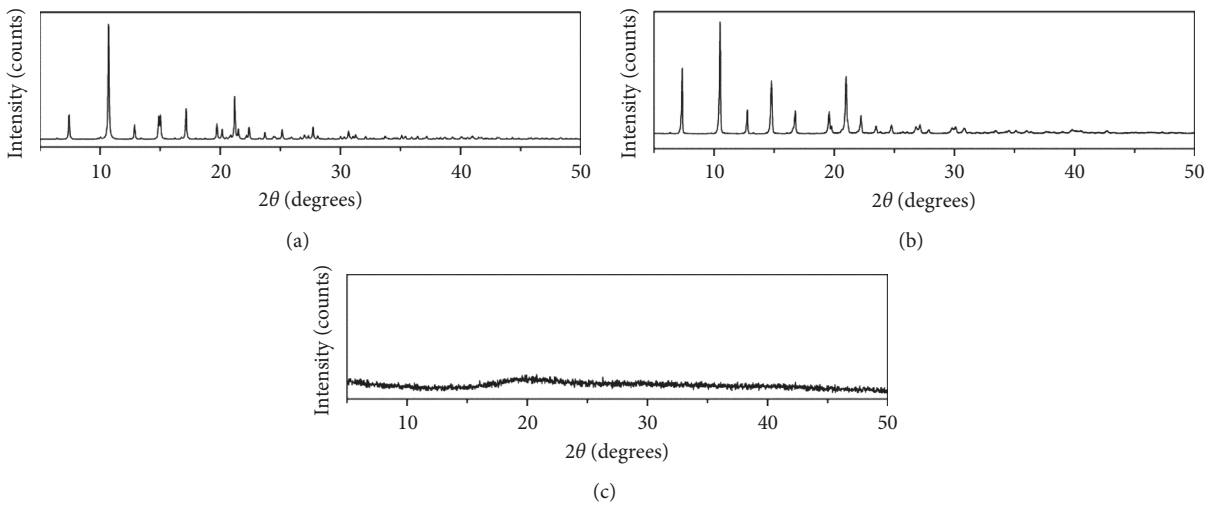


Figure 5: Diffractograms of the complexes: (a) simulated for LISZn2, (b) experimental for LISZn2, and (c) experimental for LISZn1.

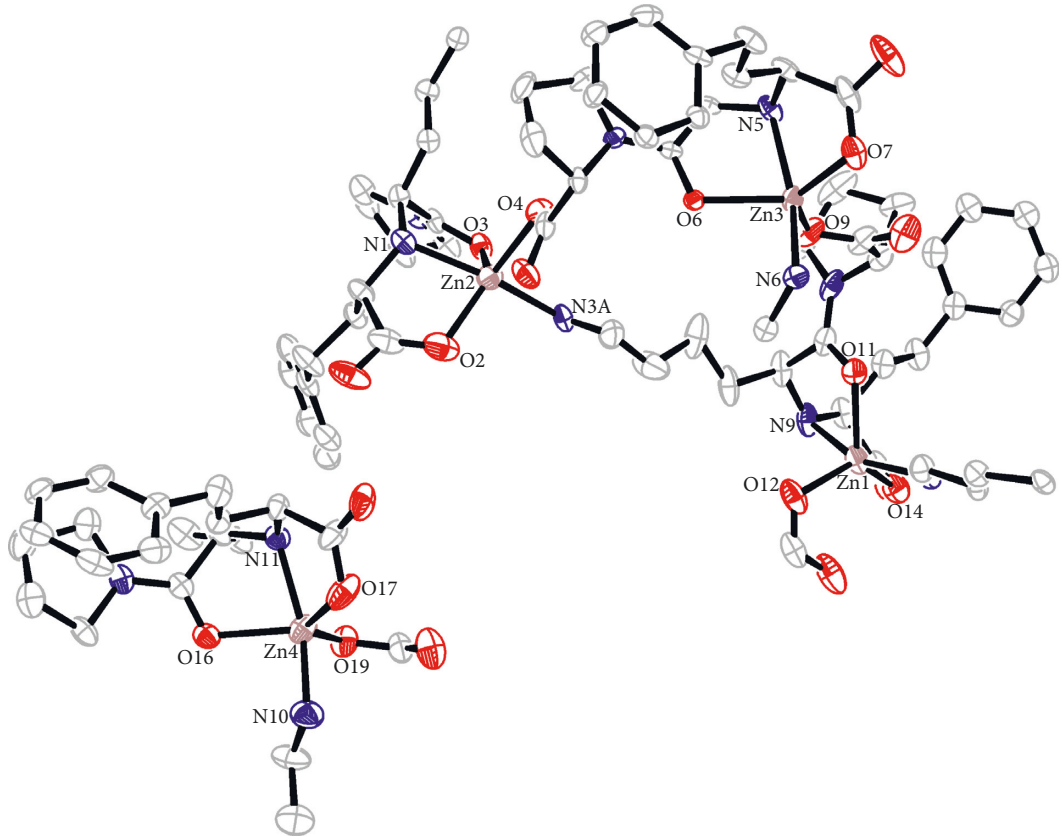


Figure 6: The asymmetric unit of the LISZn2 complex. Thermal ellipsoids are drawn at the 30% probability level. Some atoms are omitted for clearness.

The disorder refined from O31A, O35A, O36A/O31B, O35B, O36B, and C64A/C64B shows occupational values of 0.488(6):0.512(3) and 0.800(3):0.200(2), respectively. The amine chain atoms were refined together with the same occupation value. Each group is associated with one occupational value, and both contain the same atoms, however, with different crystallographic positions. The C47A, C48A, and N3A atoms are the first component of the disorder with an occupational distribution of 51%, and the C47B, C48B, and N3B atoms are the second component with an occupational distribution of 49%. The four crystallographically independent Zn^{2+} ions are pentacoordinated. In Zn1, Zn2, and Zn3 metal sites, a distorted square pyramidal geometry was observed and confirmed by the calculation of the t values, which presented values of 0.45, 0.33, and 0.48 respectively, similar to those observed in copper-lisinopril

Table 2: Crystal data for LISZn2 compound.

Compound	LISZn2
Chemical formula	$C_{84}H_{148}N_{12}O_{36}Zn_4$
Formula weight ($g{\cdot}mol^{-1}$)	2163.61
Crystal system	Trigonal
Space group	$P3_2$
a (Å)	27.4727(7)
b (Å)	27.4727(7)
c (Å)	11.4613(3)
α (°)	90
β (°)	90
γ (°)	120
Volume ($Å^3$)	7491.5(4)
Z	3
Temperature (K)	120.0(1)
$d_{calc.}$ ($g{\cdot}cm^{-3}$)	1.439
μ (KαCu) (mm^{-1})	1.835
Crystal size (mm)	0.12 × 0.11 × 0.09
Radiation	λ = 1.5418 Å (KαCu)
θ limits (°)	3.1980–72.5730
Refl. measured/independent	24164/15047
Refl. observed [$F_{obs} > 4\sigma_{(Fobs)}$]	11695
Parameters	1189
Flack parameter	0.023(11)
R_{int}	0.0356
R [$F_{obs} > 4\sigma_{(Fobs)}$]	0.0609
R indices for all data	0.0777
wR [$F_{obs} > 4\sigma_{(Fobs)}$]	0.1635
Goodness-of-fit (GOF)	1.06
Weighting scheme	$W = 1/[\sigma^2(Fo^2) + (0.1137P)^2 + 0.0000P]$ Where $P = (Fo^2 + 2Fc^2)/3$
$(\Delta\rho)_{min}$, $(\Delta\rho)_{max}$ ($e{\cdot}Å^{-3}$)	−0.71, 1.55

complex described in the literature [10]. Three positions in the basal plane are occupied by oxygen atoms of central carboxylate (Zn-O 2.101(2) Å) and carbonyl (Zn-O 2.164 (3) Å) groups as also the secondary amine nitrogen (Zn-N 2.122(2) Å) of one lisinopril ligand, while the fourth is occupied by primary amine nitrogen (Zn-N 2.035(2) Å) of a second lisinopril ligand. An oxygen atom of the prolyl carboxylate group of a third lisinopril ligand is located at the apex with an average Zn-O bond distances equal to 2.025(2) Å. The Zn4 metal site has a very much distorted trigonal bipyramidal geometry with t value equal to 0.58. The Zn4 metal site is coordinated to oxygen atoms of central and prolyl carboxylate (Zn-O 2.062(5) Å and Zn-O 1.999(4) Å, respectively) and carbonyl (Zn-O 2.171(5) Å) groups in the basal plane as well as primary and secondary amine nitrogen atoms (Zn-N 2.012(8) Å and Zn-N 2.126 (6) Å, respectively) in the axial positions. The average values found for the Zn-O and Zn-N bonds distances are 2.092(3) Å and 2.076(1) Å, respectively. The average Zn-O bond distance is similar to that observed in complex lis-enzyme described in the literature [9].

In Table 3, selected bond lengths (Å) and angles (°) of LISZn2 are listed. The interaction *in vitro* among lisinopril and Zn^{2+} ion is similar to which is suggested *in vivo*, once the lisinopril coordination occurs through the oxygen atom of the central carboxylate moiety [9]. In the structure of lis-enzyme, the Zn^{2+} ion also is coordinated to two histidine molecules by two nitrogen atoms of the imidazole ring and to one glutamic acid by the oxygen atom present in the environment. In the LISZn2 was observed that the coordination environment around zinc ion is formed by oxygen atoms from prolyl carboxylate and carbonyl groups, as also by nitrogen atoms of primary and secondary amines.

Furthermore, the crystal packing stability occurs through classical hydrogen bonds (OH ⋯ and NH ⋯ O) formed among water molecules and carboxylate and amine groups of the LIS ligand. Other hydrogen bonds among water molecules in the structure are also observed. The O ⋯ O distances from classical hydrogen bonds are in the 2.808 to 3.069 Å range (Table 4).

In this compound, we describe the structure considering the symmetry operation from the space group $P3_2$ and to facilitate the description; only the equivalent general positions were used providing an insight between structure and symmetry. The space group diagram within the structure is given in Figure 8(a). Note that there are four different Zn atom sites specified in the unit cell, numbered Zn1, Zn2, Zn3, and Zn4; the atomic coordinates of Zn atoms are shown in Table S1 (Supplementary Material). The 3_2 screw axis running parallel to the c-axis and all atoms must be placed in equivalent general positions making two similar one-dimensional chains. The first chain is localized in the vertex of the unit cell, and it is formed by Zn4–Zn4 coordinate bond motifs that propagate along the 3_2 screw axis, as is possible to see in Figure 8(b). This representation was performed by TOPOS program package [23]. The second chain built by Zn1–Zn2–Zn3 is replicated three times, by the application of the symmetry screw axis. Thus, the unit cell contains four chains that interact by hydrogen bonds with water molecules. The pyrrolidine ring of the ligand is represented with a solid line for clarity. In addition, each chain related by symmetry equivalence is illustrated with different colours in Figure 8(a).

Comparing the LISZn2 conformation with the LIS, conformation was realized [6]. The more important dihedral angles observed in dehydrated lisinopril are 175.7(4)° (C14-C15-C16-C17), 179.6(2)° (C9-C8-C7-C1), −5.2(3)° (N22-C26-C27-O28), −76.8(1)° (O21-C20-C14-N13), 0.26(1)° (O21-C20-N22-C26), −69.3(2)° (C16-C17-C18-N19), and −17.5(4)° (N13-C9-C10-O11). The equivalent angles in LISZn2 are 175.4(9)°, −179.2(8)°, −23.1(1)°, −37.7(14)°, 176.8 (2)°, 173.9(3)°, and −38.9(17)° (Figure S4). The first and second dihedral angles of LISZn2 are similar to the angles of the LIS structure. The most important difference was observed in the other dihedral angles, which could be related to the coordination of the LIS to the Zn^{2+} ion. Similar angles in the crystal structure of lis-enzyme have the values equal to 50.6(3)°, −30.7(2)°, −0.6(2)°, 175.3(3)°, and 125.4(2)° [9]. These angles also disagreed with values found in LISZn2 due to the difference in coordination modes of LIS ligand and by the protein environment that also has a very important influence on the conformation of this molecule. The coordination of LISZn2 occurs via the oxygen atoms (carbonyl and carboxylate groups) also as the nitrogen atoms of the

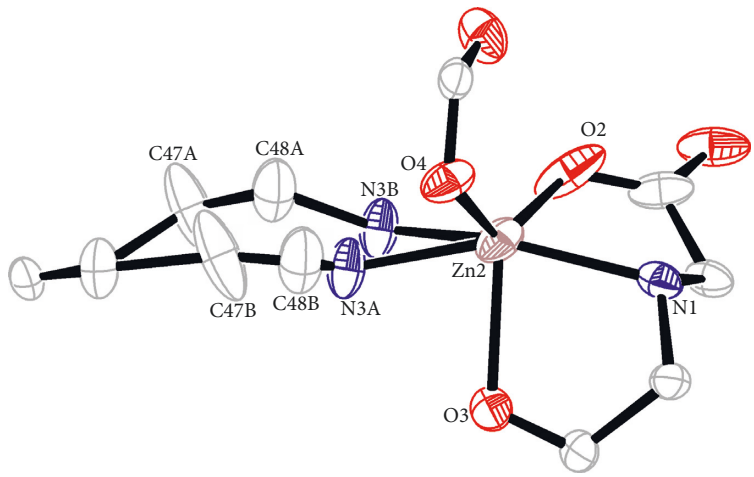


Figure 7: The carbon and nitrogen atoms with order and disorder effects in LISZn2. Anisotropic displacement ellipsoids are drawn at the 30% probability level. In order to clarify, some atoms are omitted.

Table 3: Selected bond lengths (Å) and angles (°) of the LISZn2 compound.

Bond lengths (Å)			
Zn1-O12	2.036(7)	Zn3-O7	2.094(6)
Zn1-N8	2.022(7)	Zn3-N5	2.107(7)
Zn1-O14	2.116(8)	Zn3-O6	2.171(5)
Zn1-N9	2.134(8)	Zn4-O19	1.999(6)
Zn1-O11	2.158(7)	Zn4-N10	2.012(8)
Zn2-O4	2.033(6)	Zn4-O17	2.062(7)
Zn2-O2	2.092(9)	Zn4-N11	2.126(7)
Zn2-N1	2.125(7)	Zn4-O16	2.171(7)
Zn2-O3	2.164(6)	N7-C43	1.314(10)
Zn3-O9	2.005(7)	N7-C40	1.501(14)
Bond angles (°)			
O12-Zn1-N8	99.6(3)	O9-Zn3-O7	127.2(3)
N8-Zn1-N9	157.7(3)	O7-Zn3-N5	79.7(2)
O14-Zn1-O11	125.9(3)	O19-Zn4-N10	100.5(4)
N3A-Zn2-O2	100.8(8)	N10-Zn4-N11	160.9(4)
O4-Zn2-O3	102.0(2)	O19-Zn4-O16	106.9(3)
N3A-Zn2-N1	154.3(6)		
Torsion angles (°)			
C76-C77-C78-C79	175.2(9)	O16-C80-N12-C81	176.7(12)
C67-C68-C69-C70	−179.8(8)	C78-C79-C64A-N10	173.9(3)
N12-C82-C65-O19	−22.9(1)	N11-C67-C66-O17	−38.9(17)
O16-C80-C76-N11	−37.7(14)		

Table 4: Hydrogen-bonding geometry of LISZn2 compound.

D-H···A	D-H (Å)	H ⋯ A (Å)	D ⋯ A (Å)	D-H ⋯ A (°)
N1-H1A ⋯ O21	0.9800	2.0700	3.010(12)	160.00
N5-H5A ⋯ O26	0.9800	2.0800	2.999(18)	156.00
N11-H11A ⋯ O29	0.9800	1.8300	2.759(17)	158.00
O23-H23D ⋯ O25	0.8200	2.0200	2.808(15)	161.00
O24-H24C ⋯ O14	0.8400	2.4100	3.069(15)	135.00

amine groups, whereas that of the complex lis-enzyme occurs only by oxygen atom of the central carboxylate group of lisinopril molecule.

4. Conclusions

In this work, two new Zn^{2+} complexes with the antihypertensive drug lisinopril were obtained from different synthetic routes and structurally characterized by thermal, spectroscopy, and X-ray diffraction techniques. The synthesis of LISZn2 involved solvothermal conditions, while the synthesis of LISZn1 involved only using stirring. The synthetic differences resulted in the formation of two zinc complexes with notorious structural differences once LISZn1 is amorphous while LISZn2 is crystalline. Furthermore, chemical differences were also observed, wherein LISZn1 complex contains perchlorate ions indicating that in this complex, the lisinopril molecule is neutral. On the contrary, in LISZn2, the results show that the lisinopril species are in ionic form. Moreover,

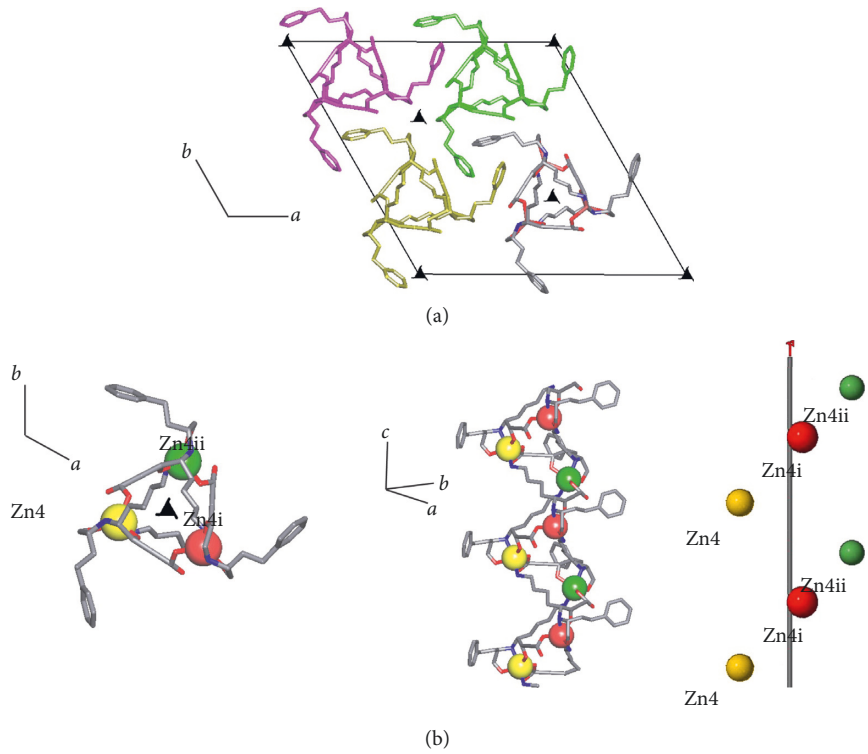


FIGURE 8: (a) Unit cell and space group diagram within four one-dimensional chains for structure. (b) Zn4–Zn4 coordinate bond motifs that propagate along a 3_2 screw axis parallel to the c-axis crystallographic. Symmetry codes: (i) $-y, x-y, z+2/3$ and (ii) $-x+y, -x, z+1/3$. Some atoms were omitted for more clearness.

the LISZn1 presents water and triethylamine molecules in the lattice, while in LISZn2, only water molecules were observed in the lattice. The X-ray diffraction data show that LISZn2 is 1D coordination polymer and exhibits the LIS coordinated to the metal site via oxygen and nitrogen atoms. The interaction between the lisinopril and the Zn^{2+} ion in LISZn2 is similar only in the Zn-O coordination bond. The spectroscopic data confirm that the coordination of lisinopril with zinc ion occurs by carboxylate, carbonyl, and amine groups, which agrees with the crystallographic analysis, and that LISZn1 coordination probably is similar to LISZn2.

Data Availability

Crystallographic data (excluding structure factors) for the structure reported in this paper have been deposited with the Cambridge Crystallographic Data Centre, CCDC, 12, Union Road, Cambridge CB21EZ, UK. Copies of the data can be obtained free of charge on quoting the depository number CCDC-1038137 (Fax: +44-1223-336–033; e-mail: deposit@ccdc.cam.ac.uk, http://www.ccdc.cam.ac.uk).

Conflicts of Interest

The authors declare that there are no conflicts of interest regarding the publication of this paper.

Acknowledgments

The authors are thankful to Prof. Max Siebel from John Hopkins University (Baltimore, USA) for single crystal X-ray facilities and the Brazilian Agencies FINEP and CAPES for financial support and scholarship, respectively. The authors thank the Brazilian Agencies FAPEMIG (CEX-APQ-01919-17) and CNPq (307599/2017-5) for the research financial support.

Supplementary Materials

The supplementary materials for this work contain Figures S1 to S4, where are displayed the vibrational spectra (S1-S2), a section of the polymeric structure of LISZn2 (S3), and dihedral angles of the LISZn2 complex (S4). In Table S1 is listed the atomic coordinates of Zn atoms. (*Supplementary Materials*)

References

[1] F. Nobre, "VI diretrizes brasileiras de hipertensão," *Revista Brasileira de Hipertensão*, vol. 17, no. 1, pp. 4–64, 2010.

[2] Z. Su, L. Chen, Y. Liu et al., "35MHz quartz crystal microbalance and surface plasmon resonance studies on the binding of angiotensin converting enzyme with lisinopril," *Biosensors and Bioelectronics*, vol. 26, no. 7, pp. 3240–3245, 2011.

[3] J. C. Joyner, L. Hocharoen, and J. A. Cowan, "Targeted catalytic inactivation of angiotensin converting enzyme by lisinopril-coupled transition-metal chelates," *Journal of the American Chemical Society*, vol. 134, no. 7, pp. 3396–3410, 2012.

[4] L. Hocharoen, J. C. Joyner, and J. A. Cowan, "N-versus C-domain selectivity of catalytic inactivation of human angiotensin converting enzyme by lisinopril-coupled transition

metal chelates," *Journal of Medicinal Chemistry*, vol. 56, no. 24, pp. 9826–9836, 2913.

[5] R. Mukherjee, A. McCaddon, C. A. Smith et al., "Synthesis, synchrotron X-ray diffraction, and kinetic studies on the formation of a novel thiolatocobalamin of captopril: evidence for cis-trans isomerization in the β-axial ligand," *Inorganic Chemistry*, vol. 48, no. 19, pp. 9526–9534, 2009.

[6] M. Sorrenti, L. Catenacci, D. L. Cruickshank et al., "Lisinopril dihydrate: single-crystal X-ray structure and physicochemical characterization of derived solid forms," *Journal of Pharmaceutical Sciences*, vol. 102, no. 10, pp. 3596–3603, 2013.

[7] M. Miclaus, L.-G. Grosu, X. Filip et al., "Optimizing structure determination from powders of crystalline organic solids with high molecular flexibility: the case of lisinopril dihydrate," *CrystEngComm*, vol. 16, no. 3, pp. 299–303, 2014.

[8] F. Qin, D. Wang, S. Yang et al., "Quantitative determination of lisinopril in human plasma by high performance liquid chromatography—tandem mass spectrometry and its application in a pharmacokinetic study," *Biomedical Chromatography*, vol. 26, no. 6, pp. 691–696, 2012.

[9] R. Natesh, S. L. Schwager, E. D. Sturrock et al., "Crystal structure of the human angiotensin-converting enzyme–lisinopril complex," *Nature*, vol. 421, no. 6922, pp. 551–554, 2003.

[10] E. B. Gonzalez, E. Farkas, A. A. Soudi et al., "Metal complexes of the angiotensin-converting enzyme inhibitor, lisinopril. Solution studies and the crystal and molecular structure of a dimeric copper(II)–lisinopril complex," *Journal of the Chemical Society, Dalton Transactions*, vol. 21, no. 13, pp. 2377–2379, 1997.

[11] K. Fujii, H. Uekusa, N. Itoda et al., "Mechanism of dehydration–hydration processes of lisinopril dihydrate investigated by ab initio powder X-ray diffraction analysis," *Crystal Growth and Design*, vol. 12, no. 12, pp. 6165–6172, 2012.

[12] Rigaku Corporation, *CrysAlisPro*, Rigaku Corporation, Tokyo, Japan, 2015.

[13] R. H. Blessing, "An empirical correction for absorption anisotropy," *Acta Crystallographica Section A Foundations of Crystallography*, vol. 51, no. 1, pp. 33–38, 1995.

[14] G. Sheldrick, "SHELXT-Integrated space-group and crystal-structure determination," *Acta Crystallographica Section A Foundations and Advances*, vol. 71, no. 1, pp. 3–8, 2015.

[15] L. J. Farrugia, "ORTEP-3 for Windows-a version of ORTEP-III with a Graphical User Interface (GUI)," *Journal of Applied Crystallography*, vol. 30, no. 5, p. 565, 1997.

[16] C. F. Macrae, P. R. Edgington, P. McCabe et al., "Mercury: visualization and analysis of crystal structures," *Journal of Applied Crystallography*, vol. 39, no. 3, pp. 453–457, 2006.

[17] G. B. Deacon and R. J. Phillips, "Relationships between the carbon-oxygen stretching frequencies of carboxylato complexes and the type of carboxylate coordination," *Coordination Chemistry Reviews*, vol. 33, no. 3, pp. 227–250, 1980.

[18] S.-L. Wang, S.-Y. Lin, and T.-F. Chen, "Thermal-dependent dehydration process and intramolecular cyclization of lisinopril dihydrate in the solid state," *Chemical Pharmaceutical Bulletin*, vol. 48, no. 12, pp. 1890–1893, 2000.

[19] S.-L. Wang, C.-H. Chuang, and S.-Y. Lin, "pH-dependent coordination of metal–lisinopril complex investigated by attenuated total reflection/fourier transform infrared spectroscopy," *Chemical Pharmaceutical Bulletin*, vol. 50, no. 1, pp. 78–82, 2002.

[20] J. Hinojosa-Torres, J. M. Aceves-Hernández, J. Hinojosa-Torres et al., "Degradation of lisinopril: a physico-chemical study," *Journal of Molecular Structure*, vol. 886, no. 1–3, pp. 51–58, 2008.

[21] H. D. Flack and G. Bernardinelli, "Absolute structure and absolute configuration," *Acta Crystallographica Section A Foundations of Crystallography*, vol. 55, no. 5, pp. 908–915, 1999.

[22] P. Muller, R. Herbst-Irmer, A. L. Spek et al., *Crystal Structure Refinement: A Crystallographer's Guide to SHELXL*, Oxford University Press, New York, NY, USA, 1st edition, 2006.

[23] V. A. Blatov, A. P. Shevchenko, and V. N. Serezhkin, "TOPOS3.2: a new version of the program package for multipurpose crystal-chemical analysis," *Journal of Applied Crystallography*, vol. 33, no. 4, p. 1193, 2000.