This is an Accepted Manuscript, which has been through the Royal Society of Chemistry peer review process and has been accepted for publication.

Accepted Manuscripts are published online shortly after acceptance, before technical editing, formatting and proof reading. Using this free service, authors can make their results available to the community, in citable form, before we publish the edited article. We will replace this Accepted Manuscript with the edited and formatted Advance Article as soon as it is available.

You can find more information about Accepted Manuscripts in the Information for Authors.

Please note that technical editing may introduce minor changes to the text and/or graphics, which may alter content. The journal’s standard Terms & Conditions and the Ethical guidelines still apply. In no event shall the Royal Society of Chemistry be held responsible for any errors or omissions in this Accepted Manuscript or any consequences arising from the use of any information it contains.
Synthesis and structure characterization of zinc and cadmium dipeptide coordination polymers

Andreas Puškarić, a* Ivan Halasza b, Matija Gredičak c, Ana Palčić a, and Josip Bronić a

Two new coordination polymers, Zn(Gly-L-Phe)2 and Cd(Gly-L-Phe)2, (Gly-L-Phe=glycyl-L-phenylalanine), have been synthesized by reaction of Zn(NO3)2×6H2O or Cd(NO3)2×6H2O, NaOH and glycyl-L-phenylalanine. The obtained materials were characterized by infrared spectroscopy, thermal analysis, atomic absorption spectrometry, while crystal structures were determined from powder X-ray diffraction data. Both products crystallize in the chiral monoclinic C2 space group, having similar unit cell parameters, forming a two-dimensional coordination networks, two of which are interpenetrated giving a non-porous structure. Both products show enhanced thermal stability (over 300 °C).

"active sites" (–COO, –NH2 and some side chain groups) where metal cations can be attached to form different MOFs. Because of their disposition/availability and molecule chirality, they have received notable attention as potential ligands. At the same time, great disadvantage of use of the peptides as ligands comes from the fact that the synthesis of crystals from solutions can be hard, due to the thermodynamically non-favorable formation of crystalline phase and its purity [9].

Recently, Rosseinsky and coworkers have synthesized several rigid and flexible metal-dipeptide frameworks ([Zn(Gly-L-Ala)2] (solvent) [10], [Zn(Gly-L-Thr)2]·CH3OH [11], Zn(Gly-L-Ser)2·2CH3OH [12] and Zn(β-Ala-L-His) [13]) with permanent porosity. It was shown that different structures, with distinct adsorption properties, can be synthesized by slightly changing side chain group of the peptide. For example, ([Zn(Gly-L-Ala)2] is flexible and has adaptable porosity while [Zn(Gly-L-Thr)2] exhibits rigid porous framework. Hydrogen bonding, arising from –OH group of threonine, is responsible for stability even after removal of the remaining solvent molecules.

On the other hand, thermal stability as well as consistency in water is one of main research issues in the metal-peptide polymers chemistry.

So, the main idea of this work was to use of relatively large side chain part of dipeptide molecule, with ability to stabilize synthesized product - a new metal-dipeptide MOF of enhanced properties: resistance to water solubility, greater thermal stability, and structure flexibility.

Experimental

Materials and methods

All chemicals were analytical grade and have been used as received, without further purification. Enantiomerically pure H-Gly-L-Phe-OH was acquired from Bachem, Zn(NO3)2×6H2O, ZnCl2, ZnBr2, Cd(CH3COO)2×2H2O, CdI2, Cd(NO3)2×4H2O and NaOH from commercial sources. Powder

---

a Ruder Bošković Institute (RBI), Division of Materials Chemistry, Bijenička 54, HR-10002 Zagreb, Croatia.
b RBI, Division of Physical Chemistry

Electronic Supplementary Information (ESI) available: DOI: 10.1039/x0xx00000x
XRD data were collected on Phillips PW3710 diffractometer with CuKα source. FT-IR spectra were recorded on Bruker TENSOR 37 spectrometer using KBr pellets, in the range from 400 to 4000 cm⁻¹. Thermogravimetric measurements were performed under air, with heating rate of 10 °C min⁻¹ using Shimadzu DTG-60H instrument. Metal content was determined by atomic absorption spectrometry on Perkin Elmer’s AAnalyst 200. Scanning electron micrographs were made by Tescan's MIRA-LMH SEM instrument. Elemental (CHN) analysis was performed on Perkin Elmer 2400 Series II CHNS System.

**Synthesis of Zn(Gly-L-Phe)₂**

Synthesis procedure was adopted from ref. [10] and slightly modified. Dipeptide H-Gly-L-Phe-OH (66.7 mg, 0.3 mmol) was dissolved in 2 mL of aqueous solution of NaOH (c=0.1 mol dm⁻³). 1.5 mL of methanol solution of Zn(NO₃)₂·6H₂O (c=0.1 mol dm⁻³) was added to dipeptide solution. Reaction mixture was diluted with 4 mL of deionized water and 4.5 mL of methanol. Clear reaction solution was transferred to Teflon-lined autoclave, heated for 48 h at 85 °C and left to slowly cool down in the oven. White, thin, platelike crystals were isolated by filtration and washed with small portions of methanol (yield=77%).

**Synthesis of Cd(Gly-L-Phe)₂**

Dipeptide (66.7 mg, 0.3 mmol) was dissolved in 1.5 mL of aqueous solution of NaOH (c=0.1 mol dm⁻³) and 4.5 mL of water was added. Then to dipeptide solution, 6 mL of aqueous Cd(NO₃)₂·4H₂O solution (c=0.025 mol dm⁻³) was added. Immediately after adding cadmium solution to dipeptide reaction solution became milky. Reaction mixture was heated in screw cap vial for 48 h at 85 °C and left to slowly cool down in the oven. White rodlike crystals were isolated by filtration and washed with small portions of water (yield=77%).

**Results and discussion**

**Synthesis**

Solvothermal reaction of Zn²⁺, H-Gly-L-Phe-OH, and NaOH in mixture of water and methanol gave crystalline product [Zn(Gly-L-Phe)]₂ (1). Obtained crystals are composed of thin plates and small pieces of the same material at their surface (Fig. 1), which were not appropriate for single crystal X-ray diffraction measurements. Reaction of cadmium(II), Gly-L-Phe, and NaOH in water gave microcrystalline product, [Cd(Gly-L-Phe)]₂ (2). Rodlike crystals (Fig. 1) were also inappropriate (they are too small) for single crystal X-ray diffraction. To get crystals suitable for single crystal X-ray diffraction, layer-to-layer diffusion of reactants and vapor diffusion of triethylamine into the reaction mixture were performed. However, both methods gave only a microcrystalline product.

The influence of synthesis parameters (temperature, reactant ratio, metal source) was also examined. Increase of the reaction temperature to 120 °C or above in main system (the ratio Zn:dipeptide:NaOH = 1:2:2) causes partial decomposition of dipeptide and gives unidentified product along with ZnO (denoted by * on XRD patterns in Fig. S1).

Increase of the alkalinity of the main system (the ratio Me:dipeptide:NaOH = 1:2:2.5) causes formation of ZnO or Cd(OH)₂ as impurities alongside products 1 and 2, respectively (Figs. S2 and S3). Reaction system with metal to dipeptide ratios of 2:1, 1:1 and 1:2 at lower alkalinity (<2) of the main system (at 85 °C) gives pure crystalline product 1 or 2. Furthermore, source of metal ions was also investigated. For zinc systems, use of chloride and bromide changes the morphology of 1 from platelike to rodlike, while acetate did not affect the morphology of the product. In the case of use of cadmium salts, acetate and iodide salts gave crystalline product 2, without changes in the morphology of the product.

### Chemical composition

Table 1. Chemical composition of the calculated (theoretical values for formulae: C₃₂H₆₃N₄O₇Zn and C₉₂H₆₂N₂O₈Cd) and measured values of the samples obtained by CHN analysis, shown as wt. %

<table>
<thead>
<tr>
<th></th>
<th>C</th>
<th>H</th>
<th>N</th>
</tr>
</thead>
<tbody>
<tr>
<td>Zn(Gly-L-Phe)₂</td>
<td>* 52.03</td>
<td>5.16</td>
<td>11.03</td>
</tr>
<tr>
<td>Zn(Gly-L-Phe)₂</td>
<td>** 51.97</td>
<td>5.59</td>
<td>10.89</td>
</tr>
<tr>
<td>Cd(Gly-L-Phe)₂</td>
<td>* 47.62</td>
<td>4.72</td>
<td>10.10</td>
</tr>
<tr>
<td>Cd(Gly-L-Phe)₂</td>
<td>** 47.55</td>
<td>4.96</td>
<td>9.97</td>
</tr>
</tbody>
</table>

* calculated value
** measured values

Good agreement between theoretical and measured values obtained by CHN analysis are supplemented by thermogravimetric measurements presented in Fig. 2. TG and DTG data shows that both polymers 1 and 2 remain stable to approximately 300 °C, when they start to decompose with biggest mass loss at 347 °C for 1 and 334 °C for 2.
Decomposition of 1 ends at 500 °C, leaving ZnO as final product (16% of initial mass remained), what gives zinc to dipeptide ratio of 1:2. Good agreement for the same ratio was calculated from AAS data; obtained value is 12.7 wt. % of Zn, while theoretical value is 12.8 wt. % of Zn. Decomposition of 2 ends at slightly lower temperature than 1 (460 °C) with 27.4 % mass left (CdO), what gives cadmium to dipeptide ratio of 1:2. Cadmium content in 2 is well corroborated with AAS data; while theoretical value is 12.8 wt. % of Zn. Decomposition of 1 (460 °C) with 27.4 % mass left (CdO), what gives cadmium to dipeptide ratio of 1:2. Cadmium content in 2 is well corroborated with AAS data; obtained value is 12.7 wt. % of Zn, 3400 cm⁻¹ shown in Fig. 3. In the free dipeptide, broad band from 2000 – 2840 cm⁻¹ assigned to combination of symmetric and asymmetric stretching N–H, C–H vibrations, including intramolecular (N–H···Oamide) and intermolecular (N–H···Ocarboxylate) hydrogen bonds [15-18]. Coordination of dipeptide with metal atom, leads to disappearance of band at 2111 cm⁻¹ and aforementioned broad band became much narrower. Doublet at 3254 and 3212 cm⁻¹ in IR spectra of 1 became sharper, unlike in IR spectra of 2. These peaks are assigned to N–H stretching vibration of NH₂ group corresponding to symmetric and antisymmetric modes. Sharp peaks at 3326 and 3337 cm⁻¹ for 1 and 2, correspond to N–H amide stretching vibration, which was not present in free dipeptide, due to the hydrogen bonds. C=O amide stretching and N–H bending bands were shifted from 1686 and 1628 cm⁻¹ in free dipeptide to the 1672 and 1601 cm⁻¹ for 1 and to 1666 and 1601 cm⁻¹ for 2. Carboxylate asymmetric vibration appears at 1570 cm⁻¹, while position of symmetric vibration bond is uncertain due to overlapping of bands.

Microcrystalline samples were gently ground and deposited into Al holder. Diffraction data (graphite monochromated CuKα radiation) were collected for 8 h in the 2θ range 5–80°, and step size of 0.02°. All calculations (peak search, indexing, structure solution and Rietveld refinement) were carried out using the TOPAS software [19].

Diffraction pattern of 1 was indexed giving monoclinic unit cell (a = 29.4580 Å, b = 5.3011 Å, c = 7.4989 Å, β = 95.6024°, V=1168.2 Å³) with figure of merit of 26.07. Systematic maxima absences suggested C2, Cm and C2/m as probable space groups. Following the fact that starting dipeptide is pure chiral compound, C2 space group was selected. Background was modeled with Chebyshev function and peaks shape with fundamental parameters. Unit cell and profile refinement were carried out using Pawley method [20], which gave good agreement Rwp = 0.1507, Rp = 0.1140. Structure solution was performed by the simulated annealing technique, implemented in TOPAS. Dipeptide was input as the rigid body having translational and rotational degrees of freedom with torsion angles as variables. Zinc atom was entered independently with translational degrees of freedom. Simulated annealing gave sensible solution in which Zn atom was found at the special position and linked to dipeptide. Obtained structural model gave a good fit to the experimental pattern, and it was introduced into Rietveld refinement. [21] For Rietveld refinement, the dipeptide moiety was again treated as a rigid body, and y coordinate of Zn atom was refined while x and z coordinates were fixed by symmetry of the special position. Two different isotropic temperature factors were included in refinement: one for the Zn atom and another for all other atoms. Preferred orientation was modeled using spherical harmonics function. Final Rietveld refinement plot is shown in Fig. 4, while crystallographic and refinement data are reported in supplement Table S1.

The same procedure, for the structure determination of Cd(Gly-L-Phe)₂, was used. The diffraction pattern of 2 was indexed giving monoclinic unit cell with following parameters: a = 30.5011 Å, b = 5.3419 Å, c = 7.6336 Å, β = 111.350°, V=1158.4 Å³ (figure of merit 30.18). Systematic maxima absences suggested C centered lattice with C2, Cm and C2/m as probable space groups. Since the starting dipeptide is pure chiral compound, C2 space group was selected. Background was modeled with Chebyshev function and peaks shape with fundamental parameters. Unit cell and profile refinement were carried out using Pawley method which gave excellent agreement Rwp = 0.0684, Rp = 0.0491. Structure solution was performed by the simulated annealing technique, implemented in TOPAS. As in case of 1, dipeptide was input as rigid body.
having translational and rotational degrees of freedom with torsion angles as variables. Cadmium atom was entered independently with translational degrees of freedom. Simulated annealing gave rational solution in which Cd atom was found at the special position and linked to dipeptide. Obtained structural model gave a good fit to the experimental pattern and it was introduced into Rietveld refinement. For Rietveld refinement, the dipeptide moiety was again treated as a rigid body and y coordinate of Cd atom was refined, while x and z coordinates were fixed by symmetry of the special position. Isotropic temperature factors and preferred orientation were included in refinement as in structure determination of 1. Final Rietveld refinement plot is shown in supplement Fig. S4, while crystallographic and refinement data are reported in supplement Table S1.

**Crystal structure of Zn(Gly-L-Phe)_2**

Asymmetric unit of 1 consists of zinc(II) ion bonded to one dipeptide via monodentate amino group of glycyl moiety (Fig. 5). Zinc(II) ion is tetrahedrally coordinated: twice through amino groups of glycine moiety and twice through carboxylate groups of phenylalanine moiety. Both amino and carboxylate groups are in monodentate coordination mode. Zn–N distance is 2.266 Å, and Zn–O distance is 2.128 Å, what is in accordance with distances in similar compounds [11].

![Asymmetric unit of Zn(Gly-L-Phe)_2](image)

Figure 5. Asymmetric unit of Zn(Gly-L-Phe)_2. Color notation: white - H, red - O, purple - Zn, blue - N, grey - C.

Dipeptide ligands bridge zinc atoms giving rise to two-dimensional coordination polymer. Two types of hydrogen bonds connect/stabilize adjacent coordination polymers (Fig. 6 and S5). Hydrogen bond N2–H16···O2 has length of 1.819 Å and bond angle N2-H16-O2 of 161.1°. The second hydrogen bond, N1–H14···O3, which includes terminal amino group and
coordinated carboxylate oxygen, is significantly longer (2.405 Å) with smaller bond angle (150.5°). Those parameters show, that bond N2–H16···O2 is stronger and its contribution to structure stabilization is more pronounced than the N1–H14···O3 hydrogen bond. It is not surprising because O3 atom is already bonded (coordinated) to zinc.

Figure 6. A part of Zn(Gly-L-Phe)₂ network showing directions of H bonds, which are connected to another part of structure (not shown here) making interpenetrated structure. Color notation: white - H, red - O, purple - Zn, blue - N, grey - C.

Coordination polymers propagate in two dimensions forming square grid network with 4,4 topology in which potential pores are occupied by another neighbouring part of peptide chain, thus giving interpenetrated framework (for 1 - Fig S6, for 2 - Fig. 7). In the structure, phenyl rings are oriented in such way, forming hydrophobic sheets, which enhance stability towards water (Fig. S7). At the same time, large side chain groups fill the intramolecular space, reducing microporosity of the crystals.

Crystal structure of Cd(Gly-L-Phe)₂

Asymmetric unit of 2 comprises of cadmium ion bidentately linked to one molecule of dipeptide via carboxylate group of phenylalanine moiety (Fig. S8). Cadmium is hexacoordinated by four dipeptide ligands of which two are bonded through amino groups of glycine, while two carboxylate groups are chelating, as mentioned above. Dipeptide ligands are μ²-bridging as in 1. While distance between Cd and O3 is 2.288 Å, what is in agreement with metal-peptide framework compunds in ref. [22], distances Cd–O2 (2.599 Å) and Cd–N1 (2.485 Å) are little longer than usual, indicating possibly weaker bonding. Hydrogen bonds are also present in this structure. Interaction between N2–H16···O2 (N–H from peptide bond) has length of 1.918 Å and bond angle of 165.4°. Other hydrogen bond is between terminal amino group and O3 having distance of 2.097 Å and bond angle of 150.9°. The similarity of structural elements, and hydrogen bonds, of products 1 and 2 results in isostructural twofold interpenetrated network (Figs. 7 and S6).

Conclusions

Two novel coordination polymers composed of zinc or cadmium and glycyll-phenylalanine were synthesized and characterized using various techniques. Crystal structures were determined and refined from powder diffraction data obtained on an in-house diffractometer. Both coordination polymers are two-dimensional and crystallize in non-centrosymmetric space group (C2) with similar unit cell parameters having isomorphous structures. Due to the hydrogen bonds between adjacent coordination polymers and certain effect of bulky phenyl group of phenylalanine moiety, twofold interpenetrated structure is determined.

Such structural feature has not yet been observed in metal-peptide frameworks, and it is another step towards the design of these materials, providing another insight of influence of the side chain group of peptides on thermal stability of the final products.

Acknowledgement

We appreciate financial support from Croatian Ministry of Science, Education and Sport.

Notes and references

†CCDC 1432895 and 1444302 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12, Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

19 TOPAS version 4.2, Bruker-AXS, Karlsruhe, Germany.
20 G. S. Pawley, J. Appl. Cryst., 1986, 14, 357
Twofold (black, red) interpenetrated network of Zn(Gly-Phe)$_2$ coordination polymer, with hydrogen bonds (green) between neighboring layers.