

Toward the Construction of 3D Dipeptide–Metal Frameworks

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ABSTRACT: Single amino acids have been vastly used to generate metal–biomolecule frameworks. Three-dimensional (3D) frameworks based on di- and tripeptide frameworks remain nevertheless quite scarce. We report the preparation of unique 3D dipeptide–metal frameworks in which both amino acid residues participate in metal coordination and in the construction of the networks.

INTRODUCTION

Amino acids and small peptides have been frequently used, either alone or conjugated with other linkers, to form microporous crystals. Hydrophobic dipeptides crystallize in a peculiar fashion, forming head-to-tail hydrogen bonded helices. The crystal frameworks resist solvent removal ultimately leading to one-dimensional nanotubes.¹ The dipeptide microporous crystals may selectively adsorb small gas molecules opening the door for the development of several relevant applications.² Oligopeptides may also be used as organic linkers to build metal–biomolecule frameworks (MBioFs),³ a subclass of the well-known metal–organic frameworks (MOFs). MOFs are classified as crystalline hybrid material, constructed by connecting organic linkers with metal ions, often resulting in two- or three-dimensional periodic structures.⁴ Endless possibility of metal with organic ligand combinations makes MOFs interesting in a wide range of applications such as catalysis,⁵ separation and selective adsorption,⁶ biomedicine,⁷ and others. MOFs constructed from single amino acids, dipeptides, and tripeptides have been reported to show interesting gas adsorption properties. Rosseinsky et al. tailored Zn²⁺ cations to three Gly-X (Ala,⁸ Thr,⁹ and Ser¹⁰) dipeptides and multi-peptide solid solutions of mentioned X residues.¹⁰ They reported distinct sorption behavior for the produced crystals: while [Zn(Gly-Ala)₂] displays an interesting adaptable structure to the variation of the loading guests, the [Zn(Gly-Thr)₂] shows an enhanced rigidity and robustness facilitating the storage and handling; moreover, [Zn(Gly-Thr)₂] exhibits a good CO₂/CH₄ sorption selectivity. [Zn(Gly-Thr)₂] and [Zn(Gly-Ala)₂] both form one-dimensional (1D) channels through the assembly of 2-dimensional (2D) layers. In the case of [Zn(Gly-Thr)₂] the interaction between adjacent layer is stronger due to the presence of Thr, and the crystal three-dimensional (3D) stability becomes reinforced. As for [Zn(Gly-Ser)₂] the structure changes from porous to a nonporous when removing the guest molecules, which is due to the connection of hydrogen to the hydroxyl side-chain of serine peptide. Very recently a new framework was synthesized by the same group composed of Zn²⁺ and the natural dipeptide carnosine (β -alanyl-L-histidine).¹¹ The imidazole side chain of the histidine provides an extra coordination possibility, which results in a generation of a 3D framework.

Here we have explored two different strategies to attempt to generate dipeptide–metal 3D frameworks: introduce an amino acid that allows side chain coordination (Asp) and the substitution of the metal ion (Zn²⁺ by Co²⁺) to obtain different coordination modes (in number and configuration).

RESULTS AND DISCUSSION

Two new dipeptide–metal frameworks were prepared and isolated in large amounts: [Zn(Gly-Asp)] · H₂O (1) and [Co(Gly-Asp)] · H₂O (2). Crystals of 1 were obtained by reacting Gly-Asp dipeptide with zinc nitrate in a water/methanol solution at pH of 5.6 (see Supporting Information). Colorless slab-like crystals (mono-clinic P2₁) suitable for X-ray diffraction were formed. The crystal structure of 1 was solved using synchrotron radiation at ESRF (see Supporting Information).

There is a 1:1 crystal stoichiometry of Zn^{2+} and Gly-Asp. Each Zn^{2+} ion is penta coordinated, and each dipeptide connects four Zn^{2+} ions through a five-membered glycinate chelate ring, a $\mu_1\text{-O}_4$ coordination mode of the β -carboxylate of the aspartic acid side chain and via $\mu_2\text{-O}_2\text{:O}_3$ connection of the C-terminus carboxylate (Figure 1).

In the *ab* plane, rings formed by two Zn^{2+} centers linked by two dipeptide molecules are continuously fused along the *b*-axis. The rings stack 4.8 Å apart along the *c*-direction remaining linked via the $\mu_2\text{-O}_1\text{:O}_2$ interaction. As a result, 2D layers parallel to the *ab* plane are defined. The conformation of Gly-Asp remains very rigid in 1, and interlayer hydrogen bonds are established between the glycine terminal nitrogen and the free β -carboxylate oxygen of the aspartic acid. Additional interactions are mediated by water molecules trapped in the intersheet plane.

The Asp side chain is in fact involved in metal bridging in 1, but the resulting framework is bidimensional. The perspective that an additional metal-binding site of Co^{2+} could generate a 3D framework prompted the synthesis of 2. The reaction conditions were similar to those of 1 except for the pH, which was adjusted to 6. Purple needle crystals were obtained, which were suitable for X-ray data collection using our in-house equipment (Gemini PX-Ultra, see Supporting Information).

Compound 2 crystallized as orthorhombic crystals belonging to the space group $P2_12_12_1$. The framework is in fact three-dimensional; Co^{2+} is hexa-coordinated, and each dipeptide molecule connects four metal ions, but the Asp residue in 2 is involved in a $\mu_3\text{-O}_2\text{O}_4\text{:O}_3\text{:O}_5$ coordination mode. A unique seven-membered ring formed through the coordination of a Co^{2+} metal ion with alpha and beta carboxylate groups of the Asp residue of the dipeptide (Figure 2b). The Asp side chain bridges two Co^{2+} ions (Figures 2b and 3) expanding the network dimensionality.

The Asp side chains rigidly linked to the Co^{2+} ions bisect what would be 1D pores running along the *b* axis (Figure 3). Water molecules are trapped in these obstructed nanochannels.

The water guest molecules can be easily removed from 1 but not from 2. Thermogravimetric analysis (TGA) of 1 confirms a weight loss of 6.5% (calculated water content 6.7%) in the temperature range of 60–100 °C followed by degradation initiated at 250 °C. The TGA profile of 2 under air indicates a slow decomposition in the temperature range of 115–200 °C with 6.8% weight loss (equal to the fraction of water in the framework) accompanied by decomposition up to 285 °C (Figure 4). The weight loss due to solvent removal and due to decomposition cannot be clearly distinguished. Moreover, overnight regeneration of 2 at 230 °C in atmospheric air resulted in a mass loss of 57%. The remaining sample kept overall crystallinity. X-ray diffraction of one of these crystals revealed that the overall structure is maintained and that the water molecules are partially removed.

TGA of compound 2 was also performed under nitrogen flow to try to delay degradation. The sample showed slower decomposition in nitrogen atmosphere, but a plateau in the temperature profile corresponding to the calculated mass of the desolvated form of 2 was not observed (see Supporting Information).

The effect of temperature on the crystallinity of the two materials was also investigated by variable-

temperature powder X-ray diffraction (VTPXRD, Figure 5). Compound 1 remains highly crystalline up to 360 °C with a notable change in the overall structure around 100 °C (Figure 5), most likely due to the removal of the water molecule of crystallization (in good agreement with the thermogravimetric studies mentioned above). The cobalt structure (2) is slightly less stable: a gradual decrease of the overall crystallinity is observed up to 290 °C (Figure 5, bottom).

The adsorption isotherm of CO₂ at 15 °C of the partially regenerated sample of 2 (overnight regeneration at 230 °C in atmospheric air) was determined (see Supporting Information). It was observed that the CO₂ uptake was marginal. Thus, we concluded that the interesting adaptable sorption behavior shown by some examples of this class of materials^{11,12} is not shared by compound 2 whose structure is presumably too rigid to release all the water molecules and uptake the CO₂.

There are other promising opportunities besides gas adsorption for such expensive raw materials as dipeptide–metal frameworks. It was our aim to synthesize Gly-Asp based MOFs to obtain a precursor material for postsynthetic modification with the Arg-Gly-Asp tripeptide. The Arg-Gly-Asp tripeptide is a well-known linker of $\alpha_v\beta_3$ integrins, a protein overexpressed in many tumors. Such materials would certainly find interesting biomedical applications. There are examples of full ligand exchange¹³ and the synthesis of core–shell MOFs.¹⁴ The second strategy looks more promising for compact structures as compound 2.

CONCLUSIONS

Two new dipeptide-metal frameworks are presented here: [Zn(Gly-Asp)]·H₂O (1) and [Co(Gly-Asp)]·H₂O (2). Compound 2 constitutes a rare example of a 3D framework of this class of materials. The Gly-Asp dipeptide potentiates the generation of 3D frameworks through the extra coordination opportunity provided by the Asp side chain. Compound 2 is, however, incapable of adsorbing appreciable quantities of small guest molecules because water molecules are trapped in its crystal structure and cannot be completely removed without degradation.

As a future plan for biomedical applications, we hope that the use of Gly-Asp as the linker will facilitate the postsynthetic replacing by Arg-Gly-Asp at the surface of the framework.

ASSOCIATED CONTENT

Supporting Information

Synthetic procedure, X-ray single-crystal data collection and analysis, thermogravimetric analysis, powder X-ray diffraction, and gas adsorption. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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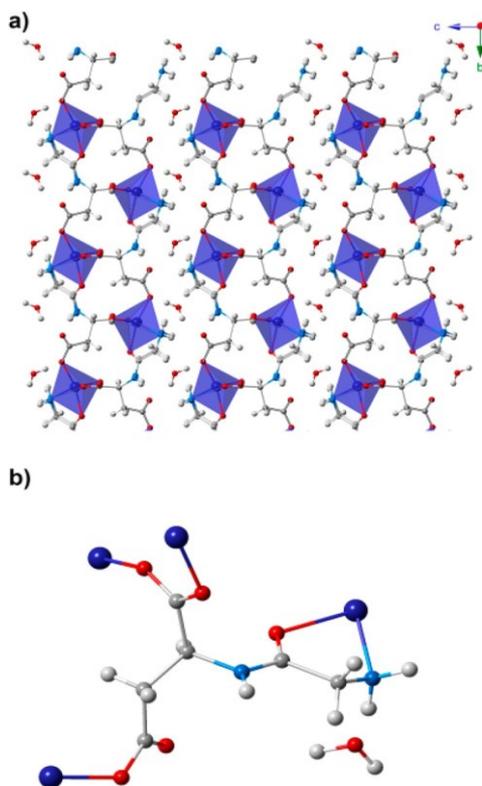


Figure 1. (a) Structure of [Zn(Gly-Asp)] · H₂O (1). (b) Coordination modes of Zn²⁺ ions around the dipeptide Gly-Asp in compound 1. Zn, dark blue; O, red; C, gray; N, blue; H, white.

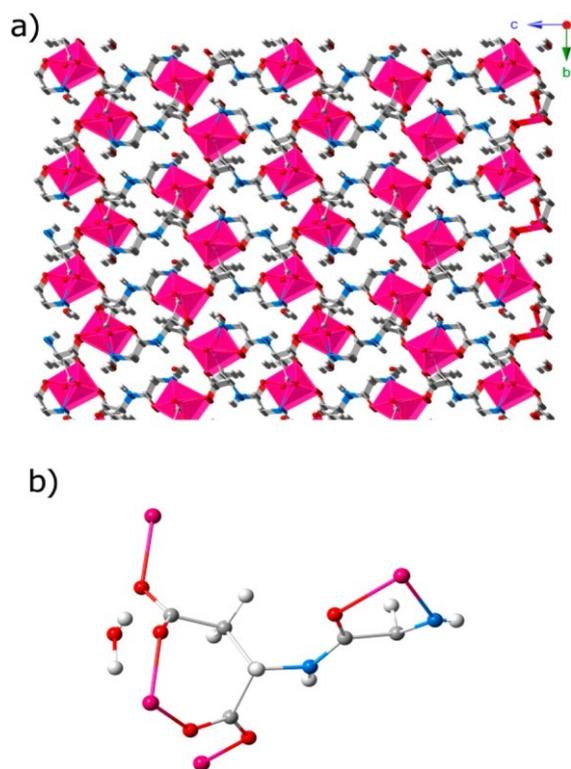


Figure 2. (a) Representation of the 3D structure of [Co(Gly-Asp)] · H₂O. (b) Coordination modes of Co²⁺ ions around the dipeptide Gly- Asp in compound 2. Co, violet; O, red; C, gray; N, blue; H, white.

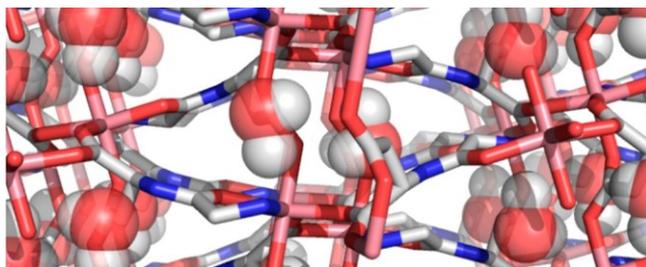


Figure 3. Close view of compound 2 along the *b* axis. The Asp side chains bridge two Co²⁺ metal ions obstructing the channel. Two columns of water molecules are trapped along the *b* direction intercalated between the Asp side chains. The water molecules are shown with 20% transparency, and the H atoms of the crystal framework were omitted for clarity. Co, violet; O, red; C, gray; N, blue; H, white.

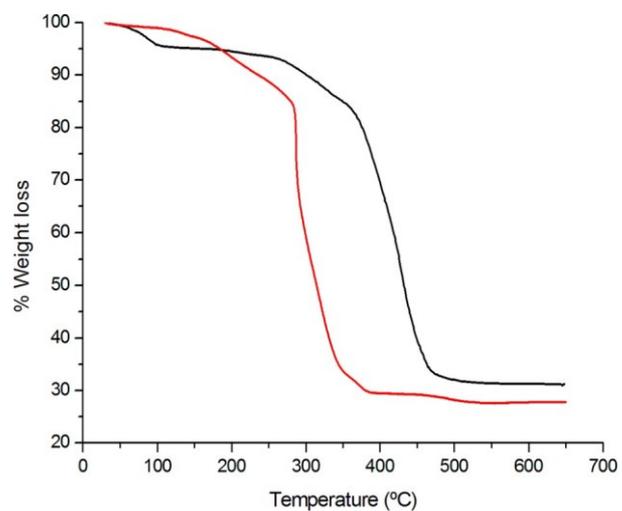


Figure 4. Thermogravimetric analysis of $[\text{Zn}(\text{Gly-Asp})] \cdot \text{H}_2\text{O}$ (1) (black) and $[\text{Co}(\text{Gly-Asp})] \cdot \text{H}_2\text{O}$ (2) (red) under air flow.

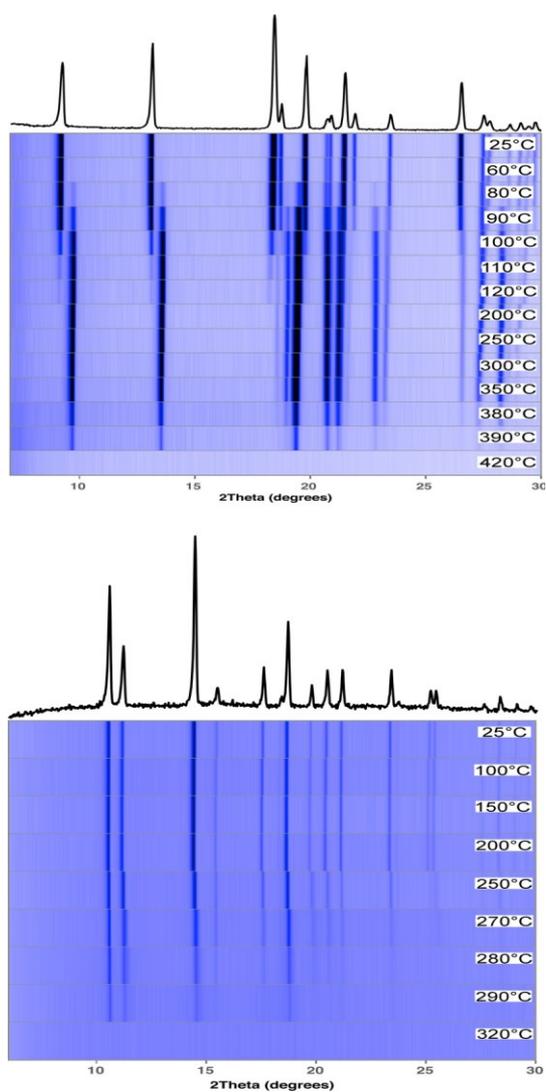


Figure 5. Variable temperature powder X-ray diffraction of $[\text{Zn}(\text{Gly-Asp})] \cdot \text{H}_2\text{O}$ (1) (top) and of $[\text{Co}(\text{Gly-Asp})] \cdot \text{H}_2\text{O}$ (2) (bottom).