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Hydrogen-Bonding-Driven 3D Supramolecular Assembly of Peptidomimetic Zipper

Peng Teng,[†] Zheng Niu,[†] Fengyu She, Mi Zhou, Peng Sang, Geoffrey M. Gray, Gaurav Verma, Lukasz Wojtas, Arjan van der Vaart, Shengqian Ma,* and Jianfeng Cai*

Department of Chemistry, University of South Florida, 4202 E. Fowler Avenue, Tampa, Florida 33620, United States

Supporting Information

ABSTRACT: Hydrogen-bonding-driven three-dimensional (3D) assembly of a peptidomimetic zipper has been established for the first time by using an α/AApeptide zipper that assembles into a *de novo* lattice arrangement through two layers of hydrogen-bonded linker-directed interactions. Via a covalently bridged 1D 4_{13}-helix, drastic enhancement in stability has been achieved in the formed 3D crystalline supramolecular architecture as evidenced by gas-sorption studies. As the first example of an unnatural peptidic zipper, the dimensional augmentation of the zipper differs from metal-coordinated strategies, and may have general implications for the preparation of peptidic functional materials for a variety of future applications.

Metal-coordination or electrostatic interactions driven supramolecular self-assembly[1] has been extensively documented, benefiting from fewer synthetic steps and tunable structures. This approach has been applied in many frontier areas such as catalysis, gas capture, and photosensing.[2] Recently, there has been a growing interest in the exploration of porous hydrogen-bonded supramolecular architectures.[3] Hydrogen-bonded architectures could be easily synthesized and characterized via single-crystal X-ray diffraction. In addition, they possess low energy consuming regeneration process, good thermal stability,[4] as well as promising potential as porous crystalline functional materials.[5] However, most of the core building units in reported H-bonding supramolecular architectures are limited to small organic ligands, and there is a need to explore new types of building units to access *de novo* architectures bearing novel frameworks.

Peptides represent attractive building units for creating ordered supramolecular assemblies as they provide countless chemical and structural diversity and possess inherent functions in the development of catalysis and molecular recognition. Natural peptides have been extensively explored, leading to complex architectures made by the folded structure of the underlying building blocks.[6] Stable, porous scaffolds inspired by ordered architectures in 3D protein lattices have also been synthesized for catalytic reactions that are carried out under nonbiological and harsh conditions.[7] Notably, unnatural peptides have also been explored to form highly ordered supramolecular polymeric architectures,[8] among which, AApeptides (oligomers of *N*-acylated-*N*-aminoethyl amino acids, Figure 1a) have been pursued as a new type of peptidomimetics relying on predictable hydrogen-bond-driven assembly,[9] where AApeptides folding could create ordered supramolecular polymers.

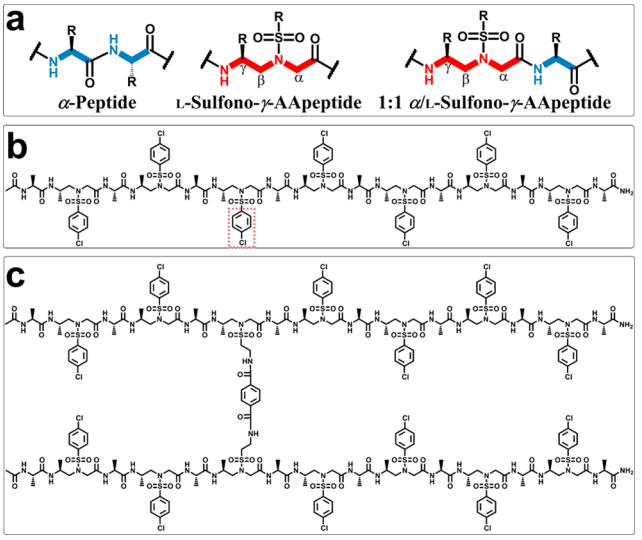

Figure 1. (a) General structures of α-peptides, L-sulfono-γ-AA peptides, and 1:1 α/L-sulfono-γ-AA hybrid. (b) Sequence structure of monomer **1**. (c) Sequence structure of dimer **2**.

Although a π-helix-resembling right-handed 4.5_{16-14} helix composed of D-sulfono-γ-AApeptides and α amino acids was recently discovered,[9] *de novo* foldamers based on L-sulfono-γ-AApeptides with new architecture remains elusive. We envisioned that the hybridization of L-sulfono-γ-AA and L-amino acids can also form new type of crystalline materials with interesting new applications.

Herein for the first time we report the crystal structure of a 1:1 α/L-sulfono-γ-AA hybrid peptide, which reveals a defined hydrogen-bonded right-handed 4_{13}-helix (Figure 1b). Furthermore, the crystal packing suggests a *de novo* type of hydrogen-bonded 1D crystalline unnatural peptidic frameworks (HPFs) held by both head-to-tail intermolecular and intramolecular hydrogen bonding inherent in peptidomimetics. Intriguingly, we are able to boost the dimension and enhance the stability of the corresponding architecture by making a dimeric foldamer by introducing a simple covalent linker. Specifically, the stably

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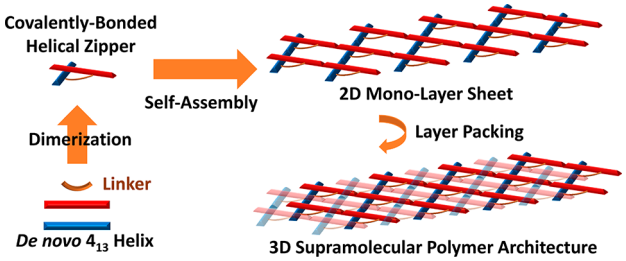
folded peptides were engineered to form protein-like coiled-coil tertiary structure (α/AApeptide zipper, Figure 1c) before assembling into a higher ordered 3D porous framework. Peptide-based porous materials have also been investigated in recent decades, including macrocyclic peptidic cylinders, peptidic MOFs, and dendritic peptides.[10] However, the arrangement of the helical foldamer motif into an ordered porous 3D framework structure remains extremely challenging, given that peptide foldamers with secondary structure stack very tightly due to various side chains appended on the peptide scaffold, thus there is hardly any space available to form permanent porosities. To the best of our knowledge, our α/AApeptide zipper-based 3D porous framework is the first examples of such architectures.

As shown in Scheme 1, the monomer helix features both strong intramolecular and head-to-tail intermolecular hydrogen

Scheme 1. Concept of Self-Assembly Processes from Monomeric Foldamer to 3D Supramolecular Polymer



bonding, and it forms an infinite 1D helical thread in the crystal lattice. However, the crystalline packing of the monomer is too tight to render any porosity. When conjugated by a proper linker at a tuned position, a dimer could be formed and further assembled into an extended 2D monolayer sheet. The sheet could stack on top of each other laterally to form a stable 3D supramolecular polymer architecture. Because of the angle between the covalently linked helical dimer, permanent porosity could consequently result.

Monomer **1** was synthesized on solid phase by using alternative L-sulfono-γ-AA peptide and α-alanine in a 1:1 repeat pattern (Scheme S1) following the standard protocol of Fmoc chemistry, whereas the shorter oligomers bearing diverse side chains were shown to have helical structure by NMR-based solution studies.[11] Gratifyingly, crystals of **1** were readily grown from CH_3CN/CH_2Cl_2 (4:1, v/v) at room temperature with resolution of 1.0 Å and a $P4_12_12$ space group. This conclusively shows that the 1:1 α/L-sulfono-γ-AA oligomers could form stable helical structure in the solid phase. Single-crystal X-ray diffraction revealed a right-handed helical scaffold with virtually identical helical pitch of 5.34 Å and radius of 3.05 Å (Figure 2a). The side chains were almost perpendicular to the helical axis and pointing away from the peptide axis. More importantly, the crystal structures also revealed a neat and uniform 13-hydrogen bonding pattern between the backbone carbonyl group of each residue and the amide N−H of the fourth residue ($i + 3 \rightarrow i$ hydrogen bonding) with distance of 1.95−2.11 Å (C═O···HN). Herein the 4_{13}-helix is designated for this class of helical foldamers. It should be noted that the final refined model showed the presence of translational disorder, which led to apparent "infinitely polymeric" helices with (pseudo)-2_1 screw symmetry axis oriented along [100] and [010] crystallographic directions.

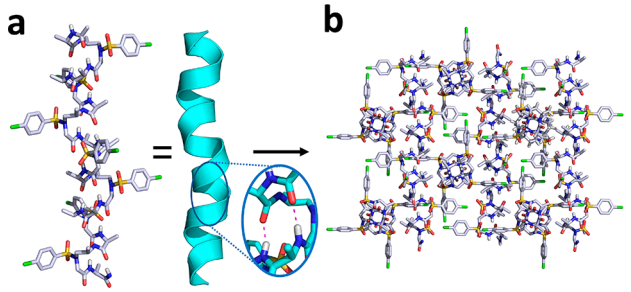


Figure 2. (a) Crystal structure of monomer **1** stabilized by intramolecular hydrogen bond (magentas dashed line in inset). (b) Crystal packing model of **1**. The disordered acetonitriles are excluded from the crystal lattice of **1**.

Despite the fact that monomer **1** forms stable secondary structure, with heavily disordered acetonitrile molecules occupying void spaces between the peptides, no permanent porosity was observed (Figure 2b). Noncovalent metal coordination has been extensively used to build up coiled-coil structures where peptide self-assemble into ordered supramolecular architectures but mostly without any functionality of porous materials,[12] whereas the assembly of covalently linked coiled-coil structures could be distinct from those held by metal coordination. Indeed, the 3D supramolecular frameworks based on covalent-bonding stabilizing coiled-coil peptidomimetic structures have been rarely reported so far. To test our hypothesis, sequence **2** (Figure 1c), which is the dimer of **1** linked at the sulfono side chain, was synthesized.

Dimer **2** was synthesized straightforwardly by dimerization of dimer **1** at the third sulfono side chain using terephthaloyl dichloride in the presence of DIPEA at room temperature (Figure 3, Scheme S2). To gain atomic level structural

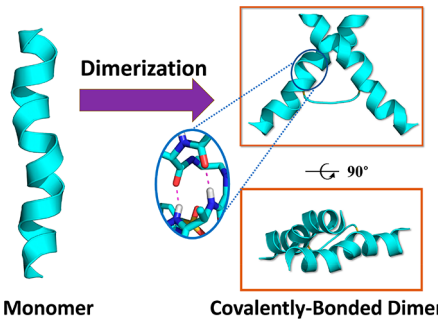


Figure 3. Cartoon representation of X-ray crystal structures from monohelix **1** to the covalent-bonded zippered dimer **2**. Dashed red lines highlight the intramolecular hydrogen bond in dimer **2**.

information between monomer **1** and dimer **2**, **2** was also subjected to single crystal growth. Crystals of **2** were obtained from a mixed solvent of THF/CH_3CN (1:1, v/v) at room temperature, and crystallization occurred in space group $P2$. Single-crystal X-ray diffraction reveals a right-handed helical scaffold with helical pitch of 5.34 Å and radius of 3.05 Å, the same as that of monomer **1**. However, held through covalent amide bonding, the dimer revealed a rare zipper-like tertiary structure, with an angle of 80° between two helical strands. Through extensive head-to-tail intermolecular hydrogen binding (1.98−2.03 Å (C═O···HN)), a stable two-dimensional (2D) supramolecular network was formed across the pseudorhombus with a diagonal distance of 33.4 Å (Figure

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4a). The combination of intermolecular and intramolecular hydrogen bonding renders the dimer **2** as a stable coiled-coil

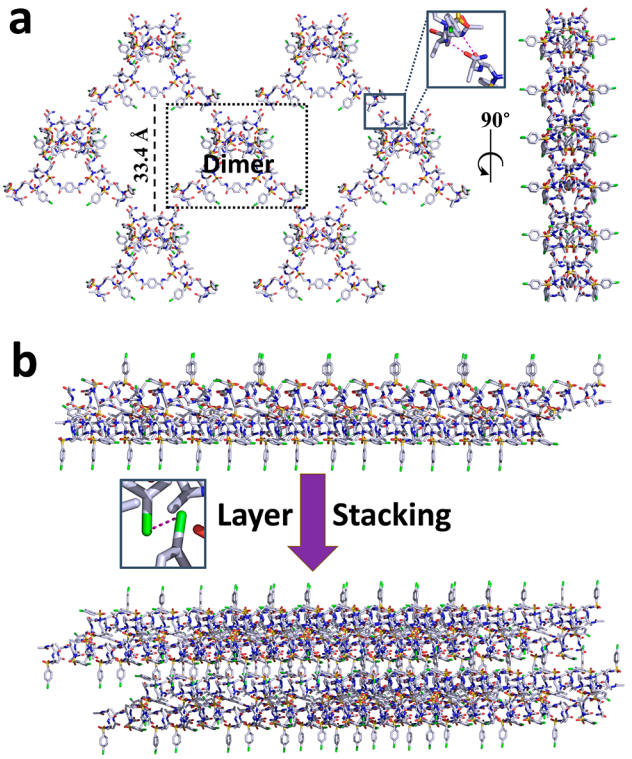

Figure 4. (a) 2D supramolecular network of dimer **2** (shown in dashed black box) formed through 2D self-assembly in terms of intra/intermolecular hydrogen bond interactions (magentas dashed line in inset). Acetonitriles and THF are excluded from the crystal lattice of **2**. (b) Adjacent 2D supramolecular networks in the 3D network were packed laterally and held by the C—Cl···Cl—C halogen bond and hydrophobic interactions. Inset: representation of C—Cl···Cl—C halogen bond (magentas dashed line).

peptidic structure. A second layer of the 2D supramolecular network stacked on top or down laterally, with the joint part of the scissor located in the center of the pseudorhombus (Figure 4b), making the space across the rhombus reduced to 1.0 and 0.8 nm. The dimers between adjacent layers were also held by two weak C—Cl···Cl—C halogen bonds with a distance of 3.2 Å and interaction energy of −2.0 to −2.8 kcal/mol per halogen bond. These interaction energies (Table S5) were estimated from high level DFT calculations of the difference in interaction energies between clusters of 4-chlorobenzenesulfonamide and benzenesulfonamide molecules in the configuration of the crystal structure. In addition, hydrophobic interactions between side chains on the adjacent dimers further stabilized the layers.

Further investigation revealed that the stacked 3D supramolecular polymer, propagated by multiple interactions, including hydrogen bonding, C—Cl···Cl—C halogen bonding and hydrophobic interactions, demonstrates an ordered pseudorhombus architecture (Figure 5a). The evenly distributed porosity was formed in the space of the scissors (Figure 5b,c). This outcome is agreement with our expectation, and prompted us to investigate potential applications of this porous supramolecular peptidic polymer.

Low-pressure gas adsorption isotherms were measured to investigate the adsorption and porosity properties of monomer **1** and dimer **2**. As shown in Figure 6a, monomer **1** exhibits little

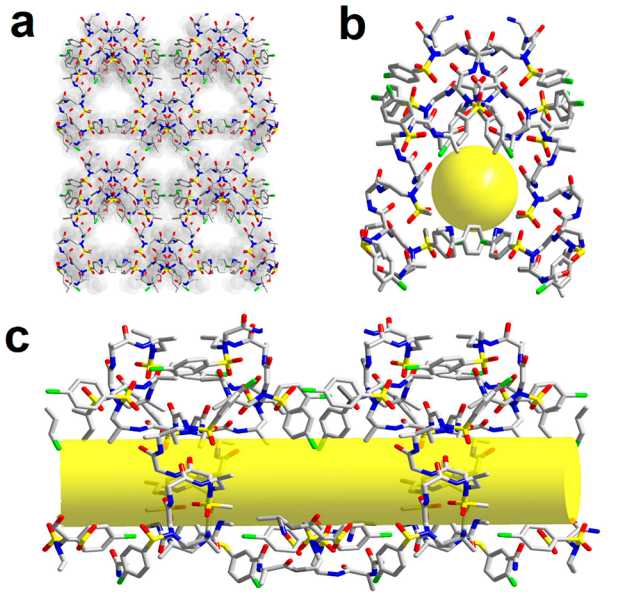

Figure 5. (a) Three-dimensional supramolecular network of dimer **2** formed through 3D self-assembly in terms of intra/intermolecular hydrogen bonding and interhelical C—Cl···Cl—C halogen bonding interactions. Acetonitriles and THFs are excluded from the crystal lattice of **2**. (b) Space-filling model of dimer **2**. (c) Porous architecture formed by dimer **2**.

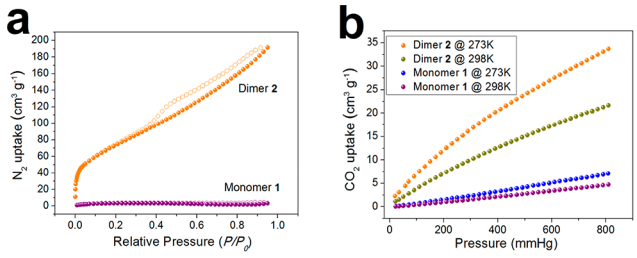

Figure 6. (a) N_2 adsorption isotherms of the monomer **1** and dimeric zipper **2** at 77 K. The solid and hollow circles stand for the adsorption and desorption isotherms, respectively. (b) CO_2 adsorption isotherms of the **1** and **2** at 273 and 298 K.

N_2 uptake amount at 77 K, which indicates poor porosity of monomer **1**. In contrast, the N_2 isotherm of dimer **2** at 77 K shows the obvious microporous adsorption behavior, with a Brunauer−Emmett−Teller (BET) surface area of 234 m^2/g. Therefore, the induced covalent bond in dimer **2** significantly enhances the stability of the porous structure. A similar trend of improvement was also observed for CO_2 uptake at 273 and 298 K. Given the covalent bond between the chains and multiple hydrogen bonds in/between the chains, dimer **2** can achieve a CO_2 uptake under 1 bar of 21 and 32 cm^3/g at 298 and 273 K respectively, compared with 4 and 7 cm^3/g at 298 and 273 K for monomer **1**. Given the limited N_2 uptake by the dimer **2**, the separation ratios of CO_2 versus N_2 were calculated from the ratio of the initial slopes of the adsorption isotherms, resulting in a ratio of 62 at 298 K. Consequently, the weave strategy provides an efficient route to remold the unstable compound as a stable porous material for separation applications.

In summary, we have reported the first example of an unnatural crystalline 4_{13}-helical foldamer constituted of L-sulfono-γ-AA/α-amino acids, stabilized by both intramolecular and intermolecular hydrogen bonding, and with a unique

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secondary structure, in which the side chains were arranged in a highly ordered orientation. More intriguingly, dimerization of the 4_{13}-helix through covalent bond at deliberately selected position formed a stable α/AApeptide zipper, with a unique tertiary structure based on the L-sulfono-γ-AA scaffold. The high-resolution crystallographic structure of the dimer revealed intriguing 3D self-assembly driven by intra/intermolecular hydrogen bonding and C—Cl···Cl—C halogen bonding to form a stability-enhanced novel porous supramolecular polymer architecture that exhibits promising gas adsorption properties. Our finding paves a new way for the supramolecular assembly of synthetic tertiary peptides or other building units into novel architectures with enhanced stability and discrete functions.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.7b11997.

Synthetic procedures and HRMS for the monomer **1** and dimer **2**; ^{1}H NMR spectra of **1** and **2**; crystal data and structure refinement of **1** and **2**; computational methods; TGA and DSC measurements; low-pressure gas sorption measurements (PDF)

X-ray crystallography for **1** (CIF)

X-ray crystallography for **2** (CIF)

■ AUTHOR INFORMATION

Corresponding Authors

*jianfengcai@usf.edu

*sqma@usf.edu

ORCID

Peng Teng: 0000-0002-7412-9646

Arjan van der Vaart: 0000-0002-8950-1850

Shengqian Ma: 0000-0002-1897-7069

Jianfeng Cai: 0000-0003-3106-3306

Author Contributions

†These authors contributed equally.

Notes

The authors declare no competing financial interest.

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