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MINIREVIEW

Exploring Helical Peptides and Foldamers for the Design of Metal Helix Frameworks: Current Trends and Future Perspectives

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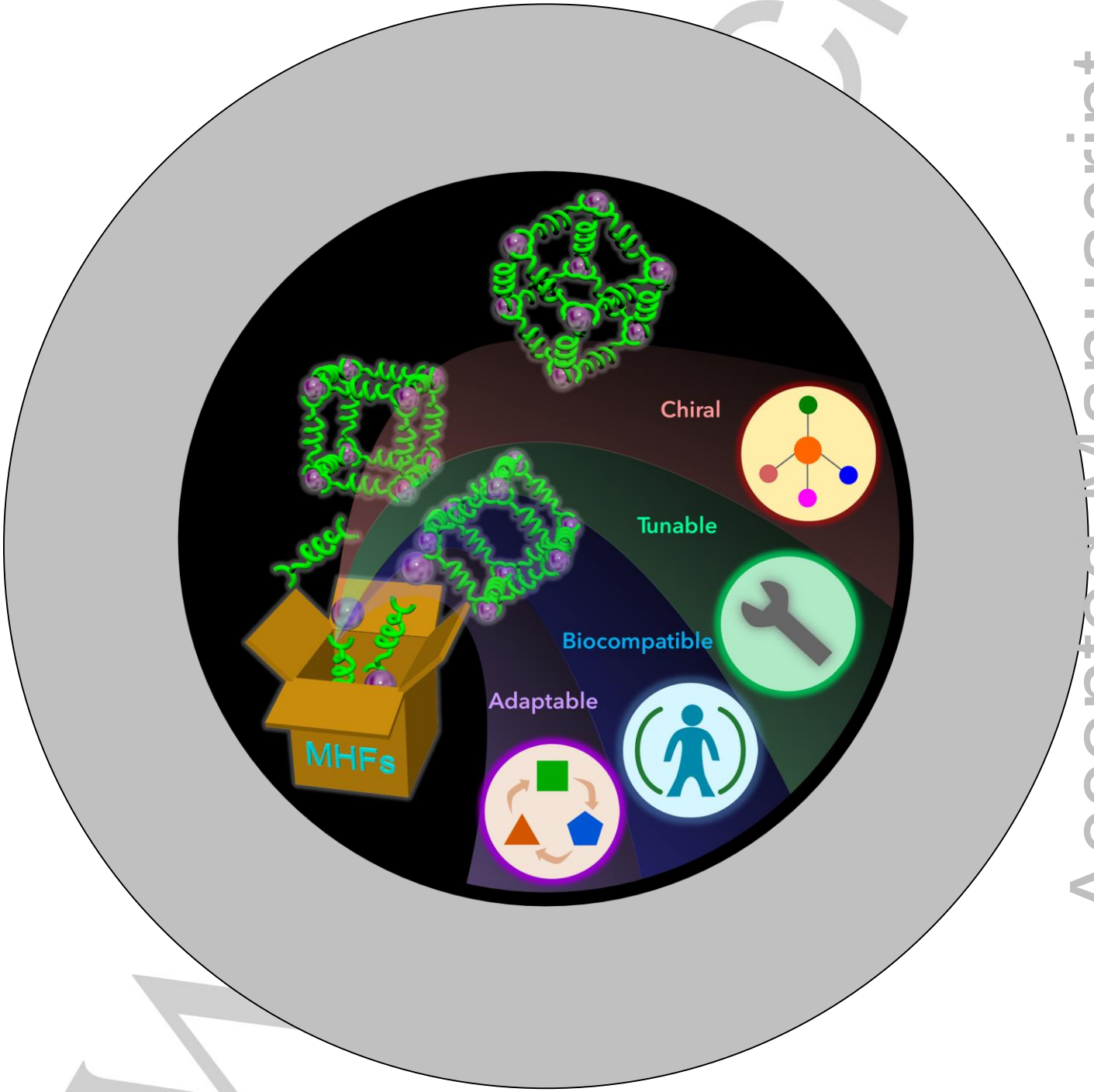

This review summarizes the recent progress of **metal peptide frameworks (MPFs)** comprised of helical peptides and foldamers for future energy storage, chiral recognition, and biomedical applications.

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Abstract: Flexible and biocompatible metal peptide frameworks (**MPFs)** derived from short and ultra-short peptides have been explored for the storage of greenhouse gases, molecular recognition, and chiral transformations. In addition to short flexible peptides, peptides with specifically folded conformations have recently been utilized to fabricate a variety of metal helix frameworks (**MHFs**). The secondary structures of the peptides govern the structure-assembly relationship and thereby control the formation of three-dimensional (3D)-**MHFs**. Particularly, the hierarchical structural organization of peptide-based **MHFs** has not yet been discussed in detail. Here, we describe the recent progress of metal-driven folded peptide assembly to construct 3D porous structures for use in future energy storage, chiral recognition, and biomedical applications, which could be envisioned as an alternative to the conventional metal-organic frameworks (MOFs).

1. Introduction

Metal-organic frameworks (MOFs) are crystalline, porous coordination polymers built from metal-based nodes (typically metal ions or clusters) bridged by organic linkers.[1-3] The careful selection of metal ions and organic ligands has led to the discovery of two-dimensional (2D) or three-dimensional (3D) extended porous architectures with high internal surface area and high thermal and chemical stability. These intriguing properties of the MOFs make them ideal candidates for a variety of applications such as gas sorption,[4] molecular separation,[5] energy storage,[6,7] chiral recognition,[8,9] catalysis[10,11], and drug delivery.[12,13] Detailed investigations of the extensive database of MOFs indicated that most of the frameworks are composed of metal ions linked by rigid conjugated aromatic motifs.[1-3] Despite their impressive versatility, MOFs generated from rigid conjugated organic templates lack many desirable properties such as conformational flexibility, biocompatibility, and enantioselectivity which is important for biomolecular recognition. In this context, metal-peptide frameworks (**MPFs**), which are fabricated from the higher-order assembly of metal ions and peptides, have several advantages and could be utilized to address the current drawbacks of rigid porous materials.[14-18] Peptides, especially short peptide-based ligands, are attractive as they are inherently chiral and biocompatible.[19-24] In addition, short peptides are easy to synthesize and their metal-dependent higher-order self-assembly can be readily manipulated by simply altering the side chain of the amino acids. For instance, Rosseinsky and coworkers developed a number of **MPF**-based systems to construct porous materials that are adaptable and tunable to capture greenhouse gases.[16-20] Furthermore, because of their intrinsic chirality, peptides can also serve as a template for chiral molecular recognition, typically for chiral separation and transformation of biomolecular materials.[15] However, short peptides comprising **MPFs** have a large conformational space that prevents them from adopting a specific conformational feature, making the construction of crystalline **MPFs** highly challenging. Thus, despite the several benefits of **MPFs**, certain limitations such as very high conformational flexibility and lack of symmetry have hindered their frequent use as crystalline porous materials.[25]

In contrast, longer peptides and peptidomimetics have a higher propensity to form rigid and specific conformations. It has been shown that non-natural synthetic oligomers formed definite and predictable folded architectures which can mimic the structures and functions of proteins (typically, 'foldamers')[26,27] and self-assembled into rigid supramolecular architectures.[28] Moreover, the incorporation of certain homologous non-natural and stereochemically constrained amino acids into native alpha peptide sequences facilitates a folding propensity and allows the formation of stable secondary structures even in extremely short sequences.[29,30] More importantly, these structures are resistant to proteolysis which is highly desirable for biomedical applications.[31]

Recently, inspired by the diverse functions of natural metalloproteins[32,33] and enzymes[34] in living organisms, researchers have attempted to develop higher-order assemblies employing structurally rigid peptides and metal ions.[35,36] In addition, these peptides have also been used to design **MPFs**. The advantage of employing specific structure-based peptides and peptidomimetics (typically, helical peptides, cyclic peptides, and foldamers) in the construction of **MPFs** is pore size adjustability by changing the amino acid side chains.[37] Even more intriguingly, in contrast to short flexible peptides, the pore cannot easily collapse due to the specific rigid conformations of the peptide ligands. Notably, conventional MOFs are remarkably stable to different external stimuli.[38]

In this minireview, we discuss the state-of-the-art of metal-driven helical frameworks that are exclusively composed of helical peptides and foldamers. The review will devote particular attention to how design principles are derived, structural characteristics, and the importance of such frameworks in the storage of clean energy and medical and biological applications.

2. Peptide Secondary Structures and their Higher-order Assemblies

Peptides, which are composed of amino acid chains connected through amide bonds, can adopt many diverse secondary structures upon folding. These secondary structures are primarily classified as helices or β-sheets and show a distinct hydrogen bonding pattern between the NH and CO groups of the peptide backbone.[39] In a β-sheet, two or more β-strands are connected through intermolecular hydrogen bonds and further stabilized by hydrophobic, aromatic, and electrostatic interactions between the adjacent side chain motifs to form an extended sheet (Figure 1a). These extended structures are responsible for higher-order self-assembly of β-sheets into fibrils and are related to a variety of human amyloid pathologies, including Alzheimer's and Parkinson's disease.[40] Despite the connection between the formation of amyloid fibers and a variety of neurodegenerative diseases, such structures also serve a crucial role in nature as cellular and extracellular components.[41] Thus, the majority of amyloid-inspired peptide materials developed to date are fabricated from extended self-assemblies of β-sheets and have shown promising applications in tissue engineering, drug delivery, wound healing, and as potential new energy sources.[42]

β-hairpin is another protein structural motif where two antiparallel β-strands are linked through a loop or β-turn (Figure 1b). A β-turn is typically comprised of a four-residue sequence (denoted as *i* to *i + 3* residues) which are classified as type I, II, and III turns based on the dihedral angles ϕ and ψ of the *i+1* and *i+2* residues. β-

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hairpin peptides are also explored to design functional biomaterials. In the case of β-hairpin, the random coil peptide undergoes intramolecular folding into a folded β-hairpin conformation which is subsequently assembled into β-sheet-rich fibrils.[43] In contrast, alpha-helix (α-helix) is the major secondary structure largely found in globular proteins. The structure of the α-helix conformation is a right-handed screw that constitutes 3.6 residues per turn and 13 atoms are involved in the hydrogen bond pseudo cycle (Figure 1c). A hydrogen bond is formed in every amide N-H proton of the *i* and C=O group of the *i* + *4* residues. Unlike α-helix, the structure of 3_{10}-helix (Figure 1d), which is rarely found in proteins, is described by 3 residues per turn and 10 atoms in the hydrogen bond pseudo cycle between the *i* and *i* + *3* residues. On the other hand, a polyproline-II (PPII) helix is a left-handed helix comprised of repeating proline units found in collagen triple-helix structures. The backbone torsion angles of PPII helix are approximately -75° and 150° and *trans* isomers of their peptide bonds (Figure 1e). In contrast to α and 3_{10} helices, the PPII helix has no internal hydrogen bonding and has 3 residues per turn.

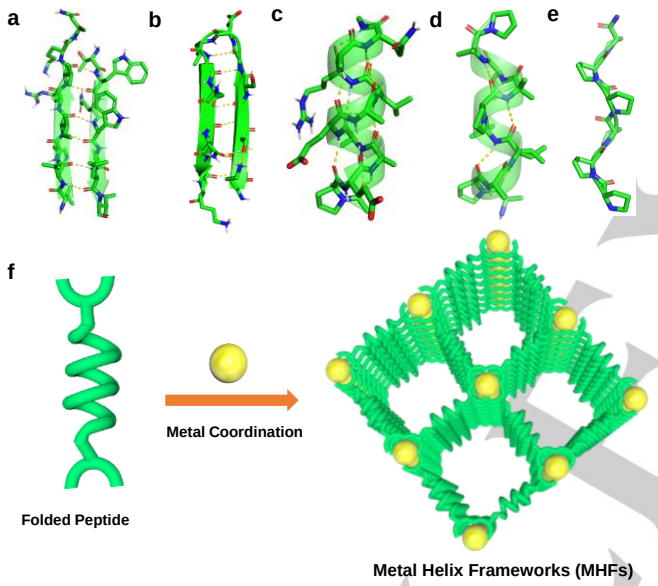

Figure 1: a-e) Representation of secondary structural components of proteins. a) Antiparallel β-sheet (PDB code: 6wmk), b) β-hairpin (PDB code: 1axc), c) α-helix (PDB code: 1h75), d) 3_{10}-helix (PDB code: 7qdi), and e) polyproline-II helix. f) Schematic illustration of metal-induced self-assembly of helical peptides into an **MHF$_s$**.

The β-structures are preferentially assembled into one-dimensional (1D) architectures, such as needle-shape crystals or fibrils, due to their strong infinite intermolecular hydrogen bonding between the strands. However, helical structures such as 3_{10}, α, and PPII helix can form higher-order nanostructures from 1D to 3D due to their different modes of intermolecular organization.[44] The infinite head-to-tail hydrogen bonding interactions and adjacent non-covalent interactions mediated by side chains of the helices are responsible for their higher-order assembly. More intriguingly, unlike the β-structure, the intermolecular organizations of α- helical peptides can be easily manipulated by altering their side-chain interactions. Self-assembling helical peptides are often designed using one of two design principles: they are constructed either from naturally existing helical proteins or by integrating non-natural amino acids with higher helical propensities into the host sequences.[45] The detailed investigation of the structure assembly relationship of helical peptides and foldamers has led to the design of several types of biomaterials with sophisticated functions.[45,46] In addition to the design of divergent supramolecular biomaterials, folded peptides and artificially folded oligomers have recently been used as a template for the construction of metal helix frameworks (**MHFs**) (Figure 1f). Folded peptides participate in the **MHFs** self-assembly process via two important orthogonal driving forces (primarily, folding and metal coordination or metal-directed) to produce a new multi-functional material. Recently, Fujita and coworkers have presented a perspective on concerted folding and self-assembly processes for the design of metal-driven frameworks.[47] The convergence of these two disciplines is relatively new, yet the work published so far shows intriguing potential for the generation of novel functional materials.

3. MHFs Derived from Synthetic Coiled-coil Peptides

Coiled-coil is one of the super-secondary-structure protein motifs where two or more α-helices are coiled together and form a super coil. Coiled-coils are crucial in many biological processes, including protein-protein interaction, transcription, and molecular recognition.[48-51] The canonical coiled-coil structure is described by a heptad repeat, labeled as *abcdefg*, in which *a* and *d* are typically hydrophobic residues and *e* and *g* are hydrophilic residues. The non-polar hydrophobic residues of one helix at the *a* and *d* positions interact with another helix through hydrophobic interactions and thus form a coiled-coil structure. In addition to the hydrophobic interactions, inter helical electrostatic interactions between the charged residues at the *e* and *g* positions also contribute to the formation of coiled-coil structures and to their stability. The residues at the *b*, *c*, and *f* positions have a minor impact on the oligomerization of the coiled-coil structure but afford its thermodynamic stability. Remarkably, coiled-coil peptides are well-known for their fascinating supramolecular assembly functions and are extensively used to design and fabricate artificial responsive biomaterials. The simple design rule and programmable sequence of these architectures make them an excellent candidate for the development of cutting-edge supramolecular materials.[52]

In addition, coiled-coil peptides are also used as a template for the formation of metal-driven self-assembled structures. The appropriate natural or synthetic metal binding residues of the folded peptide linkers can be introduced to the metal-ion-containing solution, where they bind the metal ions and simultaneously form higher-order structures. A large body of research has highlighted the potential of combining metal ions and coiled-coil peptide self-assembly to fabricate programmable supramolecular 1D materials.[53-55] However, only very few studies have described their use for generating 3D **MPFs**. In one such interesting example,[56] Horne and coworkers designed a new class of crystalline materials containing coiled-coil peptides that were intended to form oligomers. To make use of the peptides as ligands for metal coordination, the surface of each of the folded peptides was modified with one or two metal-binding unnatural 2,2′:6′,2″-terpyridine (Tpy, X) functionalized residues (Figure 2a).

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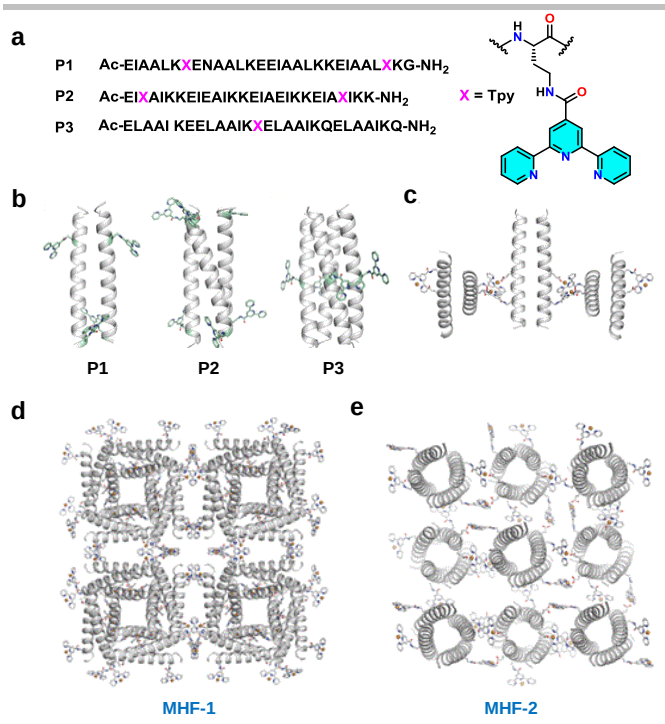

Figure 2: a) Sequence of the coiled-coil peptides **P1, P2,** and **P3** and chemical structure of the metal binding non-natural ligand-containing Tpy unit. b) Crystal structure of dimeric, trimeric, and tetrameric coiled-coil formed by peptides **P1, P2,** and **P3**, respectively. c) 1D coordination polymer formed by coiled-coil peptide **P1** through metal coordination modes. d and e) Extended 3D-framework and 2D-net formed by the coiled-coil peptides **P2** and **P3**, respectively, via Tpy–Cu^{2+}–Glu linkages. Reproduced with permission from ref. 56. Copyright © 2017 American Chemical Society.

Circular-dichroism and high-resolution structural characterization revealed the formation of coiled-coil structures and oligomerization states by two, three, and four units of the folded peptides **P1, P2,** and **P3**, respectively (Figure 2b). A dimeric coiled-coil was formed by peptide **P1** bearing four Tpy residues binding a divalent copper ion (Cu^{2+}) and assembled linearly through a Tpy–Cu^{2+}–carboxylate motif resulting from a glutamic acid (Glu) side chain (Figure 2c), whereas a trimeric coiled-coil structure was organized by peptide **P2** assembled into extended 3D-frameworks, namely **MHF-1**, via six Tpy units through the Tpy–Cu^{2+}–Glu coordination modes (Figure 2d). Peptide **P3** was crystallized in the presence of a Cu^{2+} ion and the asymmetric unit was composed of six helices with one Tpy unit in each. Each Tpy residue was connected to the nearest tetramer of the lattice by a Tpy–Cu^{2+}–Glu linkage, which propagated an extended infinite chain of a two-dimensional (2D) net **MHF-2** (Figure 2e). The intriguing metal-coordination and coiled-coil peptide-directed self-assembly presented in this work could open the way for designing materials of novel functionalities with various potential applications.

4. MHFs Derived from Collagen-inspired and Double-helical Peptides

Collagen is the most ubiquitous structural protein in mammals. and found in a variety of structures including skin, cartilage, connective tissue, blood vessels, and extracellular matrix.[57,58] Collagen is a triple helical structure, comprising three parallel left-handed PPII helices consisting of a repeating unit of proline-hydroxyproline-glycine (Pro-Hyp-Gly) intertwined with each other to form a right-handed bundle. The widespread acknowledgment of the role of collagen fibrils in the extracellular matrix has fueled the development of collagen-mimicking peptides and the investigation of their self-assembly behavior.[59,60] Furthermore, there is a growing interest in studying collagen higher-order structures via metal-driven self-assembly. Metal ions have been shown to promote the rapid self-assembly of collagen mimetic peptides and form a variety of nanostructures.[61,62] Apart from the functional nanostructures formed by the metal-mediated self-assembly of longer collagen-like peptides,[63-65] it has been recently discovered that metals can stimulate the self-assembly of short collagen-inspired peptides into porous 3D-crystalline materials.

Fujita and co-workers investigated metal-driven self-assembly of short synthetic collagen mimetic peptides.[66] They selected a short peptide sequence of Gly-Pro-Pro, which is a repeating unit of collagen, and modified it at both termini by metal binding 3-pyridyl groups **P4** (Figure 3a). ^{1}H-NMR studies of the peptide ligand suggested conformational flexibility and the presence of three major conformations in solution.

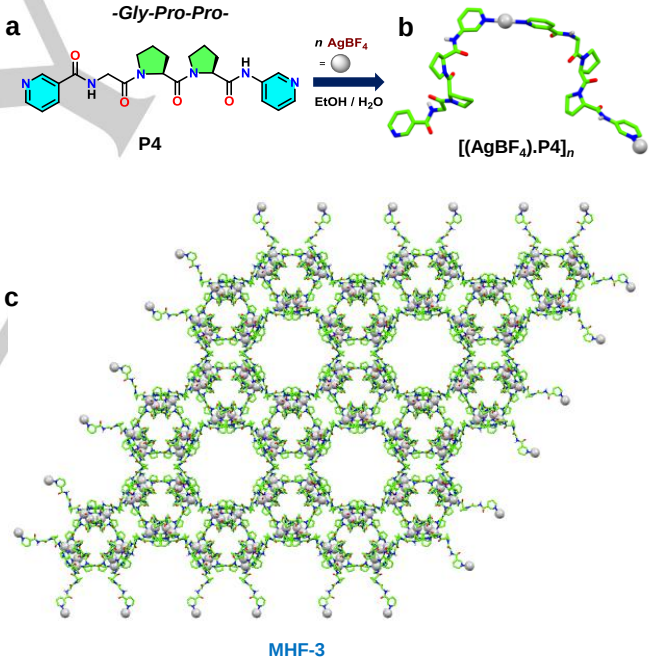

Figure 3: a) Chemical structure of the Gly-Pro-Pro ligand and formation of the complex in the presence of $AgBF_4$. b) Coordination modes of the $[(AgBF_4)\cdot\mathbf{P4}]_n$ complex. c) A 3D porous structure showing the higher-order arrangement along the *c*-axis of the $[(AgBF_4)\mathbf{P4}]_n$. Reproduced with permission from ref. 66. Copyright © 2020 WILEY-VCH Verlag GmbH & Co. KGaA, Weinheim.

Circular dichroism studies further demonstrated the conformational denature of ^{3}Py-Gly-Pro-Pro-^{3}Py. However, X-ray single crystal diffraction analysis of a metal complex resulting from Ag^+ coordination revealed that the peptide was folded into the PPII conformation. The average dihedral angles φ and ψ extracted from the single crystal analysis closely resembled regular PPII helices. The peptide ligand was connected through

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the nitrogen atoms of the pyridyl (Py) motif appended at both termini and leading to the formation of Py-Ag^{+}-Py coordination modes (Figure 3b). Furthermore, the entanglement of the PPII helical peptide chain produced the 3D-honeycomb framework **MHF-3** with two distinct chiral channels of different pore diameters (Figure 3c). The authors also investigated the chiral recognition ability of the larger channel, ~2.2 nm in diameter, which was found to encapsulate the R-isomer of 1,1′-bi-2-naphthol over the S-isomer, with 48% enantiomeric excess. In addition, the larger channel demonstrated an excellent molecular recognition ability of larger biomolecules. For instance, maltopentaose, a linear pentasaccharide molecule comprised of five D-glucose units, was encapsulated within a channel through strong hydrogen bonding between the hydroxyl group of the maltopentaose and the amide carbonyl residue of the peptide.

A subsequent study by the same authors demonstrated that the different pore sizes and symmetry of porous framework can be generated by altering the counter anion of the metal and by a slight modification of the peptide ligand.[67] The authors showed that upon complexation with $AgTf_2N$, the same ^{3}Py-Gly-Pro-Pro-^{3}Py ligand formed a 3D-framework with a different structural topology. In contrast to the hexagonal honeycomb framework observed in the previous study upon complexation with $AgBF_4$, two square-shaped pores, ~1.5 nm × 1.5 nm and ~1.4 nm × 1.4 nm, were observed, while the peptide ligand retained its original conformation. Further, engineering the interior dimension of the pores was also achieved by modification of the N-terminal pyridine with a fluoro and hydroxypropyl group. These findings demonstrate the significance of the secondary structure of peptide ligands and metal-driven coordination self-assembly in the generation of 3D-frameworks with a variety of structural topologies and functional properties.

Inspired by their previous finding, which showed that chiral 1,1′-bi-2-naphthol could be successfully trapped in the host **MPF** comprised of ^{3}Py-Gly-Pro-Pro-^{3}Py and $AgBF_4$, the group demonstrated a direct observation of chiral guests trapped within metal–peptide porous frameworks using X-ray single-crystal analysis (Figure 4). The authors judiciously redesigned the peptide ligand by replacing the flexible Gly residues with stereochemically constrained 2-aminoisobutylic acid (Aib) residues (**P5**). By complexation with silver ions, the peptide ligand assembled into A_2B_2 rectangular (cross-sectional pore size: 1.8 x 0.7 nm^2) porous network structures (**MHF-4**) where two conformers of the peptide were present (Figure 4b and 4c).[68] The dimethyl groups in each Aib residue imposed steric restrictions that distorted the normal PPII helix structure. Interestingly, the authors were also able to show the encapsulation of various types of guest molecules such as chiral alcohol and ketone within the porous framework through various noncovalent interactions. The authors further demonstrated the enantioselective transformation of 1,2-diketone to the corresponding hemiacetal through ethanol adduct in the A_2B_2 porous framework. Hemiacetal formation is rarely observed and identified, yet the authors were able to show that their designed metal-peptide porous framework could trap such a transient intermediate, which was crystallographically observed, and comprised of various non-covalent interactions.

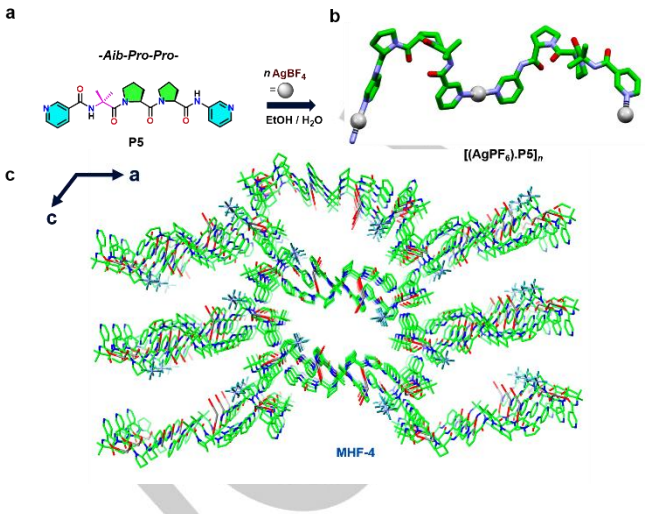

Figure 4: a) Molecular structure of the peptide **P5**. b) Coordination modes of **P5** linked with Ag^{+} ions. The complex formation of **P5** with $AgBF_4$ in this instance led to the formation of needle-shaped crystals of [$(AgPF_6)$.**P5**]n. Single-crystal X-ray diffraction examination of **MHF-4** indicated the existence of the PF_6 anions, which were likely introduced by the use of impurity reagent grade $AgBF_4$. c) Representation of the higher-order packing porous structures. Reproduced with permission from ref. 68. Copyright © 2020 WILEY-VCH Verlag GmbH & Co. KGaA, Weinheim.

The formation of **MPFs** by longer structured peptides was first described by Wennemers and colleagues.[69] They designed and synthesized a hexapeptide composed of six proline residues which is well known to adopt a PPII conformation (**P6**) (Figure 5a). For metal coordination, the N-terminus of the peptide ligand was modified with terephthalic acid and the C-terminus was kept as a carboxylic acid. Importantly, the absence of a classical hydrogen bond donor site in the rigid peptide backbone minimizes the possibility of a self-aggregation driven process, which is one of the major advantages of polyproline sequences over short flexible peptides. Intriguingly, when the peptide was treated with divalent Zn^{2+} ions in the presence of potassium hydroxide (KOH) as a base, followed by 7 days of heating and slow cooling, high-quality diffractive needle-like crystals were formed. Inspection of the X-ray single crystal structure revealed that the peptide adopted a PPII conformation. The asymmetric unit is comprised of two oligoproline ligands, one Zn^{2+} and one alkali metal-ion (typically, K^{+} or Rb^{+}) and one-disordered dimethyl formamide (DMF) solvent molecules. The two oligoproline ligands were found to be different at the N-terminal amide bond orientation (either *cis* or *trans* configured). The emergence of the 2D pleated sheet could be realized through coordination between the *trans*-oligoproline ligand to Zn^{2+} and K^{+} (or Rb^{+}) ions with the N- and C-terminal carboxylic motif in a zig-zag arrangement (Figure 5b). The higher-order arrangement of 2D pleated sheets led to a channel **MHF-5** with a diameter of 3.5 × 7.6 Å (Figure 5c). The key feature of this PPII helix **MPF** is that the peptide ligands interact with each other via non-covalent interactions such as electrostatic and London dispersion contacts, which help to stabilize the entire peptide framework. These findings highlight the effect of the peptide ligand secondary structure on the formation of **MPF** architectures and lay the foundation for designing new **MPFs** based on folded peptide ligands for multifunctional smart-material applications.

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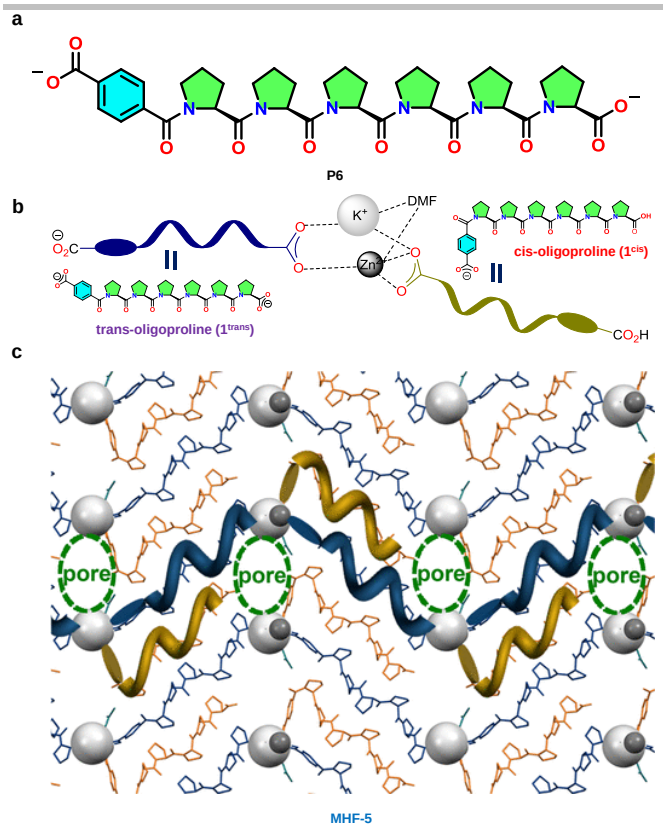

Figure 5: a) Chemical structure of the hexaproline peptide **P6.** b) Coordination modes of the peptide **P6** after complexation of Zn^{2+}. The peptide adopted a PPII conformation and coordinated with Zn^{2+} in a head-to-tail manner. The disordered proline and some of the coordinated DMF atoms are removed for the structural clarity. c) The **P6** ligand adopts two discrete isomers within the 2D stacked pleated sheets and generates a porous structure. Reproduced with permission from ref. 69. Copyright © 2021 American Chemical Society.

In addition to the development of higher-order porous structures through metal-driven self-assembly of short synthetic collagen mimetic peptides, very recently Fujita and co-workers demonstrated the formation of parallel and antiparallel β-double helical structures through metal-driven folding and assembly strategy.[70] From the parent sequence Boc-(L-Val-D-Val)4-OMe (**P7**), which has a tendency to form a double helical structure, a series of octapeptides was designed by replacing one or two L-Val sequences with (3-pyridyl)-L-alanine residues (Figure 6a). Interestingly, the coordination of the pyridyl ligand with metal resulted in different types of double helical structures depending on the position of the peptide ligand-binding sites. For instance, the (3,5)-coordinating peptide ligand **P8** with ZnI_2 resulted in the formation of an uncommon parallel double helical structure. On the other hand, the complexion of Zn^{2+} ions with other pyridyl-containing peptide structures, typically 5,7-coordinating peptide (**P9**) and 3,7-coordinating peptide (**P10**) produced different types of anti-parallel double helices (Figure 6b). Notably, the formation of bundles of β- double helical configurations was facilitated by hydrophobic and π-stacking interactions through folding and metal-coordination self-assembly processes. More intriguingly, a larger porous structure **MHF-6** with a 3-nm diameter was observed in the higher order arrangement of the $(ZnI_2)_2$(**P10**)$_2$ complex through hydrogen bonding at both ends of the helices (Figure 6c).

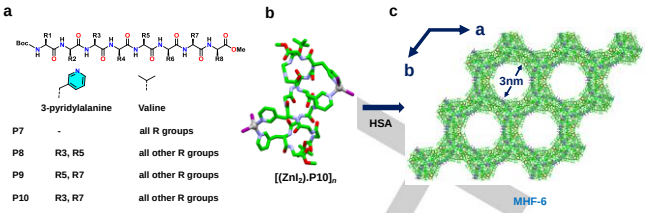

Figure 6: a) Chemical structure of the octapeptides **P7-P10.** b) Coordination modes of the peptide **P10** after complexation of Zn^{2+} ions. The peptide adopted an anti-parallel helical conformation and coordinated with Zn^{2+} ions (side chain of valine and H-bonds are removed for structural clarity). c) Crystal packing structure of $(ZnI_2)_2$(**P10**)$_n$ shows the porous frameworks 3-nm in diameter. Reproduced with permission from ref. 70. Copyright © 2021 WILEY-VCH Verlag GmbH & Co. KGaA, Weinheim.

5. MHFs Derived from Peptide Foldamers

Foldamers are synthetic peptidic or abiotic oligomers or discrete chain molecules that adopt a rigid conformation in a solution state and are capable of mimicking the structures and functions of proteins.[71,72] Peptidic foldamers offer several advantages over their natural counterparts, including high stability, tunable folding, and the ability to modulate the structure-properties relationships. Over the years, several non-natural amino acids have been introduced to mimic the structure and function of proteins such as stereochemically-constrained α-amino acids,[26] β- and its higher homologated amino acids.[31] Among these, β-amino acids are widely studied building blocks. Gellman,[73] Balaram,[29] and others[74] have extensively utilized a variety of cyclic and acyclic β-amino acids to design diverse folded β-peptides that can mimic the secondary structure of proteins and show improved biostability and potential therapeutic applications. In addition, β-peptides were also shown to exhibit excellent self-assembling properties and form well-ordered nanostructures.[75] Moreover, helical β-peptides have also been used for metal coordination to form complex structures that exhibited enhanced catalytic properties.[76] More recently, β-peptide foldamers have been utilized as adaptable spacers for the design of a variety of **MHFs**.

Lee and coworkers designed a series of β-peptides **P11-P14** comprised of *trans*-2-aminocyclopentanecarboxylic acid (*trans*-ACPC) modified with 4-pyridyl moieties at both the N- and C-termini for metal-binding coordination (Figure 7a).[77] Single crystal structures of the shorter oligomers **P11 to P13** in the absence of metal revealed a right-handed 12-helical conformation stabilized by *i* to *i+3* C=O···H-N intramolecular hydrogen bonds while the **P14** hexamer showed an unusual 16-helical conformation. Complexation of the **P11** trimer with Ag^+ revealed the presence of two distinct helical conformations comprising 12- and 8-helix architectures (Figure 7b). The higher-order self-assembly revealed these distinct helical conformations of the peptide ligand to alternatingly bind with the metal-ion via Py–Ag^+–Py linkages to form porous coordination frameworks (Figure 7c). Interestingly, the 3D-porous network **MHF-7** was further stabilized by classical hydrogen bonds of the helices, metal coordination and aromatic pi-stacking of the pyridyl linkers. However, the complexation of the **P12** tetramer with $AgBF_4$ (Figure 7d) in methanol/water solvent systems resulted in a new framework (**MHF-8,** Figure 7e) different from **MHF-7**.

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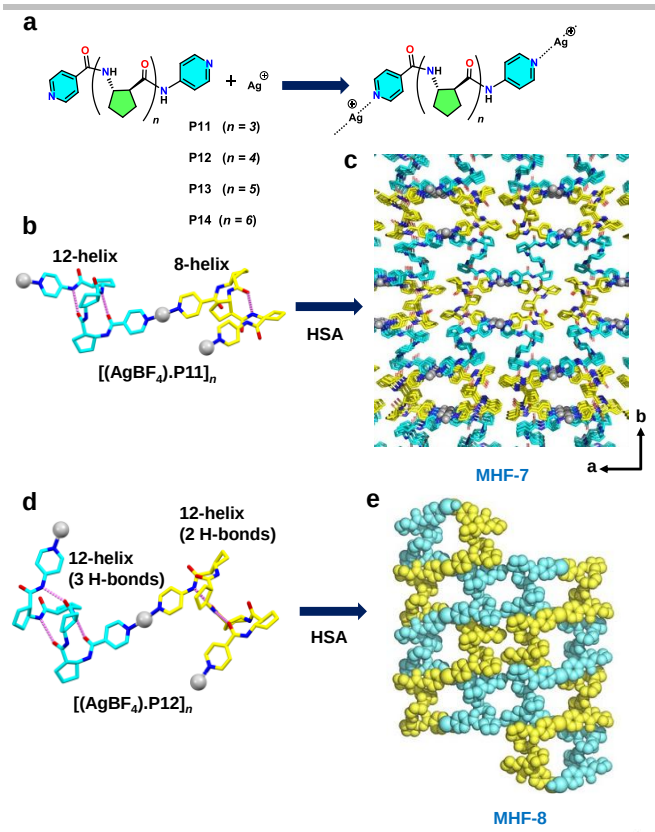

Figure 7: a) Schematic representation of Ag^+ coordination-driven helical polymerization of pyridyl-appended (S, S)-*trans*-ACPC oligo β-peptide foldamers (**P11-P14**). b, c) Representation of (b) the silver complex of the β-peptide foldamer **P11** and (c) its higher-order organization along the c-axis leading to the formation of a nanochannel. d, e) Projection of (d) the metallo β-peptide foldamer **P12** and (e) formation of a double helix comprised of two superhelical coordination polymer chains. Reproduced with permission from ref. 77. Copyright © 2022 WILEY-VCH Verlag GmbH & Co. KGaA, Weinheim.

In the asymmetric unit, two 12-helix peptides were linked by a Py-Ag-Py linear bond. In one 12-helix, three intramolecular hydrogen bonds were observed, while in the other 12-helix, a water molecule formed two hydrogen-bonded structures with the 12-membered helix, resulting in a moderately distorted conformation (Figure 7d). A single-coordination chain of the tetramer was arranged in a right-handed superhelix and the adjacent two tetramer coordination chains were connected via head-to-tail hydrogen bonds and metallophilic interactions to form the double helix structure **MHF-8** (Figure 7e). In contrast, amorphous aggregates were formed following the complexation of Ag^+ ions with the **P13** pentamer and **P14** hexamer. The work highlights the conformational adaptability of metal-driven β-peptide frameworks and opens the possibility of designing new foldamer-based **MPFs** for a variety of applications.

In comparison to β-peptides, γ-peptides are less investigated due to challenges associated with the synthesis of stereochemically pure γ-amino acids.[78] Nevertheless, in their seminal work, Seebach,[79] and Hanessian[80] highlighted the helical secondary structure formation using γ-peptides. Furthermore, Hoffman and coworkers predicted a wide diversity of helical architectures from γ-peptides using quantum chemical computations.[81] Recently, in addition to homooligomers, hybrid peptides comprised of α, γ-amino acids have gained much attention due to the possibility of forming diverse helical structures by altering the stoichiometries and the arrangement of monomer units.[82] The group of Balaram[83] and Gopi[84] reported stable 12-helix secondary structures derived from various types of α, γ-hybrid peptides comprised of various proteinogenic side chains containing γ-amino acids. The striking feature of these hybrid peptides is that the helical structure can be achieved using an extremely short sequence due to the strong helical propensity of γ-amino acids. These remarkable structural features of α,γ-peptides are further used as spacers for the construction of **MPFs**.

Gopi and coworkers designed an ultrashort α,γ-hybrid peptide terminated at both ends with a 4-pyridyl residue.[85] The designed tripeptide **P15** consisted of stereochemically-constrained Aib residues, flexible γ-amino acids and natural leucine residues (Figure 8a). The incorporation of Aib residues promoted the peptide to adopt a helical secondary structure. Crystallographic analysis revealed that the peptide adopted a 12-helix conformation stabilized by intramolecular hydrogen bonding between the *i* and *i+3* residues.

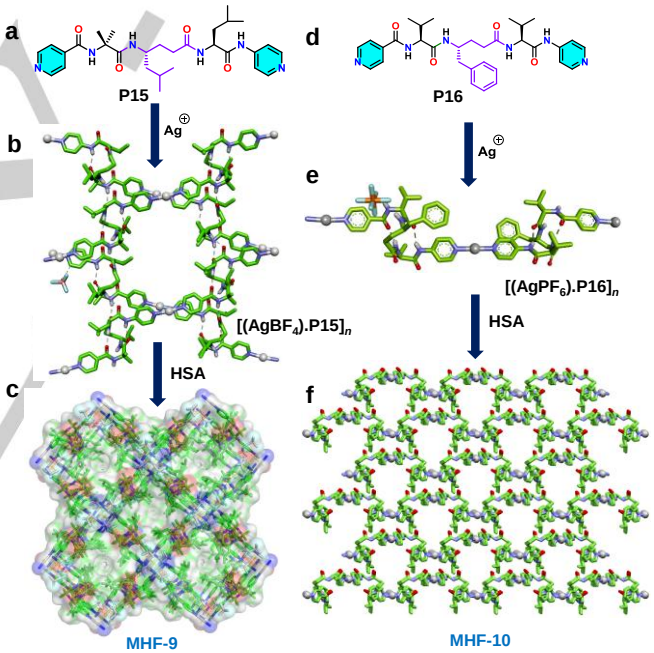

Figure 8: a) Chemical structure of the α,γ-hybrid peptide **P15** ligand comprised of stereochemically constrained Aib residues and terminated by 4-pyridyl residues at both ends. b) Infinite head-to-tail hydrogen bonding along the vertical direction and silver ion coordination mediated polymerization between the helices observed in the higher-order packing of the $[(AgBF_4)\cdot\mathbf{P15}]_n$ complex. c) A 3D porous helical framework formed along the *c*-axis. Reproduced with permission from ref. 85. Copyright © 2019 WILEY-VCH Verlag GmbH & Co. KGaA, Weinheim. d) Chemical structure of the α,γ-hybrid peptide **P16** comprised of β-sheet promoting Val residues and flexible γ-Phe amino acids. e) "Head-to-head" coordination of silver ion of two helices in the crystal packing of $[(AgPF_6)\cdot\mathbf{P16}]_n$. f) The porous 3D helical framework observed after packing along the *c*-axis. Reproduced with permission from ref. 86. Copyright © 2021 WILEY-VCH Verlag GmbH & Co. KGaA, Weinheim.

Complexation of the peptide in the presence of $AgBF_4$ showed that the 12-helix structure in the complex remained intact and two

12-helix peptides were associated in a head-to-tail manner through silver ion coordination and formed a linear coordination polymer. In addition, the two N-terminal amide NH groups and the two C-terminal amide CO groups were engaged in intermolecular head-to-tail hydrogen bonding with other helices (Figure 8b). The infinite silver ion coordination mediated helical polymerization along the horizontal direction and extended head-to-tail intermolecular hydrogen bonds along the vertical direction resulted in a 3D-porous **MHF-9** network with a pore size of 5.9 A° (Figure 8c). Intriguingly, the **MHFs** could capture CO_2 at 195 K, indicating their potential use as future energy storage materials.

Recently, Gopi et al. demonstrated that an ultrashort α,γ-tripeptides can fold into a 12-helix conformation even without steric constraints.[86] They designed an α,γ,α tripeptide **P16** comprising of two β-sheet inducing valine (Val) residues and flexible γ-phenylalanine (Phe) amino acids connected by both ends with metal-coordinating 4-pyridyl ligands (Figure 8d). Surprisingly, even in the presence of two β-sheet promoting Val residues in the backbone, a single γ-amino acid was sufficient to facilitate the 12-helical folding of the hybrid peptide. The hybrid peptide formed metallogels in the presence of Ag^+ and Cu^{2+} ions. Interestingly, crystals obtained from the metallogel matrix of $AgBF_4$ revealed that the 12-helix structure was preserved in the gel phase and two helices were connected by silver ion coordination to form a linear coordination polymer. However, the complexation of $AgPF_6$ led to the formation of a 3D porous coordination polymer **MHF-10** in which two 12-helices were connected in a head-to-head manner (Figure 8e and 8f). This remarkable metal-driven self-assembly of 12-helix peptide templates will stimulate the development of new functional metal-driven foldamer frameworks for a variety of future applications by altering the side chain and length of the peptide sequence.

6. Conclusion and Future Outlook

In conclusion, we have highlighted recent advances in exploiting the helical structure of peptides and peptidomimetics for the development of MOFs. The field of metal coordination and peptide-directed structures self-assembled into porous frameworks is relatively new and may give rise to the significant development of new materials with distinctive properties and functions. In comparison to the large aromatic spacers, the helical peptide and foldamers offer significant advantages in the design of MOFs including conformational tunability, adaptability, biocompatibility, side chain diversity, and processability, thereby increasing the likelihood of overcoming the shortcomings hindering the field of advanced porous materials. In addition, these **MHFs** show an excellent ability to recognize various biomolecules, such as oligosaccharides, from aqueous environments suggesting that they may have potential therapeutic implications in the near future.[66] Furthermore, due to the intrinsic chirality of the peptide frameworks, enantiomeric separation can be more effectively achieved by the highly enantiospecific host-guest interactions, ultimately leading to the development of chiral membranes. In addition, it is intriguing to note that the **MHF** derived from the hybrid peptide foldamer **MHF-9** is capable of adsorbing the greenhouse gas CO_2, which is crucial in the current state of global warming.[85]

In nature, proteins and enzymes are excellent examples of the molecular frameworks which can give rise to diverse functions. Interestingly, the folded conformation is one of the primary contributors to the extraordinary functions of proteins and enzymes. Thus, it is anticipated that complex porous structures produced by metal-induced self-assembly of folded peptides will mimic metalloenzymes and help to catalyze various organic transformations. The chiral porous helical framework also provides an asymmetric environment for various chiral transformations. For instance, the porous framework of **MHF-4** provides an asymmetric environment for the enantioselective transformation of 1,2-diketone to the corresponding hemiacetal.[68]

More recently, metal-organic porous materials have also been investigated as potential drug delivery systems. The perspective of using MOFs for drug delivery applications is intriguing, yet is largely limited by the lack of biocompatible ligand linkers and metal ions.[87,88] In contrast, peptides, which are fragments of proteins, are naturally biocompatible. Therefore, the development of biocompatible porous materials for use in biomedicine is extensively pursued. For example, peptides employed as ligands and appropriately-selected metal ions, which can exhibit less cytotoxicity and immunogenicity, can be utilized for drug-delivery applications.

Another exciting future perspective of these helical frameworks is their application as piezoelectric energy harvesters providing the demanding global energy consumption and technological progression. Traditional energy harvesters based on inorganic ceramic oxides, piezoelectric polymers, and organic and hybrid organic-inorganic materials show excellent energy harvesting performance.[89,90] However, these materials pertain to certain limitations such as the presence of toxic lead and heavy metal content, high density, high stiffness, high-temperature synthesis, and lack of bio-compatibility, hindering their use for flexible and wearable electronic applications.[91] In contrast, bio-inspired amino acids[92], short peptides[93] and ultrashort helical collagen-mimicking peptides[94] have shown great potential for piezoelectric energy harvesting applications due to their diverse structural features, including biosafety, biocompatibility, biodegradability and inherent chirality. Thus, we envision that the future use of metal peptide helix frameworks will not only provide the above advantages but also entails the benefits of helicoidal geometry with excellent stability, sensing, and durability under repetitive mechanical deformation.

Despite the plethora of advantages of longer folded peptides and foldamers in the design of **MHFs**, challenges such as the requirement to synthesize stereochemically pure monomer building blocks for the synthesis of foldamers and complexities associated with the efficient synthesis of longer helical peptides have prevented their widespread application. Furthermore, it is difficult to define specific design principles, such as which particular helical conformation peptide and metal ion would inevitably result in the generation of crystalline porous frameworks. Moreover, since the number of side chains associated with longer folded peptides and foldamers is higher than that of ultra-short peptides, their interference in the formation of pores is always a possibility, hence reducing the likelihood of the development of a porous framework. However, the field of

metal and hydrogen bond-driven helical peptide self-assembly into 3D-crystalline porous frameworks has only recently emerged and is expanding rapidly. As a result, we anticipate significant future advancements such as the establishment of specific design rules, optimizing the method to obtain high-resolution structures, and implementing these highly versatile structures in chemical biology, bio-nanotechnology, and material science.

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MINIREVIEW

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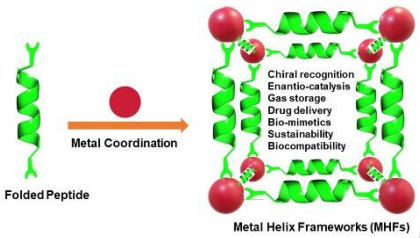
This review summarizes the recent progress of **metal peptide frameworks (MPFs)** comprised of helical peptides and foldamers for future energy storage, chiral recognition, and biomedical applications.



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