Geometrically Precise Building Blocks: the Self-Assembly of β-Peptides

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Peptides comprised entirely of β-amino acids, or β-peptides, have attracted substantial interest over the past 25 years due to their unique structural and chemical characteristics. β-Peptides form well-defined secondary structures that exhibit different geometries compared with their α-peptide counterparts, giving rise to their foldamer classification. β-Peptide foldamers can be functionalized easily and are metabolically stable and, together with the predictable side-chain topography, have led to the design of a growing number of bioactive β-peptides with a range of biological targets. The strategic engineering of chemical and topographic properties has also led to the design of β-peptide mimics of higher-order oligomers. More recently, the ability of these peptides to self-assemble into complex structures of controlled geometries has been exploited in materials applications. The focus of this mini-review is on how the unique structural features of β-peptide assemblies have been exploited in the design of self-assembled proteomimetic bundles and nanomaterials.

Introduction

Foldamers have enormous potential among synthetic self-organizing systems to mimic the regular structural behavior of biomolecules. In particular, foldamers stand out among the structured non-natural polymers because of their capability of adopting discrete secondary structures that can be exploited in the design of a wide range of bioactive compounds (Cheng et al., 2001; Estieu-Gionnet and Guichard, 2011; Guichard and Huc, 2011; Martinek and Fulop, 2012; Seebach et al., 2004).

A major class of peptidomimetic foldamers are those peptides comprising β-amino acids. β-Amino acids differ from α-amino acids in the presence of an additional carbon atom in the amino acid backbone. The two regioisomers of β-amino acids based on the location of the "extra" CH_2 are denoted β^2 and β^3 (Figure 1). While β-amino acids are generally regarded as "unnatural" amino acids, they are present in living organisms and have been identified in plants, microorganisms (Yasumoto and Satake, 1998), and mammals (Griffith, 1986). In comparison with peptides comprised of only α-amino acids, β-peptides exhibit greater chemical diversity, markedly different secondary structural motifs, and much higher resistance to hydrolysis by enzymes (Daura et al., 1997).

The vast majority of reported β-peptide structures are helical with only a few noted exceptions (Daura et al., 2001; Seebach et al., 1999, 2006). The various folding geometries of β-peptides have been described previously, and the reader is referred to a series of excellent reviews (Cheng et al., 2001; Gellman, 1998; Martinek and Fulop, 2012; Seebach et al., 2004; Wu et al., 2008). The regular geometries displayed by β-peptide foldamers, combined with their increased resistance to proteolysis, have made β-peptides an extraordinarily flexible template for the design of proteomimetic bundles and novel materials, and this is the specific focus of this mini-review. The applications in which

β-peptide foldamers have been targeted can be categorized into three general classes of molecules based on their hierarchical structure, as shown schematically in Figure 2. The first category uses peptide monomers in the design of bioactive molecules, specifically inhibitors of protein-protein interactions/receptor action and antimicrobial peptides, but this is not discussed here. The second is derived from the engineered self-assembly of β-peptide foldamers to generate artificial ion channels, helical bundles, and DNA mimics. More recently, nanomaterials derived from the supramolecular self-assembly of β-peptide foldamers have been reported, which opens up exciting new avenues of molecular engineering. These different applications all exploit the persistent helical template to allow tailored design of these foldamers to control their hierarchical self-assembly, which allows for proteomimetic bundles and new nanomaterials, all of which are discussed.

Self-Assembly of β-Peptide Foldamers

The ability of β-peptides to adopt defined secondary structures has attracted significant interest in exploring the conformational capabilities of these foldamers to imitate complex structures found in natural proteins, such as cooperatively folded tertiary and quaternary structures. The ability of these peptides to form shape-persistent structures over a variety of conditions has been the cornerstone of efforts directed toward building peptide architectures, through self-assembly, with the aim of generating a variety of superstructures, including helical bundles, ion channels, and fibers (Figure 2).

β-Peptide Helical Bundles

Gellman and coworkers have established a number of design criteria though a detailed analysis of sequence-structure relationships of β^3-peptides and α/β-hybrid peptides. One of the first examples of a 14-helical bundle assembly was the synthesis and
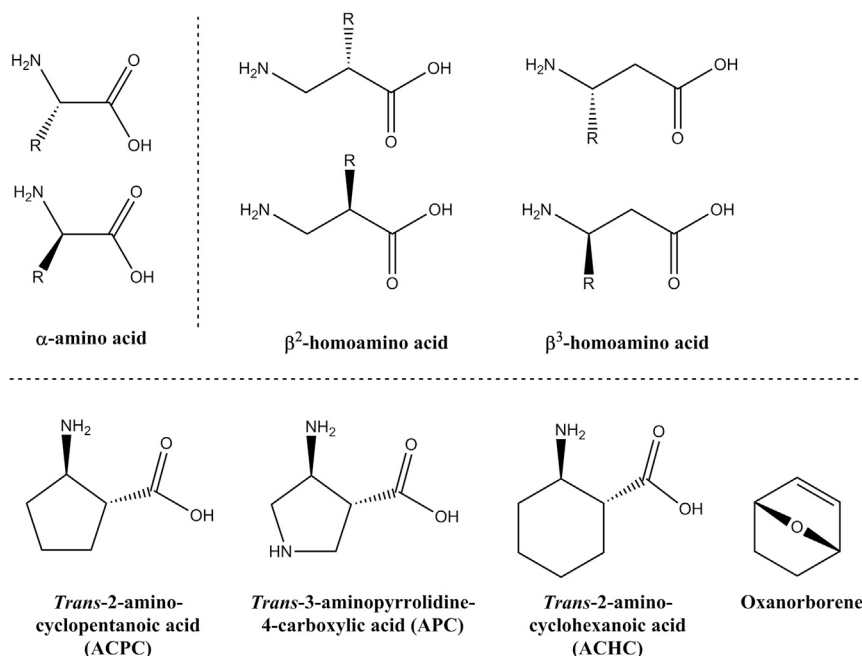
Figure 1. The Structures of α- and Various β-Amino Acids

α-amino acid

β²-homoamino acid

β³-homoamino acid

Trans-2-amino-cyclopentanoic acid (ACPC)

Trans-3-aminopyrrolidine-4-carboxylic acid (APC)

Trans-2-amino-cyclohexanoic acid (ACHC)

Oxanorborene

ated electrostatic interactions across the interface as shown with high-resolution X-ray crystallography. The controlled lateral assembly of 14 helices into tetrameric bundles instead of octameric bundles was also demonstrated by changing the residues of the hydrophobic face from β³-Leu to β³-Val (Goodman et al., 2008). The ability to alter the density of such structures with relative ease allows for the subtle yet directed modification of large structures such as ion channels. In a further study, it was shown that an octameric β³-peptide helical bundle was able to bind two cadmium ions, and this metal binding increased the thermodynamic stability of the complex (Miller et al., 2014). Characterization of the metal binding indicated a cooperative relationship between the two ion binding sites.

assembly of β³-peptides with amphipathic properties (Raguse et al., 2001). They showed that the β³-decapeptide, NH_2-β³-Tyr-(ACHC)$_2$-β³-Lys)$_3$, with two hydrophobic faces consisting of cyclohexyl rings of ACHC and a polar β³-Lys side chain self-assembled to form small soluble aggregates in water. Through sedimentation equilibrium experiments, it was shown that the aggregates were tetrameric and/or hexameric bundles. This group also showed the formation of helical quaternary bundles arranged in a parallel orientation formed by oligomers containing a mixture of α/β-peptides in different combinations in aqueous solution and in the crystalline state (Figure 3) (Giuliano et al., 2009; Horne et al., 2007, 2008, 2009; Price et al., 2010; Raguse et al., 2002). The folded structures were stabilized by close packing of hydrophobic side chains in the core with added interactions between polar residues.

Similarly, crystal structures of 14-helical β³-tetrapeptide oligomers constructed from ACHC showed the presence of two molecules in a crystal unit, each adopting a 14-helical conformation (Appella et al., 1999). These helices were aligned end to end, via intermolecular H-bonding creating an infinite H-bonded column. The packing also revealed extensive lateral interactions between H-bonded columns that were packed in a hexagonal array through strong hydrophobic interfaces using cyclohexyl rings as a "cyclohexane zipper."

The assembly of 14-helical β³-peptides comprised exclusively of acyclic β³-amino acids into octameric bundles has also been reported (Figure 3) (Daniels et al., 2007; Goodman et al., 2007; Molski et al., 2010; Petersson et al., 2007). The 14-helices that make up these octameric bundles were β³-decapeptides with three distinct faces: a β³-Leu face, a salt bridge face of alternating β³-Orn and β³-Asp residues, and an aromatic face that contains two β³-Tyr or β³-Phe residues. The peptide assembled as antiparallel helices where β³-Leu side chains formed the core of the bundle and the salt bridge faces of each antiparallel helix medi-

The first functional β³-peptide helical bundle was also recently reported (Wang et al., 2014). Dodecamers self-assembled into helical bundles, which were then able to bind substrates and catalyze ester hydrolysis. Catalytic activity centered on the geometric arrangement of arginine and histidine residues as well as the bundle assembly. Even though this is not the first report of a β³-peptide catalyst (Coffey et al., 2001; Muller et al., 2009), it clearly demonstrates that these assemblies have specific binding sites that could be further optimized for a variety of chemistries.

β-Peptides as Artificial Ion Channels

Ion channels are pore-forming membrane proteins, which function to provide and regulate membrane potential through control of ion flow across the cell membrane. The ability to design artificial ion channels provides a means to generate novel biosensors and templates for drug delivery and drug design. Ghadiri and coworkers reported highly efficient transmembrane ion channels based on acyclic β³-peptides with hydrophobic side chains cyclized in a head-to-tail fashion that self-assembled in lipid bilayers (Clark et al., 1998). These peptides were designed to adopt flat, ring-shaped conformations and stack through extensive backbone-backbone H-bonding to form tubular channel structures. The channel-forming peptides were examined in liposome-based proton transport assays and single-channel conductance experiments.

β-Peptide Templates for Nucleobase Pairing

As discussed earlier, a 14-helical conformation has almost perfect alignment of the side chains along a helical face where residues *i, i*+3 are in relatively close proximity to each other (~4.8 Å). The alignment of residues makes it a perfect candidate for complementary interactions of nucleobase pairs through H-bonding between A-T and G-C to influence the formation of peptide architectures (Brückner et al., 2003a, 2003b). Nucleobases incorporated as additional recognition elements in 14-helical peptides facilitate controlled specificity of self-association of
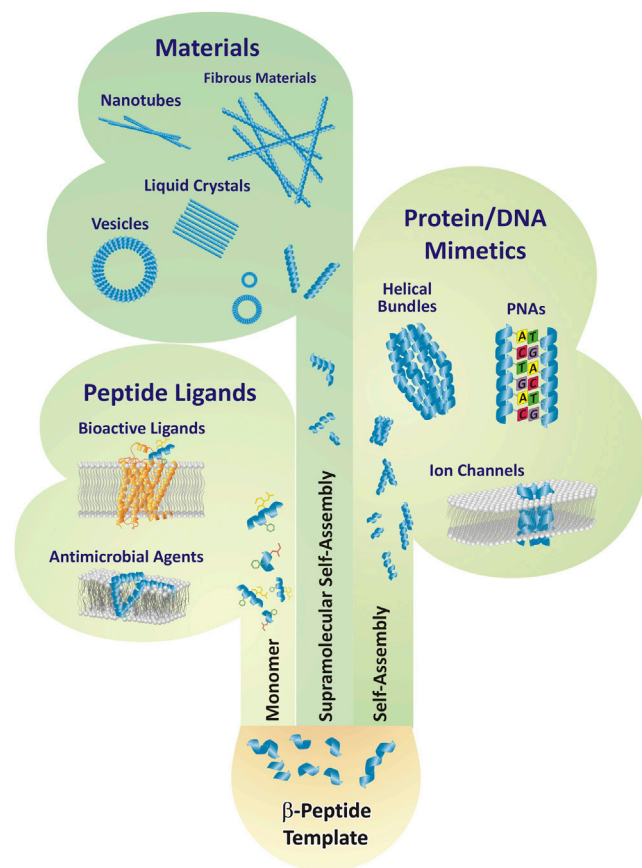
Figure 2. Different Classes of Bioactive and Nanomaterials Based on β-Peptide Foldamers

of the 14-helix (Brückner et al., 2003a, 2003b; Chakraborty et al., 2006; Weiß and Diederichsen, 2007) leading to specific base pairing. However, a complex formed in an equimolar mixture of peptides displayed significantly higher stability, indicating the formation of a stable heterodimer that had been pre-organized by a 14-helical backbone.

Recently, Diederichsen and coworkers synthesized 14-helical β³-peptides functionalized with nucleobases on two faces of the helix. The nucleo-β-amino acids were incorporated in i, $i+3$, $i+1$, and $i+4$ positions in the sequence, together with β-Lys and conformationally constrained ACHC (Srivastava et al., 2009). These peptides showed excellent pre-organization of the recognition units for specific recognition and simultaneous organization over both faces due to added H-bonding motifs. This assembly resulted in higher aggregation of the helices into either tubular or sheet-like arrangements, offering the basis for the construction of macromolecular architectures such as nanotubes and ion channels.

Development of Novel Materials through β-Peptide Supramolecular Self-Assembly

Self-assembly of peptides to give supramolecular structures by non-covalent interactions represents a powerful approach to the design of novel functional fibers and bio- and nanomaterials (Capito et al., 2008; Harrington et al., 2006; Hauser et al., 2011; Hauser and Zhang, 2010a, 2010b; Mahmoud et al., 2010; Matson et al., 2012; Ryadnov et al., 2009; Silva et al., 2004; Woolfson and Mahmoud, 2010; Zhao et al., 2010). Self-assembled peptide systems offer significant advantages over other organic and inorganic self-assembled systems, including biological compatibility, ease of synthesis, low toxicity, and functionalizability (Aida et al., 2012; Hauser et al., 2011; Mahmoud et al., 2011). The studies described above provided the basis for the production of some remarkable nanomaterials that have significantly expanded the potential applications of β-peptide foldamers. Thus, the combination of hydrophobic, ionic, and dipolar forces, which mediate the assembly of β-peptide foldamers into small bundles, has now been extended to the generation of materials through supramolecular self-assembly (Figures 2 and 4).
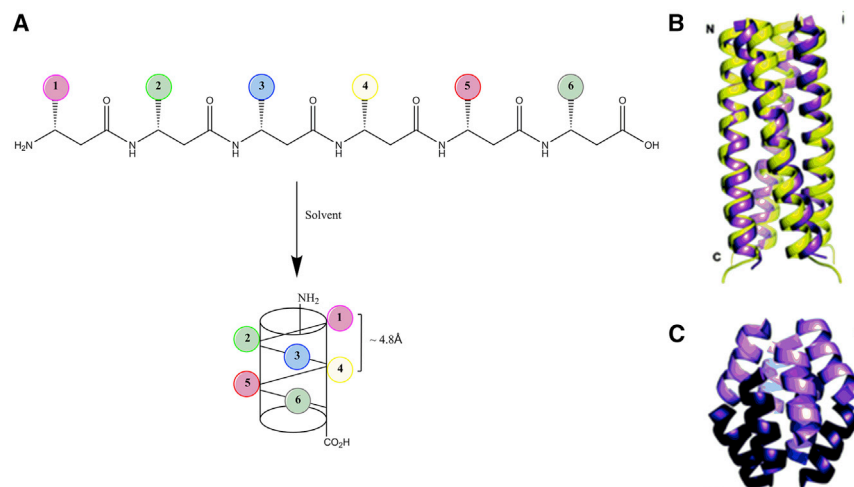
small β³-peptide helices, depending on base-pair interaction. Nucleobase recognition units were first attached to the side chains of the specific amino acids (Brückner et al., 2003a, 2003b; Chakraborty et al., 2006; Chakraborty and Diederichsen, 2005; Diederichsen and Schmitt, 1998a, 1998b), followed by incorporation into β³-peptides at i, $i+3$ positions along one face

Figure 3. Self-assembly of the β-Peptide Structural Template
Structural template of a β-peptide 14-helix illustrating (A) the topographic alignment of side chains and examples of (B) hexameric (Horne et al., 2007), and (C) octameric (Daniels et al., 2007) β-peptide bundles.
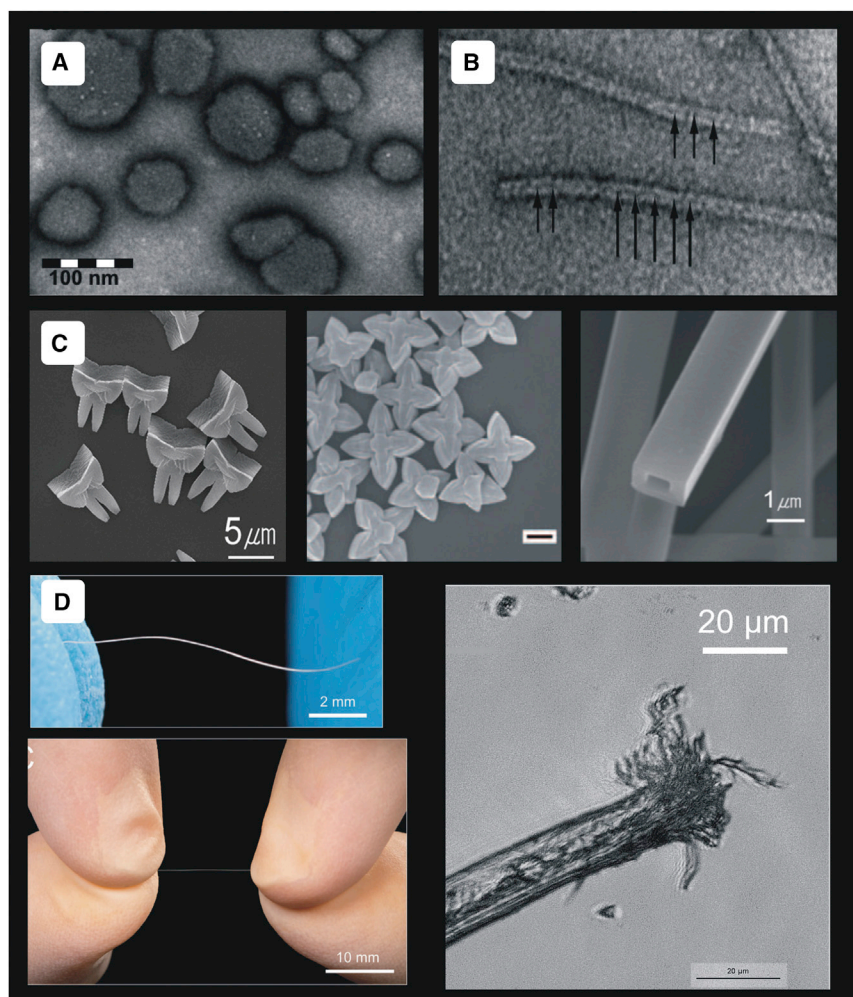
Figure 4. Supramolecular Structures Formed by β-Peptide Self-assembly

Transmission electron microscopy images of (A) self-assembled vesicles and (B) a β-decapeptide showing uniform nanofibers (reproduced with permission from Mandity et al., 2010 and Pizzey et al., 2008). (C) Scanning electron microscope images of superstructures formed from helical monomers that self-assemble laterally in an inter-digitated manner similar to that of collagen. Each monomer gives a strikingly different morphology (reproduced with permission from Kim et al., 2012 and Kwon et al., 2010, 2011). (D) Images of fibers obtained from the self-assembly of β-hexapeptides (reproduced with permission from Del Borgo et al., 2013).

the formation of liquid crystals (Pomerantz et al., 2011). Furthermore, acylation of the N terminus gave rise to nanofiber growth, which was hypothesized to be due to the elimination of charge. The reduction of charge throughout the peptide (or introduction of negative charge) was thought to enhance interdigitation of the peptide bundles, and therefore promote lateral growth of the nanofiber (Figure 4B). In addition, different lengths and sizes of acyl tails were investigated for steric packing and hydrophobicity. Two biologically active molecules, biotin and the RGD sequence that is critical in integrin binding, were introduced into the peptide sequence without any adverse effect on the ability to form liquid crystals. Furthermore, the helix dipole was shown to direct the association and that electrostatic interactions were mostly responsible for the self-assembly (Price et al., 2010). In addition, charged amphiphilic α/β-hybrid peptides with alternating α- and β-amino acids were shown to adopt sheet-like assemblies that form films through engineered charged interactions (Segman-Magidovich et al., 2011).

A striking set of structures has been observed from β-peptide self-assembly based on Boc-(ACPC)$_4$-Bzl, Boc-(ACPC)$_6$-Bzl, and Boc-(ACPC)$_7$-Bzl (Kim et al., 2012; Kwon et al., 2010, 2011). When dissolved in THF and injected into an aqueous environment, these compounds self-assembled into complex structures, as shown in Figure 4C. Most recently, peptides containing N-Boc-protected β-homoglycine coupled to dicyclohexylurea derivatives were observed to self-assemble into a variety of structures, including rods, fibers, and vesicles, depending on the environmental conditions (Kar et al., 2014). These self-assembled vesicles were able to encapsulate the drug methotrexate and release it upon salt-triggered disruption of the vesicular walls, which may be of significant importance in the drug delivery arena.

Our group discovered that N-acetylated β-tri- and hexapeptides with varied acylic amino acid sequences were able to self-assemble into fibers from nanometers to centimeters in length in aqueous or organic solvent (Del Borgo et al., 2013). Figure 4D

β-Peptides containing six-membered cyclic rings have been shown to form bundles and fibrils based on the relative configuration of the peptide sequence (Hetenyi et al., 2005; Mandity et al., 2010; Martinek et al., 2006). β-Hexapeptides comprised of *cis*-ACPC residues, which displayed a 10/12-helical structure by circular dichroism and nuclear magnetic resonance, were shown to self-assemble into ribbon-like fibrils, while *cis*-ACHC-containing β-hexapeptides formed vesicles of over 100 nm in size (Figure 4A). Importantly, even minor changes to the peptide lead to a loss of vesicular morphology.

The first reported study to show the formation of liquid crystals by β-peptides was based on a series of β-peptides with seven or ten cyclic and acyclic residues thought to be due to the amphiphilic nature of the peptides (Pomerantz et al., 2006). Further work led to the formation of nanofibers that exhibited a width of approximately 75 Å with a hollow core of radius 15 Å on transmission electron microscopy and small-angle X-ray scattering analysis, and a hollow amphiphilic model was proposed (Pizzey et al., 2008; Pomerantz et al., 2008). This work led to the design of a series of β-decapeptides with at least three ACHC residues on one face to stabilize the 14-helical structure and to promote self-assembly through a cyclohexyl zipper-like motif, leading to

shows macroscopic fiber threads formed following dissolution of β-hexapeptides in methanol and water. Many other fibers not visible to the naked eye are found within the solution. Interestingly, X-ray crystallography revealed that the helical structure was maintained in the N-acetylated β-tripeptide nanorods and that the structure of two tripeptide monomers was superposable with a β-hexapeptide. Furthermore, X-ray crystal studies show a unique three-point H-bonding motif that enables lengthening of the self-assembling fiber where the N-acetyl group plays a critical role in supplying an H-bond donor and acceptor, and without this acetyl group, no fibers were formed. The crystal structure showed the formation of antiparallel nanorods that were similar to the theoretical findings of two different groups (Czajlik et al., 2008; Miller et al., 2008). It is this "head-to-tail" self-assembly mechanism, in combination with the unique helical structure of the peptide monomer, that offers the opportunity for the introduction of a wide variety of functions to the new fibers based on straightforward modification of the side chains of the component amino acids, without perturbation of the self-assembly motif (Bergman et al., 2009; Gopalan et al., 2012). Moreover, we have seen that a single peptide monomer is able to self-assemble into a variety of fibrous morphologies depending on the solvent utilized for self-assembly (Seoudi et al., 2015a, 2015b).

Conclusions and Outlook

β-Peptide foldamers have been studied over the past 15 years, initially due to their unique structural characteristics. In comparison with their α-peptide counterparts, β-peptides are stable to proteolytic enzymes and display distinct, defined structural properties. A number of groups have reported the unique geometry possessed by these peptides, which has led to the design of biologically active β-peptides covering a range of targets, including bacteria, viruses, and apoptotic proteins. These studies have exploited the proteolytic stability of β-peptides and/or the unique structural characteristics of β-peptides. Over the past few years there has been a significant move in β-peptide research toward focusing on the ability of these peptides to self-assemble into a variety of structures. Indeed, self-assembly has been used to great effect by a number of groups to develop novel compounds with biological activity as well as nanomaterials. Although the field of β-peptide self-assembly is still in its infancy, it provides a great opportunity to design materials with geometric precision and an ability to decorate, while giving unprecedented proteolytic stability. These are key requirements for many applications within the realms of biomedicine and nanotechnology, which are uncommon among peptide-based materials. Thus, recent achievements in this field suggest that β-peptides offer significant advantages as nanomaterials and, as a result, we predict a boom in β-peptide research building on the initial findings over the past few years.

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