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Self-assembly of cyclic peptides and peptidomimetic macrocycles: linking structure with function

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1. Introduction

Folding and hierarchical structure formation have been shown to adjust and control the dimensions, shapes and functionalities of macromolecules (e.g., proteins, nucleic acids), operating at the cellular level in nature. For example, proteins have the ability for molecular recognition, sensing, transport and catalysis which essentially depend on well-ordered and compact foldameric structures, eventually to assemble into quaternary forms. Several approaches at the interface between biology and organic chemistry have been developed to explain protein-like structures and functions. In consequence, macrocyclic and linear oligoamides have emerged as versatile units for building up self-assembled nanostructures[1–8] with potential applications in biotechnology. Among them, β-sheet forming cyclic peptides constitute a remarkable

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example of synthetic nanotube building units. A number of planar cyclic peptides are able to stack in this manner, including those comprising alternating D- and L-α-amino acids, β-amino acid residues, alternating α and γ-amino acid residues or other amino acids, or selected aromatic groups (Fig. 1). Modification of the chemical

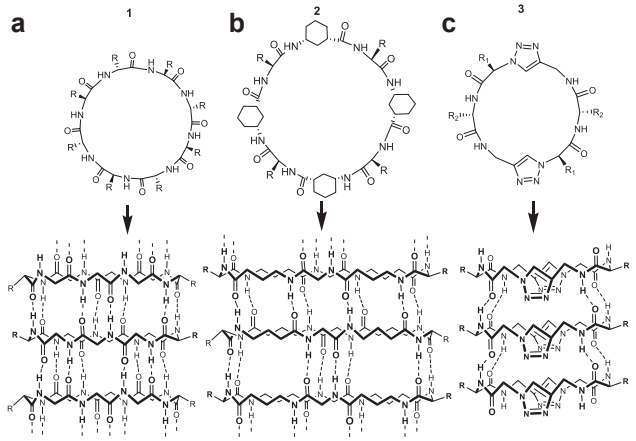

Fig. 1. Classes of self-assembling cyclic peptides through β-sheet interactions. (a) Cyclic peptides with α-alt(D,L) residues (**1**); (b) cyclic peptides with α- and γ-residues (**2**); and (c) self assembling heterocyclic peptides by incorporation of ε-amino acids (**3**). In all cases, the N–H and C=O hydrogen bond donors and acceptors are aligned with tube length. Side chains have been indicated as R for clarity.[11]

structure of the cyclic peptide moieties allows the self-assembled supramolecular architectures to be adjusted to meet the requirements of various applications, including antibacterial activity, ion channelling and ion sensing. A number of recent reviews deal with various aspects of this topic.[9–11] However, little attention has been paid to the relationship between the structures of cyclic peptides and peptidomimetic macrocycles in the context of the tendency for self-assembly to form nanostructures.

2. Self-assembly of cyclic D-,L-α-amino acid derived peptides

The possibility of assembly of cyclic peptides containing alternating D- and L-α-amino acids was originally proposed in 1974 by De Santis et al. who postulated that intermolecular hydrogen bonding between cyclic peptide rings would lead to a contiguous β-sheet structure.[12] But Ghadiri and co-workers were the first to assemble cyclic peptide nanotubes (CPNTs) by controlled acidification of a pH responsive octapeptide.[13] As illustrated in Fig. 1, the orientation of the amide bonds, which run perpendicular to the axis of the ring, leads to an equatorial dispensation of the amino acid side chains. This allows the enthalpically driven assembly of CPs into extended tubular structures. The thermodynamics of CP assembly into nanotubes has largely been studied by the use of partially *N*-alkylated CPs (*N*-alkyl CPs). By the introduction of *N*-alkylated residues, hydrogen bonding can be restricted to one face of the cyclic peptide, thus restricting assembly to dimers.

The association of CPs in water has recently been explored by Karlström and Undén using a fluorescence-quenching assay, which confirmed that this kind of activity takes place also in solution and is not just a consequence of the crystallization process.[14] In order to gain a better understanding of the stacking interactions, dimeric motifs achieved by selective backbone N-alkylation of amino acids of the same chirality were investigated. This avoids complications associated with unlimited stacking and allows the formation of only the structures having all the *N*-methyl groups pointing towards the same face of the peptide ring (Fig. 2). In 1994, Lorenzi's

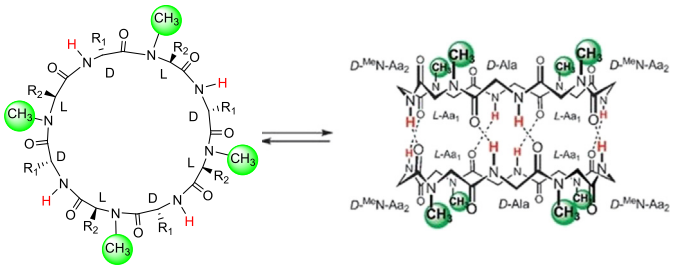

Fig. 2. Schematic representation of the antiparallel β-sheet structure of a dimeric tubulet composed of cyclic D,L-α-octapeptide subunits. Side chains excluded for clarity.

group reported an X-ray crystallographic study of the *N*-methylated hexapeptide cyclo-[(D-Leu-L-MeN-D-Leu)$_3$-], which showed the expected dimeric antiparallel β-sheet structure in the solid state, while NMR investigations revealed that the peptide dimerized in deuterochloroform with an association constant (K_a) of 80 M^{-1}.[15] Independent work carried out in Ghadiri's laboratory demonstrated analogous solution and solid-state dimerization (Fig. 2) by the octapeptide cyclo-[(L-Phe-D-MeN-Ala)$_4$-] (**4**), with higher K_a values (2540 M^{-1}).[16]

Studies of side chain–side chain interactions have shown that CPs containing homo phenylalanine can be used to induce crystal growth through the prevalent effect of dimer formation. Dimeric structures have also enabled easy comparison of the stabilities of parallel and antiparallel β-sheet structures in solution, showing that antiparallel orientations are stabler by 0.8 kcal mol^{-1} than the parallel counterparts.[17] Further confirmation of β-sheet-type hydrogen bonding was obtained by covalent consolidation of non covalently constituted CP dimers.

Peptide nanotube formation by cyclic D-,L-α peptides via antiparallel backbone to backbone H-bonding was established by the mixing of two enantiomeric cyclic peptides in solution phase (Fig. 3). This study also demonstrated that sterically demanding side chains in the peptide backbone of two enantiomeric cyclic D-,L-α-peptides **5** and **6** strongly disfavor both parallel and antiparallel stacking of peptides into nanotube formation.[18]

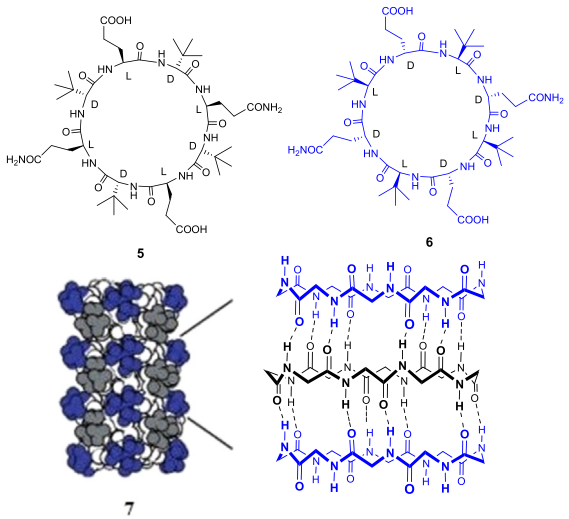

Fig. 3. Proposed modelled structure **7** towards the formation of nanotube assembly by an equimolar mixture of peptides **5** and **6**. Inter subunit hydrogen bonds are formed between homochiral amino acid residues of adjacent enantiomers. Side chains of D-*tert*-leucine (gray) and L-*tert*-leucine (blue) are effectively packed on top of sterically non-hindered side chains (omitted for clarity) of glutamine or glutamic acid.[18]

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