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Peptide Nanotubes

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*Ian W. Hamley**

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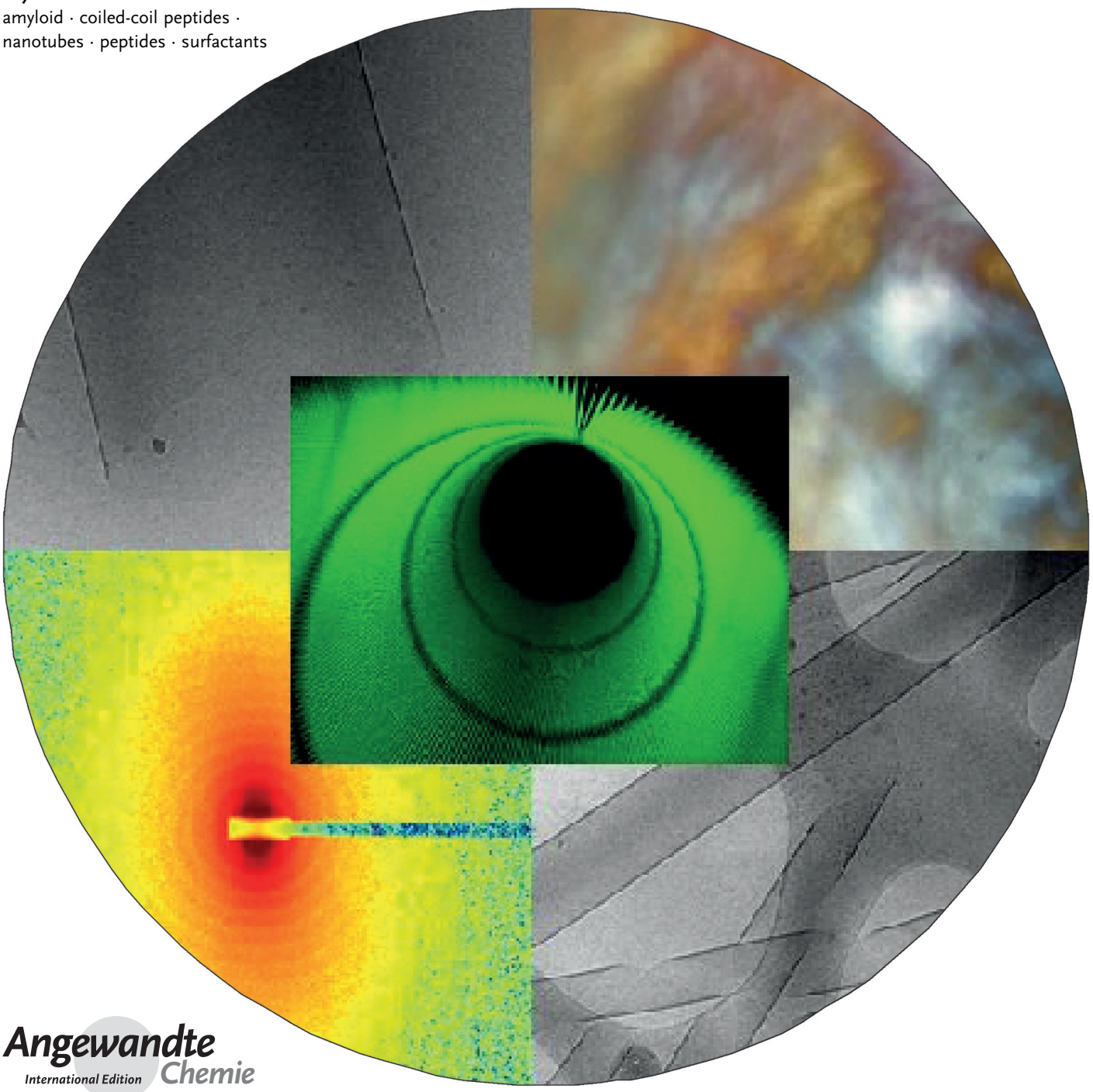

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The self-assembly of different classes of peptide, including cyclic peptides, amyloid peptides and surfactant-like peptides into nanotube structures is reviewed. The modes of self-assembly are discussed. Additionally, applications in bionanotechnology and synthetic materials science are summarized.

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1. Introduction

Nanotubes are formed through the self-assembly of many types of organic molecule, although such structures are relatively less frequently observed than more simple fibrillar 1D assemblies, or indeed 2D or 3D nanostructures. Peptide nanotubes (PNTs) are a class of organic nanotube attracting immense interest due their wide range of bio- (and other) functionalities which leads to many potential uses in nanotechnology and biomedicine. The modes of self-assembly of peptides into nanotubes and their diverse applications are the subjects of the present review.

This review covers the formation of nanotubes by peptides and short proteins, and discusses the diversity of applications of these nanotubes. The formation of protein structures with defined channels such as β-helices or β-barrels, is outside the scope of this review, although some protein structures engineered to form nanotubes are discussed in Section 8. Viruses, with a tubular arrangement of coat proteins such as tobacco mosaic virus[1] are also outside the scope of this review.

A number of longer[2] and shorter[3] reviews on PNTs have appeared. Recent edited books include much valuable information on peptide nanotube structures.[4] Reviews specifically focussed on cyclic nanotubes are available.[5] A review on self-assembling organic nanotubes features a discussion of cyclic D,L-peptide nanotubes.[6] A review on supramolecular tubular structures formed by amphiphilic molecules includes a discussion of nanotube formation by several peptide amphiphiles.[7] Reviews on the self-assembly of peptide amphiphiles also discuss nanotube formation.[8] A review on the electronic and optical properties of peptide nanostructures includes an extensive summary of data obtained for diphenylalanine (FF) nanotubes.[9]

2. Cyclic Peptide Nanotubes

Ghadiri et al. pioneered the design of PNTs based on the stacking of cyclic peptides containing even numbers of alternating D- and L- amino acids.[10] Figure 1a shows the structure of nanotubes formed by cyclic peptides belonging to this class, along with several others which have been examined so far. The diameter of the alternating D,L-cyclic PNTs increases with the length of the cyclic peptide, for example, from 7 to 13 Å from an octamer to a dodecamer.[5a]

A range of potential applications of cyclic peptide nanotubes have been proposed, including their incorporation into lipid membranes to form artificial ion channels, and as antimicrobial agents. They have also been used as scaffolds to attach other molecules such as those with electronic properties, or polymers. An excellent recent review discusses the structure and applications of cyclic peptide nanotubes.[5b] This includes a useful table listing the structures (along with channel dimensions, association constants and hydrogen-bond lengths) of a range of cyclic peptides including nanotube formers. This valuable information will not be duplicated here.

In one early example, Ghadiri's group showed that octameric or hexameric alternating D,L-cyclic peptide nanotubes have antimicrobial activity, due to membrane permeabilization.[11] Selective activity against Gram positive (*S. aureus*, MRSA) or gram negative (*E. coli*) bacteria compared to mammalian cells was demonstrated. It was also established that control peptides comprising linear sequences did not have antibacterial activity.

An octameric cyclic peptide nanotube was shown to serve as an artificial transmembrane ion channel.[12] The peptide incorporated leucine and tryptophan residues to favor its partitioning into lipid bilayers. The pores formed spontaneously upon addition of the peptide to an aqueous liposome dispersion. Single-channel conductance and proton efflux (pH-sensitive dye fluorescence) confirmed the presence of ion channels.[12] Transport of glucose across lipid bilayers via a 10-residue cyclic D,L-peptide nanotubes has been measured.[13] A cyclic D,L-peptide nanotube structure has been used as a scaffold to tether naphthalene-diimide molecules used in organic electronics.[14] This resulted in delocalized electronic states as revealed in the near-infrared spectrum.

Nanotube formation at low concentration is observed for enantiomeric mixtures of cyclic peptides such as cyclo-[(D-

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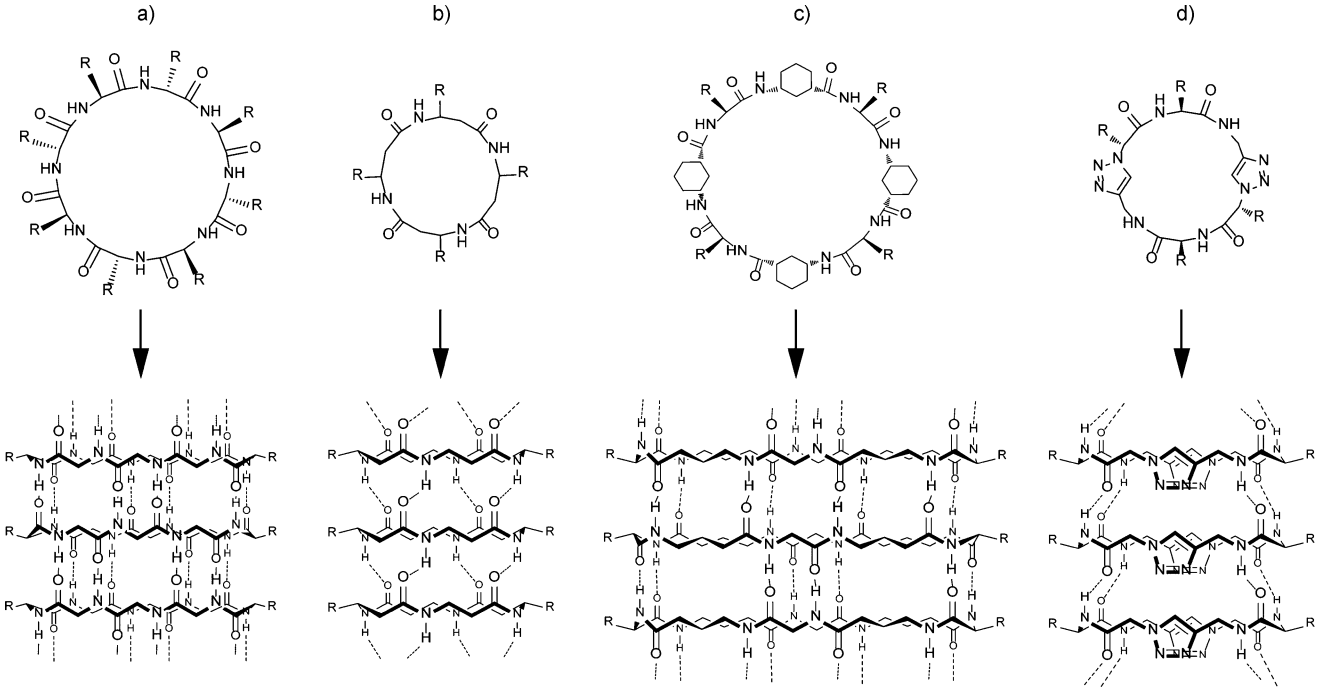

Figure 1. Classes of cyclic peptides that form nanotubes.[5b] a) Cyclic peptides with alternating D- and L-α-amino acids, b) Cyclic peptides with β-amino acid residues, c) Cyclic peptides with α- and γ-residues, and d) self-assembling heterocyclic peptides that incorporate ε-amino acids. Side chains have been omitted for clarity. In the bottom figures, hydrogen bonds are indicated by dashed lines.

Gln-L-Tle-D-Glu-L-Tle)$_2$] (Tle: *tert*-leucine), the nanotubes being stabilized by close antiparallel H-bonds.[15] Nanotube formation can also be stabilized by salt bridging, as in mixtures of cyclo-[(L-Glu-D-Leu)$_4$] and cyclo-[(L-Lys-D-Leu)$_4$].[15] Cyclic peptide nanotubes show spontaneous alignment in structured ionic liquids, and this can be used to fabricate self-standing membranes comprising ordered domains.[16]

The class of cyclic PNTs containing β-amino acids (Figure 1b) includes a range of peptides containing up to eleven β-amino acid residues, as discussed elsewhere.[5b,17] Seebach's group developed cyclic tetrapeptides of this type as mimics for the peptide hormone somatostatin.[17] Cyclic peptides containing *cis*-furanoid sugar amino acid residues and β-hGly form "sugar-coated" PNTs.[18] Cyclic trimers and tetramers of glycosylated amino acids based on pyranose rings, β-glycamino acids, also form crystalline nanotubes.[19] The sugar units are able to bind the lectin WGA (wheat germ agglutinin), forming a lectin-coated nanotube (in contrast the lectin conA disrupted the nanotube structure). Cross-linking of the bound WGA lectin enabled the "scaffold" of cyclic tri-β-peptides to be washed away, leaving a protein nanotube.[20] Nanotubes were also observed for a cyclic hexa-β-peptide composed of acetylated glycosamino acids, again with a highly ordered stacking of the rings.[21]

A class of nanotubes was developed in which *cis*-3-aminocyclo hexanecarboxylic (γ-Ach) acid residues alternate with D-α-amino acids (Figure 1c).[22] This leads to a flat ring-shaped conformation that can facilitate antiparallel β-sheet hydrogen bonding. This produces nanotubes with hydrophobic cavities (in the paper, dimers stabilized by N-methylation to block facial hydrogen bonding were studied), with a 7 Å pore diameter based on X-ray crystal structure analysis.[23] The presence of γ-Ach on the interior of the PNT cavity provides the potential to functionalize the inner surface. This class of peptide also shows single-channel conductance of alkaline cations.[24] Stable dimers are also formed by 6-residue α,γ-cyclic peptides with γ-Acp (*cis*-3-aminocyclopentanecarboxylic acid) in place of γ-Ach.[25] This class of peptide has been fluorescently labeled with distinct probes leading to FRET (Förster resonant energy transfer).[26] Larger, 8- 10- and 12-residue γ-Acp based α,γ-cyclic peptides form dimers with a larger pore diameter, up to 17 Å.[27]

Examples of cyclic peptide belonging to the class shown in Figure 1d are C_2 symmetric hexamers containing two triazole

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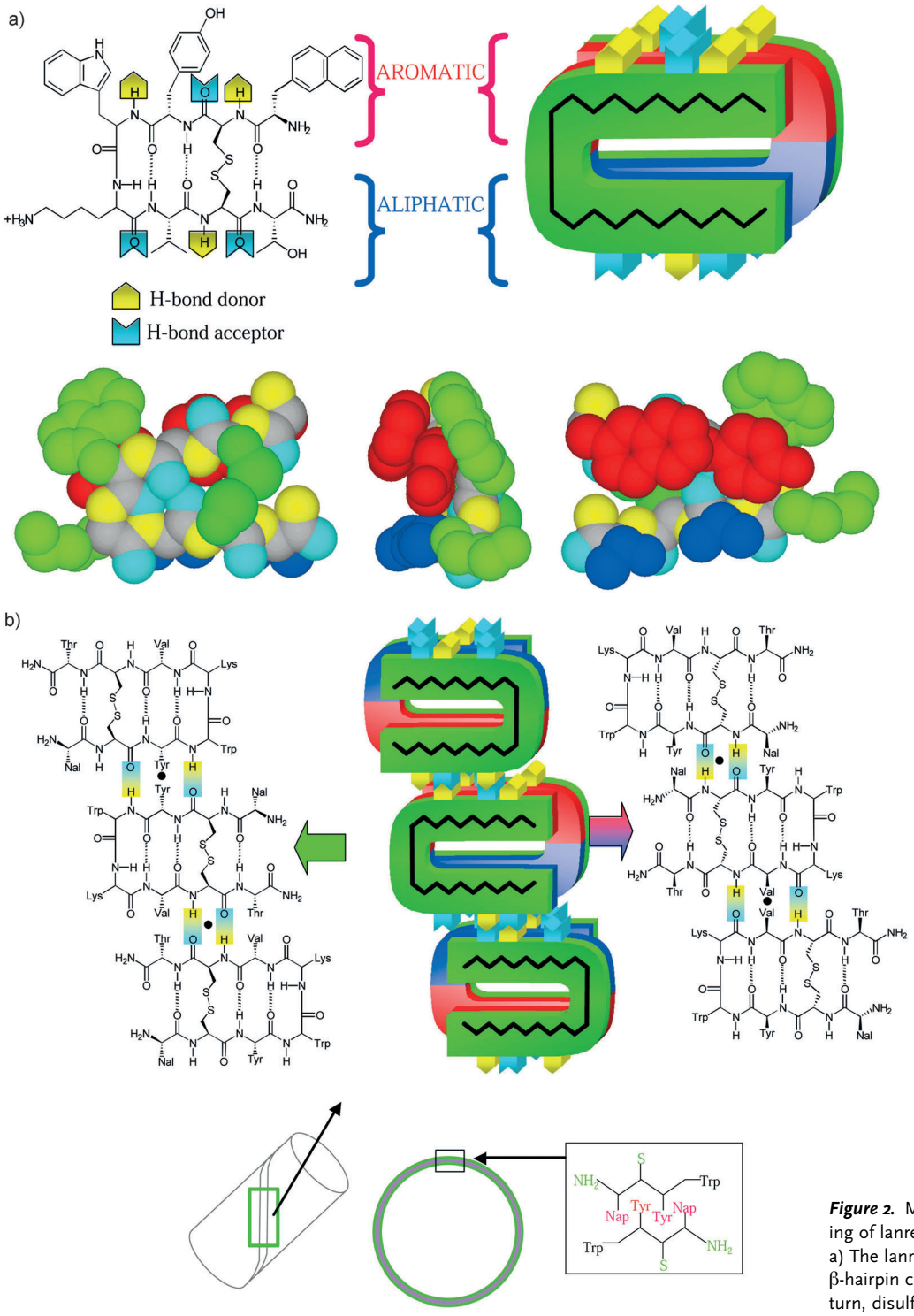

ε_2-amino acids along with four α-amino acids.[28] Heterocyclic dimers of these were also prepared by using appropriate coupling reactions.

The cyclic octapeptide lanreotide does not belong to any of the classes shown in Figure 1. The sequence is cyclo[D-Naph-Cys-Tyr-D-Trp-Lys-Val-Cys-Thr-CONH]. It is synthesized as a growth hormone inhibitor. A very thorough study of its self-assembly into nanotubes in aqueous solution has been performed, relying mainly on X-ray scattering (SAXS and XRD).[29] The tube diameter (244 Å) is significantly greater than that for other classes of cyclic PNT discussed so far in this section, and reflects a different mode of packing of the molecules in the nanotube walls. Mutations in the peptide sequence influence the tube size (in the range 10–36 nm) and a detailed model for the packing of different aromatic residues was proposed.[29c] Figure 2 illustrates a model for the hier-

Figure 2. Model for the hierarchical ordering of lanreotide into nanotubes.[29a] a) The lanreotide molecule has a planar β-hairpin conformation, stabilized by the turn, disulfide bridge, and intermolecular hydrogen bonds. On the right the packing of molecules in a dimer is shown and at the bottom CPK models of the peptide are shown; the segregation of aromatic (red) and hydrophilic (green) residues is evident. b) Stacking of dimers in the nanotube walls; the black circles show C_2 axes. c) Nanotubes formed from 26 filaments, showing dimensions. d) The nanotubes can pack into a hexagonal liquid crystal structure at high concentration.

archical ordering of lanreotide.[29a] This is based on the packing of molecules with a hairpin conformation into opposed dimers. A phase diagram for lanreotide in water is available.[29b] The pathway of self-assembly was elucidated and initial peptide dimer structures were observed, then open ribbon and helical ribbon structures, followed by nanotube closure[29d] at later times. The lanreotide tubes can be used as scaffolds for biomineralization—specifically the formation of double-walled silica nanotubes was reported.[29e] Recently, the French team investigating lanreotide self-assembly has observed the formation of double-walled peptide nanotubes in the presence of divalent counterions.[29g] Why only double-walled nanotubes form was rationalized based on a simple model for the stability of multi-wall nanotubes, balancing the adhesion force from counterions with the mechanical deformation of the nanotube wall. The influence of a series of counterions (including small anions from the Hofmeister series and also carboxylates) on the diameter of nanotubes has been examined through detailed X-ray scattering experiments.[29f] The dissociation of the counterions is influenced by the presence of the nanotubes, and in turn the nanotube diameter varies in the 19–26 nm range. Specific counterion condensation sites were identified. This study provided an explanation for the stability of dimers as opposed to monomers as nanotube building blocks, based on electrostatic interactions.[29f]

Nanotubes formed by cyclo-diphenylalanine (cyclo-FF) are discussed in more detail in Section 5 below.

Cyclic peptides have been used as templates to attach polymers. The polymers can be used to control the solubility and aggregation of the nanotubes. Biesalski and co-workers used octameric D,L-alternating cyclopeptides as templates for graft-from polymerization of *N*-isopropylacrylamide.[30] Bromoisobutyramide initiators for atom transfer radical polymerization (ATRP) were attached via lysine side chains. In the presence of the attached polymer chains, bundling of nanotubes was reduced and instead isolated short nanotubes were observed.[30] Börner and co-workers used RAFT to prepare poly(*n*-butyl acrylate) which was either coupled to alternating D,L-cyclopeptides, or the oligopeptides were used as macroinitiators.[31] This group also used ATRP to prepare polymers employing a grafting-to strategy to couple two poly(*n*-butyl acrylate) chains to a cyclic alternating D,L-octapeptide, leading to the self-assembly of polymer-coated PNTs.[32] Perrier's group have recently developed this work using copper-mediated alkyne–azide cycloaddition (CuAAC) "click" coupling chemistry to link RAFT-polymerized polymers to cyclic nanotube-forming peptides. In one example, they have investigated the coupling of alkyne-terminated poly(*n*-butyl acrylate), pBA, to azide-functionalized cyclic peptides.[33] A mixture of two, three-, and four-arm conjugates was observed. They later examined the self-assembly in TFA (trifluoroacetic acid)/DMF (dimethylformamide) mixtures of pBA–cyclic peptide conjugates containing two pBA arms, with varying polymer molar mass—increasing chain length led to increased nanotube length.[34] In another example, they investigated the thermoresponsive behavior of a conjugate comprising poly(2-ethyl-2-oxazoline), prepared by cationic ring-opening polymerization, linked via CuAAC to a cyclic peptide.[35] Nanotubes were observed in water, but these reversibly transformed into microparticles upon heating above the LCST (lower critical solution temperature) of the polymer. Self-assembly of cyclic peptide/polymer nanotubes can also be tuned by pH variation using a pH-responsive polymer such as poly(acrylic acid).[36]

Multi-shell nanotubes were observed by attachment of a block copolymer to an alternating D,L-cyclic peptide.[37] Self-assembly in water led to nanotubes with an internal channel (from the cyclic peptide), a hydrophobic inner shell (polyisoprene), and a hydrophilic external shell of poly(acrylic acid).[37] A cyclic peptide, [D-Ala-L-Lys]$_4$, that forms nanotubes, has been tethered with block copolymers via the peptide side chains.[38] Two block copolymers were investigated that microphase-separate into cylindrical or lamellar structures, respectively. The microphase-separated structures are decorated with pores formed by the PNTs. The block copolymer phase separation provides a means to direct the growth of peptide nanotubes, and the hierarchical self-assembly process can be used to fabricate flexible nanoporous thin films with aligned channels, in the case of the cylinder morphology (Figure 3).[38]

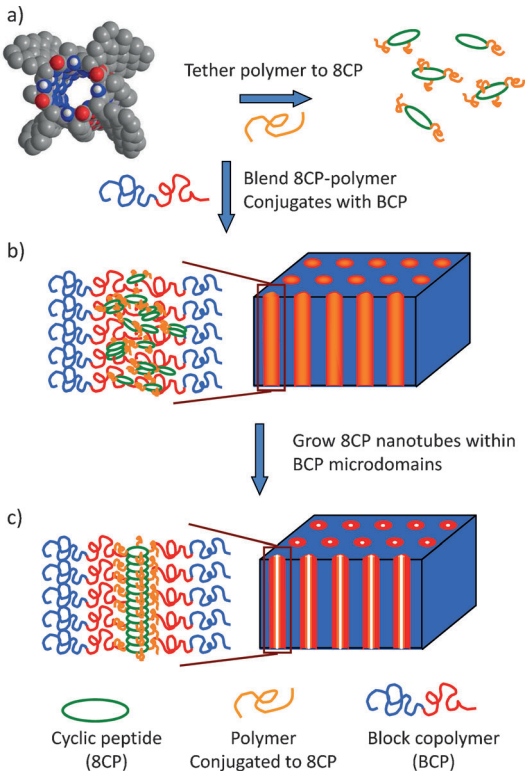

Figure 3. Method to template the alignment of PNTs formed by an octomeric cyclic peptide, termed 8CP, within a microphase-separated block copolymer hexagonal packed cylinder structure.[38]

The interior of cyclic peptides can likewise be modified by incorporation of functionalizable amino acids into the cyclic peptide design, as exemplified by incorporation of 3-amino-2-methylbenzoic acid into the D,L-alternating amino acid sequence.[39]

3. Surfactant-Like Peptide Nanotubes

SLPs are a class of amphiphilic peptide comprising a headgroup which is a short sequence of charged residues attached to a tail group of neutral residues.[40–42] Pioneering work on SLPs has been conducted by the Zhang group including A_6D, V_6D, V_6D_2 and L_6D_2.[40–42] Perutz et al. observed nanotube formation for the polyglutamine-rich $D_2Q_{15}K_2$ peptide from huntingtin, associated with Huntington's disease.[43] The suggestion that amyloid fibrils are generally water-filled nanotubes extrapolated from these findings is now discredited.

Among SLPs, several have been shown to self-assemble into nanotubes. Zhang's group reported nanotube, or at least fibril (tube formation is not clear in all cases), formation for A_6D, V_6D, V_6D_2 and L_6D_2[41] and similar peptides containing G instead of A as hydrophobic residue.[44] Adams et al., however, investigated the self-assembly of different batches of V_6D_2 and whilst the nanostructure observed (fibrils, tapes or twisted ribbons) depended on the batch (purity), nanotubes were not observed for any batch.[45] Peptide NH_2-A_6K-COOH (TFA salt) has been studied in more detail, and shown to form nanotubes in water.[46] Furthermore, a nematic phase is observed at higher concentration as orientational order of the nanotubes develops.[46] At even higher concentration, a lamellar phase comprising stacked bilayers of the peptide is noted.[47] Based on an estimated constraint from SAXS (small-angle X-ray scattering) that the wall thickness is < 1 nm,[46] a model for the packing of the peptide in the nanotube walls was proposed based on peptides parallel to the tube wall.[48] In collaboration with Madine and Middleton, we recently established that this model is incorrect, in fact the nanotube wall comprises bilayers of peptides perpendicular to the tube wall (Figure 4).[49] The wall thickness is then expected

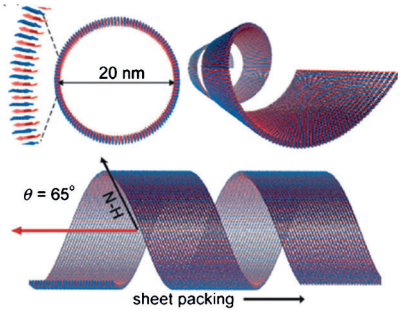

Figure 4. Model, based on constraints from solid state NMR and FTIR spectroscopy for A_6K nanotubes with interdigitated peptides forming bilayers within the tube walls.[49]

to be at least 2 nm. This agrees with Zhang's earlier model for V_6D.[43] Our model was established using solid-state NMR measurements on isotopically labeled peptides, along with transmission and ATR FTIR (attenuated total reflectance Fourier transform infrared), for labeled and unlabeled peptides. The lysine residues coating the inner and outer nanotube walls provide electrostatic stabilization. In contrast to this work, Lu and co-workers have indicated that CH_3CONH_2-A_6K-$CONH_2$ forms extended fibrils, whereas CH_3CONH_2-A_9K-$CONH_2$ forms short rod-like fibrils.[50] The fact that nanotubes are observed for the uncapped peptide A_6K but not the capped variant indicates the influence of electrostatics on the self-assembled nanostructure.

We have recently investigated the self-assembly of the cationic peptide A_6R which consists of six consecutive hydrophobic alanine residues as a "tail group" with a cationic arginine "head group".[51] We reported that this SLP can self-assemble into ultrathin sheets at low concentrations and at higher concentrations the sheets wrap around to form nanotubes and helical ribbons. This SLP also has antimicrobial properties.[52]

Very simple lipopeptides comprising a single amino acid headgroup are also able to form nanotubes. Figure 5 shows nanotubes, and partially wrapped nanotubes (helical ribbon)

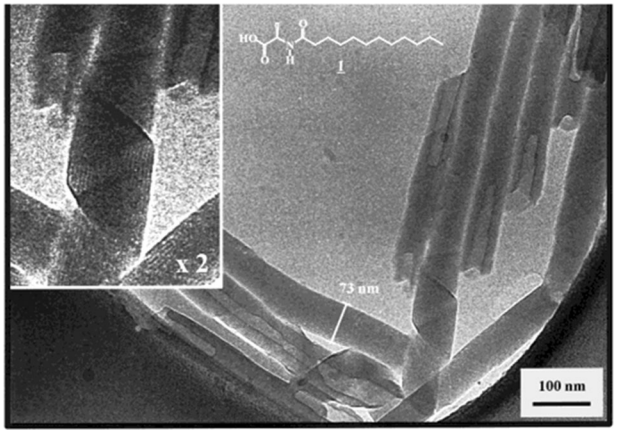

Figure 5. Nanotube and helically wrapped ribbon structures formed by L-dodecanoylserine in vitrified toluene (adapted from Ref. [53]).

structures formed by L-dodecanoylserine.[53] This lipopeptide can form these structures in toluene or water solutions (at high temperature). Similar structures were formed by the *R*-serine analogue, although only platelets were observed for the racemate. A peptide amphiphile comprising a single lysine residue, a α-(L-Lys),ω-(amino) bolaamphiphile, was shown to form nanotubes in acidic aqueous solution.[54] A peptide amphiphile incorporating an NDI (1,4,5,8-naphthalene-tetracarboxylic acid diimide) unit in the alkyl chain attached to an L-lysine headgroup can form nanotubes with different wall thickness, depending on whether the C terminus is a carboxylic acid or methyl ester.[55] The NDI units lead to interesting fluorescence properties. It was also demonstrated that a bolaamphiphile with L-lysine termini and a spacer incorporating both NDI and a tetraphenylporphyrin can form nanotubes in methanol/water mixed solvent or methanol.[56] The nanotubes are stabilized by J-type π–π stacking interactions. The presence of electron donor and acceptor moieties leads to photoinduced electron transfer causing time-dependent fluorescence decay that depends on the state of aggregation.[56]

Bolaamphiphiles containing oligo-glycine end groups form micro- or nanotubes in aqueous solution. For example

$Gly_3C_{10}Gly_3$ (C_{10} denotes a dodecyl spacer) is observed to form microtubules coexisting with vesicles.[57] The bola-amphiphile bis(*N*-α-amido-glycyl-glycine)-1,7-heptane dicarboxylate forms tubules in aqueous solution at a suitable pH value.[58] As shown in Figure 6 these tubes are very large, and

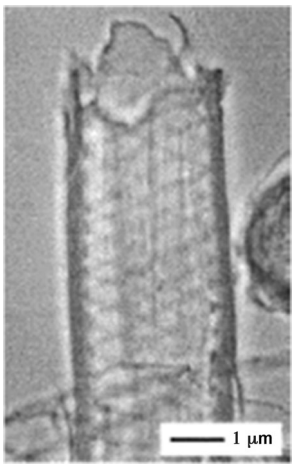

Figure 6. Optical micrograph of a tubule formed by a diglycine peptide bolaamphiphile in a pH 7 solution.[58]

can be observed by optical microscopy. A pH-driven transition between nanotubes and helical ribbons was observed.[58] The "nano"tubes are characterized by crystalline ordering of the peptides in the walls.[59] These nanotubes have been used to immobilize peptides[60] and proteins.[61] A short histidine-containing peptide was immobilized on the nanotubes and used to anchor Pt ions which were reduced to produce Pt-coated nanotubes.[60] The biomineralization of Au[62] and Cu[63] has similarly been templated using histidine-rich peptides to functionalize bolaamphiphile PNTs. The packing density of gold nanoparticles[62] or the size of Cu nanocrystals[63] can be controlled through pH. In another study, proteins were immobilized at tube ends by blocking the side walls with gold nanoparticles (attached to the nanotubes via thiol groups).[61] In a similar vein, thiolated peptide nanotubes can be assembled into Au trenches patterned on self-assembled monolayers,[64] or antibody-labeled nanotubes can be patterned on antigen arrays on gold.[65] These bolaamphiphile PNTs can also encapsulate enzymes, and catalytic activity of, for example, a lipase increased when encapsulated.[66] The synthetic peptidic lipid 2-(2-tetradecanamidoacetamido)acetic acid can form nanotubes in ethanol or metal-cation coordinated lipid nanotubes in the presence of transition metal salts. Nanotube structures with embedded silver nanoparticles show antimicrobial activity against *E. coli*.[67] Peptide amphiphiles containing C_{10} to C_{15} chains with di- or tri-glycine headgroups form nanotubes, which can be used as templates to produce metal oxide nanotubes.[68]

The bolaamphiphile *N*-α-lauryl-lysyl-aminolauryl-lysyl-amide (two C_{12}-lysines, linked via the ε-amino group) also forms nanotubes in water, through a slow kinetic process, exhibiting twisted tapes and helical ribbon structures as intermediates (Figure 7).[69]

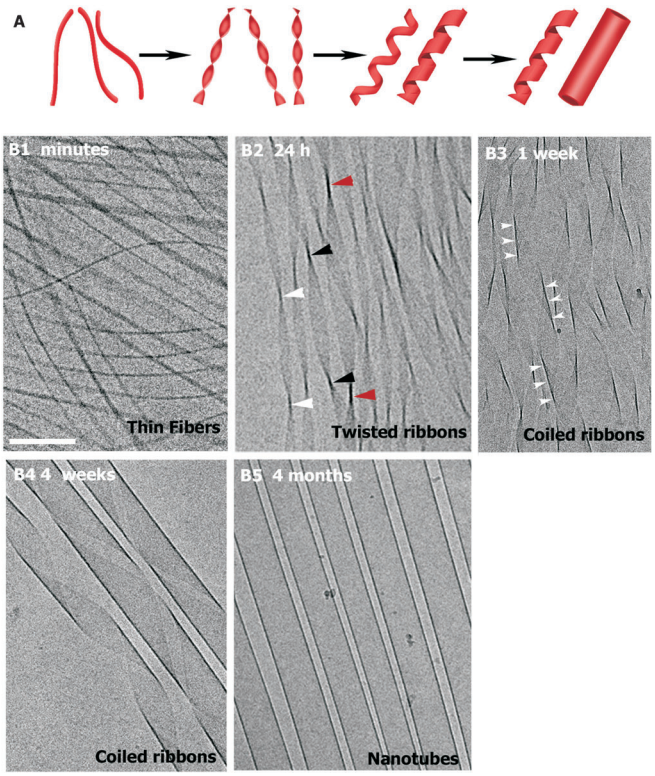

Figure 7. Pathway of formation of nanotubes by a di(C_{12}-lysine) bolaamphiphile.[69] A) Schematics; B) cryo-TEM images.

A bolaamphiphile containing two L-histidine hydrophilic headgroups separated by a lengthy spacer (*N*,*N*-eicosanedioyl-di-L-histidine) was shown, remarkably, to self-assemble into highly extended nanotubes in pH 8–9 aqueous solution.[70] These could be spun into bundled nanotube yarns with meter length (1–1.5 μm diameter) with high tensile strength. The methyl ester variant of this bolaamphiphile also forms single-wall nanotubes at low pH.[71] It was suggested that a bolaamphiphile with glutamic acid headgroups and a C_{12} dibenzoyl spacer may form nanotubes at low pH in aqueous solution.[72]

Peptide amphiphiles comprising a β-sheet forming decapeptide attached to hydrophilic linkers (amino carboxylic acids) and a biotin end group self-assemble into biotinylated nanotubes.[73] It was demonstrated that these could capture gold-labeled anti-biotin antibodies.

The lipopeptide C_{12}-KLVFFAE containing a heptapeptide from the amyloid β peptide (Aβ16–22) forms nanotubes with a 4 nm thick bilayer wall (containing antiparallel β-sheets, Figure 8).[74]

The lipopeptide C_{16}-KKFFVLK also forms nanotubes (coexisting with unwrapped nanotubes, that is, helical ribbons) at high concentration in water.[75] The nanotubes and ribbons reversibly unravel into twisted ribbons on increasing the temperature (Figure 9).[75a] This lipopeptide was designed to incorporate the KLVFF motif from the Aβ peptide (discussed in more detail in Section 4) (reading from the C to N terminus) as well as two additional lysine residues to confer water solubility. This lipoeptide forms a flow-aligning nematic phase at high concentration.

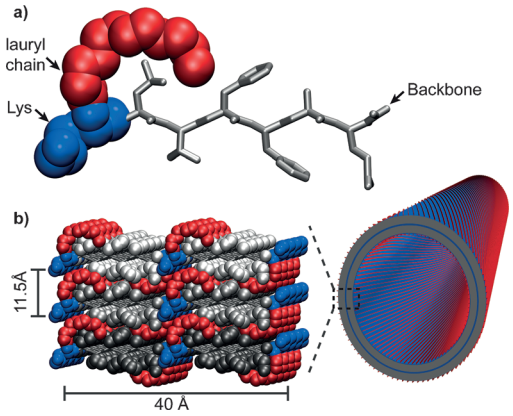

Figure 8. Model for the organization of the lipopeptide C_{12}-KLVFFAE into nanotubes.[74]

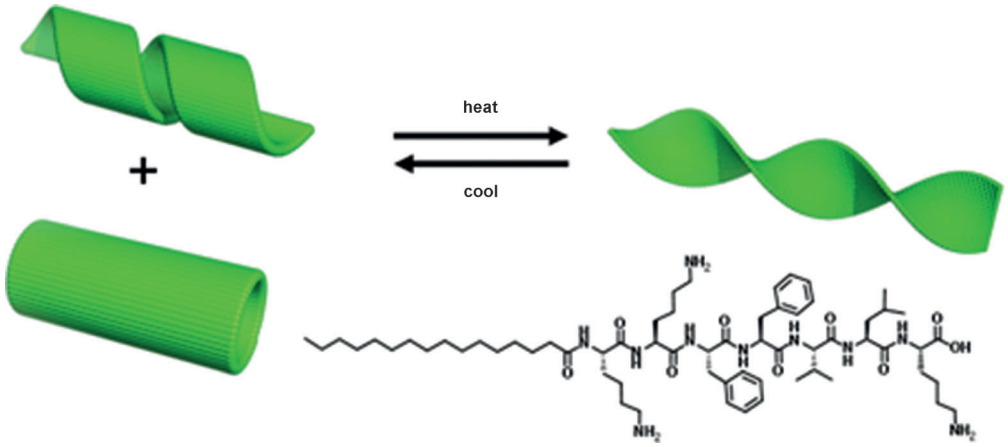

Figure 9. Schematic of the thermo-reversible transition, and (bottom right) structure of the peptide amphiphile C_{16}-KKFFVLK.[75a]

This peptide amphiphile (PA) was used as a model substrate in a study of enzyme activity on lipopeptide self-assembly.[75b] The enzyme α-chymotrypsin, expected to cleave preferentially in the region of the F residues was selected and indeed cleavage to produce both C_{16}-KKF and C_{16}-KKFF was observed. These self-assemble into spherical micelles (Figure 10), in contrast to the parent lipopeptide C_{16}-KKFFVLK.[75b]

Peptide amphiphiles incorporating peptoid (N-substituted glycine) sequences have been observed to form nanotubes. Conjugates such as $(Sar)_{27}$–(L-Leu-Aib)$_6$ (Sar: sarcosine = *N*-methyl glycine; Aib: 2-aminoisobutyric acid) initially form curved sheets in aqueous buffer solution at room temperature but can close up into nanotubes on heating.[76] The size (diameter and length) of the nanotubes can be tuned through the composition of the peptide amphiphile, as well as the stereochemistry of the peptide group.[77] Occasional 3-fold junctions of nanotubes were highlighted.[76]

The observation of self-assembled nanotubes in aqueous solutions of conjugates of FFFF with PEG (polyethylene glycol) is possible provided the PEG molar mass is sufficiently low, for example, for PEG with a molar mass of 350 g mol^{-1} [78] (at higher PEG molar mass, fibrils are observed[78,79]). The nanotubes comprise antiparallel β-sheets that are stabilized by π–π stacking of the aromatic residues.[80] Soft hydrogels arising from nanotube entanglements are reported at higher concentration.[80]

4. Amyloid Peptide Nanotubes

Lynn's group has investigated the self-assembly of the peptide CH_3CO-KLVFFAE-NH_2, a sequence from the amyloid β peptide, Aβ(16–22). This peptide self-assembles into nanotubes in pH 2 acetonitrile/water solution.[81] A model for the lamination of peptides and the curvature of peptide bilayers to form nanotubes was proposed (Figure 11), using dimensions obtained from SANS (small-angle neutron scattering) experiments. The peptide forms fibrils at pH 6.[82] Differences in the packing of the peptides in the antiparallel β-sheets (changes in strand registry, i.e. relative alignment of peptide strands) were elucidated using solid-state NMR using [1-^{13}C]L17- and [^{15}N]A21-labeled peptides, along with molecular dynamics (MD) simulations and FTIR and XRD data.[82] Isotope-edited FTIR using V18 congeners provided additional information on strand registry.[83] The formation of a salt bridge between K16 and E22 plays an essential role in the formation of fibrils at pH 6. This was confirmed since KLVFFAL formed nanotubes at both pH 2 and pH 6.[82]

Fluorescence labeling of this peptide at the K residue with a rhodamine dye enabled the nucleation and growth process upon dissolution of the peptide of amyloid assemblies to be imaged.[84] Nucleation from a higher temperature state of molten globules has also been examined, intermediate "necklace" structures being observed.[85] Bundling of KLVFFAE nanotubes into lamellar-like arrays can be induced by "salting out" using sulfate anions.[86] The congener peptide KLVFFAL also forms nanotubes and solid-state NMR spectroscopy was used to probe the bilayer ordering within the nanotube walls.[87] The bilayer leaflets are coated with the TFA counterions bound to lysine residues. The binding of the amyloidogenic dye Congo red into the grooves of this peptide was found to align along the nanotube wall (offset from the nanotube axis due to the helical packing arrangement).[88]

The extended peptide HHQKLVFFA [Aβ(13–21)] forms amyloid fibrils rather than nanotubes,[81b] highlighting the sensitivity of the aggregate morphology to peptide sequence. The QKLVFFA motif has been used to drive the self-

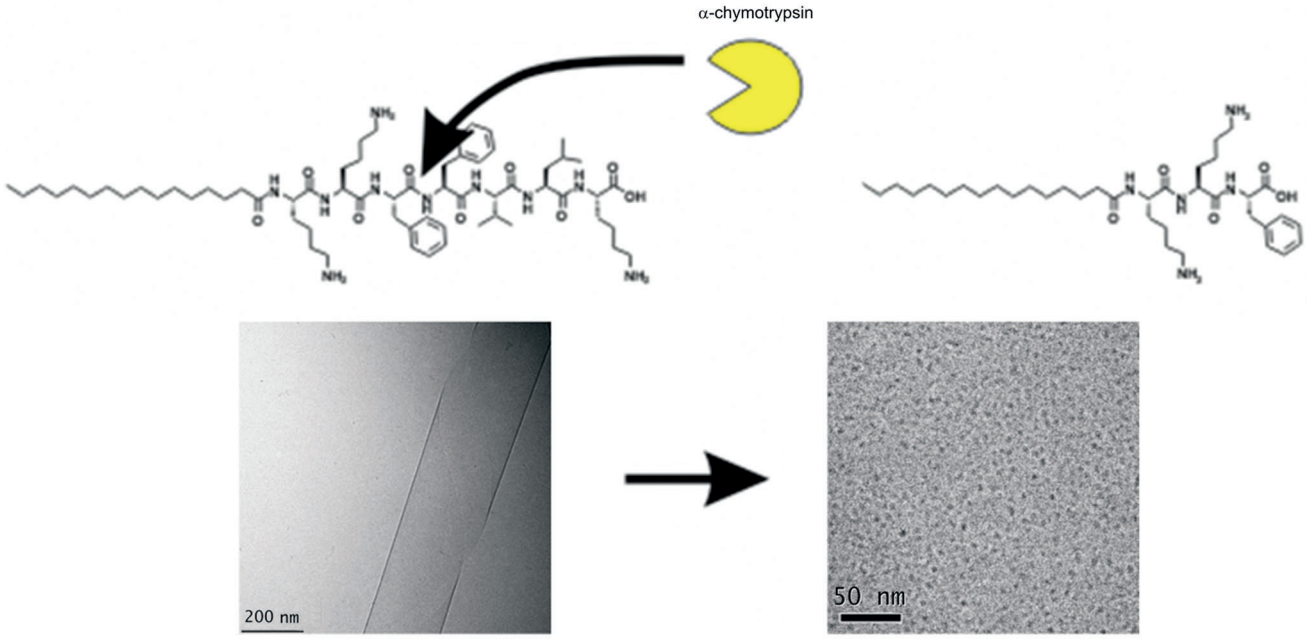

Figure 10. Enzymatic cleavage of C_{16}-KKFFVLK (which self-assembles into helical ribbons and nanotubes at room temperature) by α-chymotrypsin produces C_{16}-KKF and C_{16}-KKFF which form spherical micelles.[75b]

assembly of cytosine nucleobases incorporated within two β-(cytosine-1-yl)-alanine residues at the N terminus.[89] Nanotube formation of the nucleobase–peptide conjugate was observed through TEM and SAXS, with the nucelobase covering the outer surface of the nanotube.

In a similar vein, we showed that peptide NH_2-AAKLVFF-COOH self-assembles into nanotubes in methanol.[90] A nematic phase of the nanotubes is observed.[90] The self-assembly of this peptide is dependent on the nature of the solvent, as it forms fibrils in water.[91] We also studied self-assembly in water/methanol mixtures and observed only fibrils (high water content mixtures) or nanotubes (high methanol content) but not intermediate structures.[92] We suggested that the solvent's hydrogen bonding capacity may be one factor influencing fibril vs. nanotube self-assembly, although differences in the permittivity of the solvents will also affect electrostatic interactions between charged residues (and the termini) and hence, potentially, the preferred self-assembled nanostructure. Molecular dynamics simulations supported an antiparallel arrangement of the peptides within β-sheets. It was also possible to model the unusual observed circular dichroism spectrum.[92b] Molecular level differences underlying the formation of fibrils or nanotubes by AAKLVFF were probed by solid-state NMR experiments.[93] An offset monolayer or partially interdigitated bilayer arrangement was proposed for the nanotubes (and a steric zipper bilayer structure for the fibrils) (Figure 12).

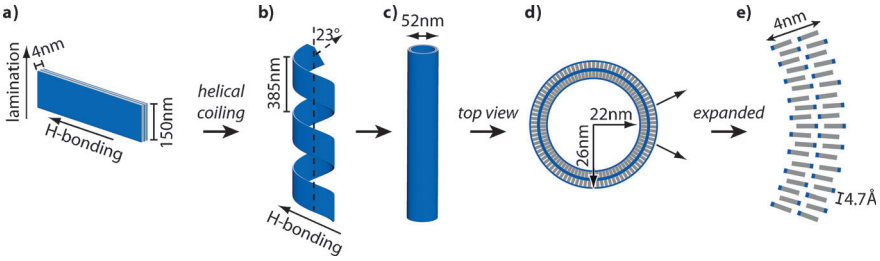

Figure 11. Model for the assembly of β-sheets of KLVFFAE into nanotubes.[81a] a) A flat rectangular bilayer, b) coiled tubular fibril with helical potch of 214 nm, c) side and d) top view of nanotube, e) detail of nanotube wall.

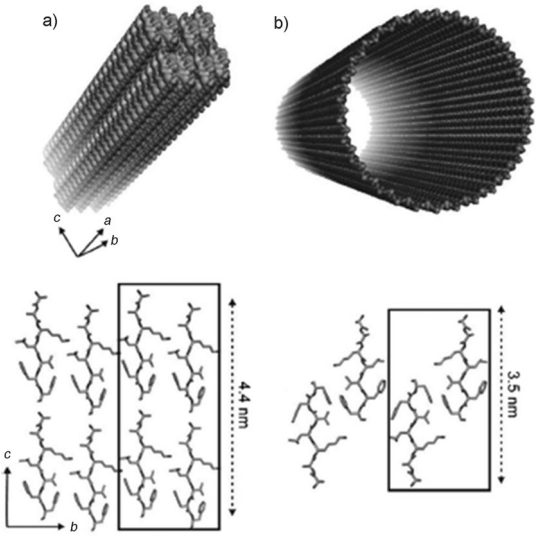

Figure 12. Models for the arrangement of AAKLVFF in a) fibrils and b) nanotubes.[93]

The kinetics and mechanisms of nanotube formation the related peptide βAβAKLVFF (containing two N-terminal β-alanine residues, the peptide being capped at both termini) into nanotubes was studied by AFM (atomic force microscopy). Figure 13 shows representative images. Nanotubes

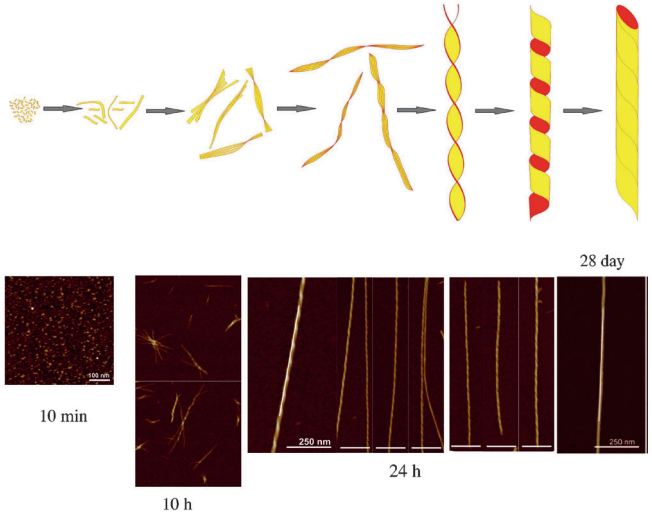

Figure 13. Top: schematic; bottom: AFM height images of structures formed during the self-assembly process of βAβAKLVFF (adapted from Ref. [94]).

formed very slowly from helical ribbons (which formed after 1 day).[94] A β-sulfonamide–peptide hybrid containing the amyloid(20–29) sequence also forms ribbons which close into nanotubes.[95] Figure 7 shows a further example. A transition from twisted ribbons into helical ribbons has been observed for the peptide amphiphile C_{16}-FFFEEE,[96] but not closure into nanotubes.

The designed amyloid peptide Ac-KFAAK-Am can template the formation of titania and silica nanotubes,[97] although it is not clear whether the peptide itself self-assembles into PNTs.

Serpell et al. have recently shown that a peptide from α-synuclein, residues 37–44 (NH_2-VLYVGSKT-COOH), forms nanotubes via intermediate helical ribbon structures.[98] The ordering of the peptides was elucidated in detail by fibre X-ray diffraction analysis. Figure 14 shows the proposed model structure.

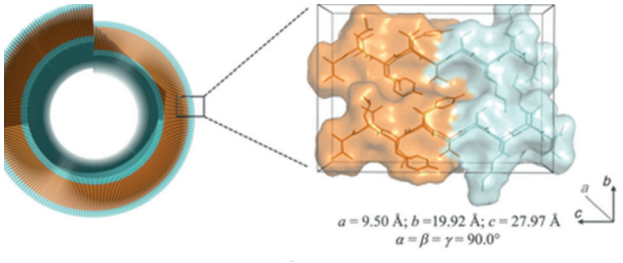

Figure 14. Bilayer structure in the wall of VLYVGSKT peptide nanotubes.[98]

5. Dipeptide-Based Peptide Nanotubes, Especially Diphenyalanine PNTs

Görbitz first noted that hydrophobic dipeptides such as FF can form channel structures through X-ray crystallographic analysis.[99] Hydrophilic channels were also found in the structures of FF, LL, LF, and FL. He later noted that the powder diffraction pattern of FF nanotubes corresponds to the single-crystal structure, indicating that the structural motif is the same.[100]

The observation of nanotube self-assembly by FF in aqueous solution by Gazit's group[101] stimulated a great deal of further research on this peptide. Gazit had previously highlighted the important role of aromatic stacking, as in FF, in the self-assembly of amyloid fibrils.[102] The NH_2-Phe-Phe-COOH peptide was dissolved in HFIP (hexafluoroisopropanol) initially, then diluted into aqueous solution. Nanotubes with a diameter in the range 100–150 nm were observed.[101] These were used as scaffolds for the reductive deposition of silver within the nanotube cavities, producing silver nanowires. D-Phe-D-Phe also forms nanotubes but in contrast to L-Phe-L-Phe exhibits resistance towards proteolysis. This peptide also forms nanotubes in water, and these were used to template the deposition of Pt nanoparticles.[103] Nanotube formation is sensitive to the solvent conditions—nanowires (fibrils) may be observed instead in aqueous solution under appropriate peptide concentration or pH conditions.[104] FF nanotubes have also served as scaffolds for the deposition of polymers.[105] Computer simulations (molecular dynamics) provide insight into the formation of ring-like networks of FF molecules in aqueous solution, in particular charged termini of neighboring peptides are involved in hydrogen-bonding interactions and the aromatic side-chains form "T-shaped" contacts.[106] In contrast to FF, it was noted that FFF forms planar nanostructures.

Modification of the termini of FF can be used to create cationic dipeptide nanotubes. NH_3^+-FF-NH_2·HCl self-assembles into nanotubes at physiological pH, and then vesicles upon dilution.[107] These can be used to deliver oligonucleotides to cells. Although the capped FF peptide CH_3CONH_2-FF-$CONH_2$ can form nanotubes, other bulky aromatic N terminal groups suppress nanotube formation.[108] The observation that the uncharged capped peptide can form nanotubes indicates that their formation is not governed by electrostatic interactions.

Dipeptides AV and VA and AI, IA, VV, VL, VI and IV also show pores (hexagonal spiral arrangement of molecules) in their crystal structures.[109] The size of the channels (observed in the crystal structure) varies in the range 3.3 to 5.2 Å depending on the amino acid side chains.[109b] The high microporosity of AV and VA these materials was characterized by measurement of adsorption isotherms, suggesting applications such as selective sorption/release.[109a] Dipeptides containing β-alanine (β-Ala-Xa, with Xa = V, I or F) also form crystalline nanotubes, onto which gold nanoparticles can be templated.[110]

FF nanotubes are robust, being stable in boiling water[111] and also in organic solvents such as ethanol and acetone[111] and acidic/alkaline conditions. However, at high temperature,

they can be indented by an AFM tip in a thermomechanical manipulation procedure.[112] FF nanotubes can be patterned using inkjet printing technology.[113] Electrospinning of FF nanotubes from HFIP has also been demonstrated.[114] FF nanotubes can be aligned by depositing magnetic nanoparticles (ferrofluid) onto the tubes and aligning in a magnetic field,[115] or even without dopants in a strong magnetic field.[116] The peptide NH_2-Phe-ΔPhe-COOH where ΔPhe denotes the noncoded and nonchiral α,β-dehydrophenylalanine residue also forms nanotubes.[117]

Vapor deposition (at more than 240 °C) of FF leads to nanotubes of cyclo-FF.[118] By controlling deposition (spreading from a volatile solvent such as HFIP) conditions, it is possible to fabricate vertical arrays of nanotubes (Figure 15).[115,118a] The nanotubes are micrometers in length

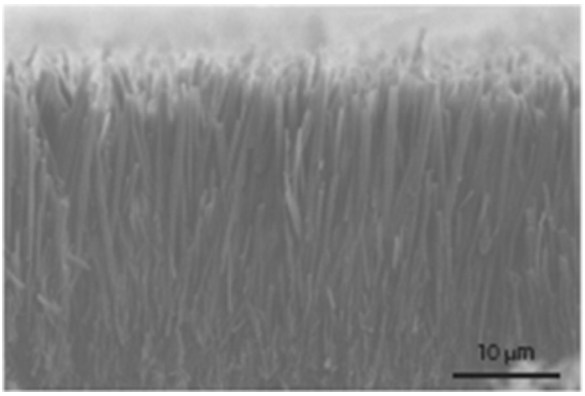

Figure 15. Side view of vertically aligned cyclo-FF nanotubes, forming a "nanoforest".[118a]

with diameters from 50–300 nm. The nanotube arrays can serve as high surface-area electrodes or ultracapacitors, among other applications.[118a] Indeed, cyclo-FF nanowires have semiconducting and photoluminescence properties.[118b] "Nanoforest" surfaces of vertical nanotubes were used to produce highly hydrophobic surfaces.[118a] A mechanism for self-assembly into nanotubes has been proposed, based on formation of an initially amorphous film, followed by nucleation of peptide nanofibers comprising cyclo-FF, formed at sufficiently high temperature.[118d] Under careful solvent casting conditions, spherulite formation is also possible.[119] On the basis of the analysis of quantum confinement effects, a model for the formation of nanocrystalline regions in FF nanotubes has been put forward.[120] These regions behave as quantum dots in terms of optical absorption and photoluminescence emission properties.

There are many examples of the interesting applications of FF nanotubes. For example, they can be used to monitor temperature in the range 0–70 °C with a precision of 1 °C by monitoring the temperature-dependent photoluminescence lifetime—that can also be used to detect local rapid temperature changes.[121] This group has also demonstrated the light-induced ferroelectricity of FF nanotubes/microtubes which arises from spontaneous polarization (dipoles associated with hydrogen bonds parallel to the tube walls) and switching under an applied electric field.[122] FF PNTs deposited onto graphite electrodes can improve their electrochemical performance, and the enzymatic production of hydrogen peroxide was enhanced.[123] PNTs may also be deposited onto carbon electrodes to produce supercapacitors, the increase in capacitance being associated with the increased functional area provided by the hydrophilic channels of the nanotubes.[124]

Diphenylalanines have been used to create photoluminescent PNTs, prepared by the incorporation of photosensitizers and/or lanthanide ions.[125] More recently, fluorescent nanotubes were created using FF with aggregation-induced emission with BSPSA (9,10-bis[4-(3-sulfonatopropoxyl)-styryl]anthracene).[126] Piezoelectric activity has also been demonstrated for FF nanotubes, with linear deformation as a function of applied voltage over a wide range of voltages.[127] Non-linear optical effects have been reported for FF nanotubes, including a second-harmonic generation response, including frequency conversion from NIR to green and blue light.[128] Waveguiding, that is, propagation of red light within the nanotube core, has also been examined.[128]

Porphyrin-doped FF PNTs have been proposed as biomimetic photosynthesis materials.[129] The FF nanotubes are coated with the tetra(*p*-hydroxyphenyl) porphyrin during the self-assembly process (co-dissolution). In addition, platinum nanoparticles were deposited onto the nanotubes to act as electron separators and transporters. Visible light-driven regeneration of the coenzyme nicotinamide adenine dinucleotide dehydrogenase (NADH) was observed.[129]

6. N-Terminus-Modified Peptide Nanotubes

Although Fmoc-FF (Fmoc = 9-fluorenylmethoxycarbonyl) itself seems to self-assemble into fibrils[108] (other papers suggest it forms tubes,[130] however the micrographs presented resemble more a fibrillar structure), this peptide has been used to template the deposition of $FePO_4$ to create nanotubes (by calcination to remove the organic core).[131] Carbonization of the inner core leads to carbon-coated $FePO_4$ nanotubes with potential as cathode materials for rechargeable Li ion batteries.

Fmoc-L_3-OH forms nanotubes via enzymatic hydrolysis of Fmoc-L_3-OMe (i.e. the methyl ester).[132] It is proposed that the nanotubes are stabilized by π–π stacking interactions. The nanotubes show electrical conductivity properties and were proposed to have potential in electrically stimulated cell differentiation.

It has also been reported that the Boc-tripeptides (Boc = *tert*-butoxycarbonyl) Boc-YVY-OMe and Boc-YIY-OMe form tube-like channels in the crystal state, as revealed by X-ray crystallography.[133] The essential role of the two terminal tyrosine residues in driving nanotube formation was later highlighted—nanotubes were not observed for a series of Boc-tripeptides in which the tyrosines were substituted with phenylalanine or leucine or isoleucine.[134] Boc-Phe-Phe can form spherical or tubular nanostructures.[108,135] Nanomechanical measurements using an AFM tip showed that the modulus is more than 100 GPa for the

spherical structures, a value higher than for other organic materials and similar to that of steel.[135]

Among other examples, a camptothecin peptide derivative CPT-G-Succ-FFYGE-ss-EEE (CPT denotes camptothecin, which is an anti-cancer drug, Succ denotes succinate and ss a disulfide unit) forms a hydrogel containing nanotubes, after addition of glutathione which reduces the disulfide bond.[136] Two or four CPT molecules have been linked to an aggregating peptide GNNQQNY from the Sup35 yeast prion with two additional charged residues at the C terminus, either K_2 or E_2.[137] Nanotube self-assembly was observed in catanionic mixtures of the two conjugates in acetonitrile/water mixtures (the individual charged peptides formed fibrillar structures).[137] Conjugates containing four CPT units linked to a tau-protein derived sequence via a biodegradable disulfylbutyrate linker self-assemble into nanotubes.[138] These conjugates can be used to deliver CPT by reduction of the linker in the presence of glutathione, which is a cancer-relevant reducing agent.

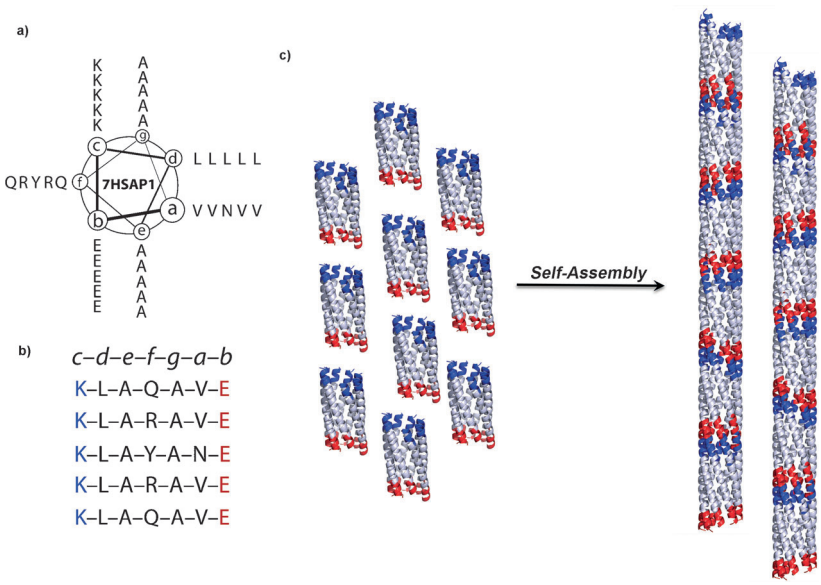

Figure 16. a) Helical wheel and b) linear depiction of the sequence of 7-helix bundle peptide 7HSAP1. c) Schematic of the proposed model for self-assembly of lock-washer structures into nanotubes, blue and red surfaces representing the positively charged (N-terminal) heptads and negatively charged (C-terminal) heptads at the interfaces between 7-helix bundle subunits. From Ref. [140].

7. Coiled-Coil Peptide Nanotubes

There are few reports on the self-assembly of coiled-coil peptides into extended nanotubes. Coiled-coil peptides do not in general form nanotubes, rather isolated bundles or, by design, fibrils. Other reviews cover the topic of coiled-coil peptide secondary structures and bundle formation in more detail.[139] Barrel structures formed by α-helices that can be considered as a type of (short) nanotube are reviewed elsewhere.[139b]

It is possible to engineer coiled-coil peptides to form nanotubes. For example, the aggregation of a 7-helix bundle of coiled-coil peptide into nanotubes via a "coil-lock washer" aggregation mechanism has recently been reported. The self-assembly was driven primarily by electrostatic interaction between structurally complementary bundle edges, comprising E and K residues (Figure 16).[140]

8. Protein Nanotubes

Proteins which adopt a β-helix structure, such as the gramicidin family, form nanotubes with a biological role as transmembrane channels.[141] Such native folded structures are outside the scope of the present review. The formation of nanotubes using bio-inspired β-helix motifs (taken from published protein structures) has been modelled by molecular dynamics simulations.[142] A system exhibiting high stability of nanotubes was noted.

Ballister et al. exploited the fact that the small 17 kDa protein Hcp1 adopts a homohexameric ring-shaped quaternary structure to create nanotubes by performing cysteine mutations capable of forming disulfide bridges between rings.[143] The nanotubes contained up to 25 subunits, and furthermore tube ends and/or interior could be independently functionalized, enabling the capping or plugging of the nanotubes. This concept was also used to drive the formation of nanotubes by TRAP (trp RNA-binding attenuation protein) which forms an 11-mer ring as its native structure.[144] Mutations of D to H were also employed to facilitate biomineralization, via metal ion co-ordination by histidine, in the central cavity of the nanotubes. A tetrameric coiled coil protein based on cytochrome C was genetically modified to incorporate histidine Zn^{2+} binding sites leading to the formation of a dimer.[145] The dimers can aggregate in aqueous solution into a helical chain through pairwise interactions involving zinc ions. This forms the wall of observed nanotube structures. Two-dimensional nanosheet and 3D crystal structures were also observed (under conditions of lower Zn^{2+} concentration).

Usually denatured proteins form amyloid fibrils, however under carefully controlled conditions it is possible to observe nanotube formation. The formation of PNTs by lysozyme under hydrolysis at pH 2 and 90 °C has been reported.[146] Nanotubes comprising alternating layers of gold nanoparticles and layers of oppositely charged human serum albumin with poly(L-arginine) have been fabricated using a layer-by-layer deposition method, onto a track-etched polycarbonate membrane with 400 nm pore diameter. This led, after removal of the sacrificial membrane support, to 426 nm outer diameter gold nanoparticle-functionalized protein nanotubes in a "nanoforest" array.[147]

9. Summary and Discussion

To date, the main classes of peptide nanotube structures comprise either stacked cyclic peptides or non-cyclic peptides/lipopeptides arranged in bilayer structures, with the peptides aligned normal to the tube walls and nanotube axis, with a twist in the β-sheets around the nanotube axis. Other architectures such as the locked washer coiled coil nanotubes[140] are less observed. Native ring-shaped proteins that can be engineered to form nanotubes also show great promise for advanced nanostructure design. Some configurations, for instance peptides aligned parallel to the nanotube walls have not been reported to our knowledge. The exact design rules for PNT formation are as yet not clearly elucidated, somewhat in contrast to the case of peptide fibrils where a number of models to account for fibril assemblies are available.[148]

As mentioned above, probably the most detailed modelling to date for PNTs has been performed for the cyclic peptide lanreotide,[29d,g] since these authors have tried to account for the curvature that selects a particular nanotube radius. Theories for the curvature of layered structures into helical ribbons,[149] and closed tubes specifically[149d] may be useful, if relevant elastic constants can be measured experimentally. As yet, to our knowledge, this has not been done, in contrast to the case of lipids. Indeed, theories or computer models specific to the case of nanotube-forming peptides (that allow for the important role of hydrogen bonding and side chain packing, absent for lipids) are needed. Understanding the dynamics and equilibria associated with nanotube self-assembly are other challenges where further research (experimental and theoretical) is required.

Nanotubes are one-dimensional assemblies which can have remarkable mechanical properties, as illustrated by FF.[135] Indeed, this very simple dipeptide forms nanotubes with a range of very interesting potential applications in optoelectronics. This molecule is in some respects the "carbon nanotube" analogue in PNTs. A better understanding of electron transport properties in PNTs and quantum confinement effects will lead to an improved basis to design materials with enhanced electronic and/or optical properties. Other, more "biomimetic" PNTs have exciting potential applications in biomedicine, where they may encapsulate cargo for targeted delivery (by functionalization of the nanotube surface) or serve as or deliver antimicrobial agents. They may also be useful in the production of porous materials, through biomineralization or templated in polymer films. It has been shown that rod-shaped "filomicelles" have enhanced delivery capacity due to extended circulation times relative to spherical micelles,[150] it remains an interesting challenge to extend this type of study to examine the role of peptide self-assembled architecture on bioactivity.

Incorporating bioresponsive elements into the nanotube (such as enzyme substrates) design offers further exceptional scope in the development of functional and remodellable peptide assemblies. Covalent capture of PNT structures by cross-linking also offers potential to tune the structural and functional properties of the assemblies and this is likely to offer new horizons in nanomaterials science. The use of peptide nanotubes as structuring agents (e.g. of tethered polymers) also merits further exploration. Finally, exploring the influence of "nano-confinement" within the tunable and biocompatible interior of nanotubes on, for instance, the structural or dynamical properties of proteins or other encapsulated molecules, is an aspect with rich possibilities for new discoveries.

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