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REVIEW

Hierarchical Self-Assembly of Aromatic Peptide Conjugates into Supramolecular Polymers: it takes two to tango

Maëva Coste,^{a,†} Esteban Suárez-Picado,^{a,b,†} and Sébastien Ulrich^{a*}

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Supramolecular polymers are self-assembled materials displaying adaptive and responsive “life-like” behaviour which are often made of aromatic compounds capable of engaging in π - π interactions to form larger assemblies. Major advances have been made recently in controlling their mode of self-assembly, from thermodynamically-controlled isodesmic to kinetically-controlled living polymerization. Dynamic covalent chemistry has been recently implemented to generate dynamic covalent polymers which can be seen as dynamic analogues of biomacromolecules. On the other hand, peptides are readily-available and structurally-rich building blocks that can endow secondary structures or specific functions. In this context, the past decade has seen an intense research activity in studying the behaviour of aromatic-peptide conjugates through supramolecular and/or dynamic covalent chemistries. Herein, we review those impressive key achievements showcasing how aromatic- and peptide-based self-assemblies can be combined using dynamic covalent and/or supramolecular chemistry, and what it brings in terms of structure, self-assembly pathways, and function of supramolecular and dynamic covalent polymers.

1. Introduction

Amino acids are the monomers that make up proteins, which perform vital functions in living organisms. The recognition and catalytic functions of proteins greatly depend upon their composition and sequence, folding, and multivalent interactions – all of which are encoded by the precise insertion of amino acids. Mainly, peptides exert this role by triggering supramolecular hierarchical self-assembly, from β -sheets and α -helix up to quaternary assemblies, with potential stimuli-responsive behaviour due to the reversibility of non-covalent interactions. Exploiting this principle, peptides have been recently introduced in building blocks that yield, by bottom-up self-assembly, macromolecules such as supramolecular polymers or dynamic covalent polymers. Due to their expressed multivalency,^{1, 2} dynamic covalent polymers, as well as supramolecular polymers have become useful tools for the biomolecular recognition of proteins^{3, 4} and nucleic acids,⁵⁻⁷ for (targeted) delivery,⁸⁻¹¹ bioimaging,¹² and applications in catalysis.^{13, 14} This strategy of inserting peptides into self-assembled polymers enables generating dynamic analogues of proteins which, thanks to the reversibility of non-covalent interactions or covalent reactions, can grow and collapse depending on the conditions, exchange building blocks/sequence, all of which greatly contribute to endowing/modulating their function. Such an approach bears a

strong degree of biomimicry for accessing supramolecular biomaterials that resemble some of the biopolymers found in the cytoskeleton like actin microfilaments,¹⁵ and are currently considered of strong potential toward functional smart polymers.¹⁶ Thus, the intertwining of the area of supramolecular polymer chemistry with the realm of peptide chemistry can be a fruitful route toward biomimetic smart materials. Indeed, the synergistic combination of multiple supramolecular interactions endowed by those different types of building blocks (e.g. hydrogen bonding, π - π interactions, etc) has been recognized as a powerful strategy for achieving a bottom-up hierarchical self-assembly.¹⁷ In this review we will summarize the achievements that have been reported in the last decade when inserting peptides into both supramolecular and dynamic covalent polymers, either for endowing them with specific structures and/or functions, or for impacting their complex self-assembly pathways.

2. Effects of Aromatics and Peptides in Dynamic Covalent Polymers

2.1. What are dynamic covalent polymers?

Dynamic covalent polymers (DCPs) are macromolecules obtained through dynamic covalent self-assembly processes that rest on the use of reversible covalent reactions.¹⁸⁻²¹ Unlike classical polymers, DCPs are therefore dynamic objects which can reversibly form and fall apart, and adapt their constitution (length, sequence) to internal (e.g. folding) and/or external (pH, redox, presence of binding partner) forces (Scheme 1). DCP can be of multidimensionality, from linear 1D to cross-linked 3D and different types of DCPs have been reported to date: poly-

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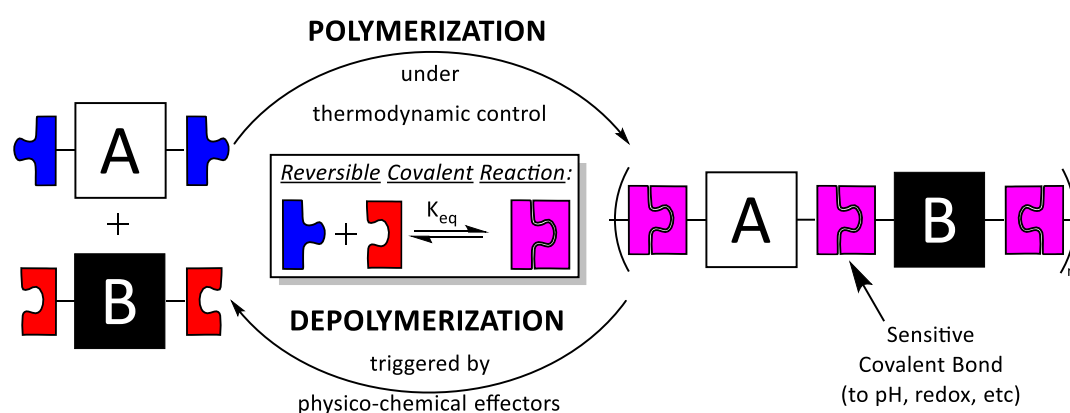
† These authors contributed equally to this work.

imines, poly-acylhydrazone,²² poly-oximes,^{23, 24} and poly-disulphides²⁵ to cite a few.

Since they are formed under thermodynamic control in an equilibrium polymerization, DCPs are polydisperse (PDI \approx 1.5-2), and they often reach a plateau in terms of size and degree of polymerization (typically upper limit of DP \approx 10-20), which probably represents the most important limitation of DCPs. In an isodesmic equilibrium polymerization (equal equilibrium constants K_{eq} for each step), K_{eq} limits the conversion ρ ($\rho = K_{eq}^{1/2}/(1 + K_{eq}^{1/2})$) which dictate the degree of polymerization according to the Carothers' equation ($DP = 1 + K_{eq}^{1/2}$).²⁶ Typically, this means that, in a closed system, DP of 100 can only be achieved with K equal to 10^4 . Moreover, as in classical step-growth polymerization, stoichiometry balance should be near ideal in order to reach high degree of polymerization. However, when cooperative effects come in action, meaning that

equilibrium constants increase throughout the multi-step polymerization process, then very long DCPs can be formed, even in conditions of imbalanced stoichiometry.²⁷ Such cooperative effects can originate from internal (e.g. activation/deactivation,^{28, 29} folding^{30, 31}) or external (e.g. template-assisted polymerization³²) forces that modulate reactivity throughout the polymerization process. Those secondary interactions can greatly assist the polymerization process, like the π - π stacking interactions that are commonly seen in the supramolecular polymerization involving aromatic compounds.

DCPs have already found numerous applications in material sciences due to their self-healing and shape memory properties,^{19,33} and are the current subject of a growing interest in biological sciences, for instance as smart and responsive delivery vectors.⁸⁻¹⁰



Scheme 1. Principle of formation of dynamic covalent polymers (DCPs) using reversible covalent reactions. The example depicted here features linear alternating DCPs made of complementary bifunctional building blocks A and B.

2.2. Functional DCPs by peptide insertion

Disulphides are redox-sensitive covalent bonds commonly found in proteins. The access to poly-disulphide DCPs can be achieved using an amino acid: cysteine. Indeed, peptides appended at both C and N termini with cysteine would lead to linear DCPs through such an oxidative polymerization.³⁴ The group of Seymour reported early on that the cationic peptide **1** – a Lys₁₀ peptide flanked with one cysteine at each end, leads, through a DMSO-promoted oxidative polymerization, to DCPs able to complex and deliver plasmid DNA (pDNA) thanks to multivalent electrostatic interactions (Fig. 1A).³⁵ Those DCPs were formed in a step-growth polymerization and have molecular weights reaching 187000 Da. In this example, one amino acid (Cys) is responsive for generating the DCPs while the others (Lys) endow the function of complexing nucleic acids through electrostatic interactions. More recent designs used cyclic disulphides that undergo DNA-templated polymerization through ring-opening polymerization.³⁶

Our group studied another class of DCPs for gene delivery applications: poly-acylhydrazones. After having established the ability of cationic poly-acylhydrazones to i) bind DNA through multivalent interactions, and ii) be pH-sensitive,³⁷ we expanded the scope of building blocks by introducing modified amino

acids bearing an aminoxy group at the N terminus and a hydrazide at the C terminus (Fig. 1B, compounds **2**).³⁸ There, the presence of amino acids imparts molecular recognition properties to the system. These building blocks undergo a step-growth polycondensation with a complementary synthetic bisaldehyde **3**, through both acylhydrazone and oxime ligations, that lead to DCPs. Cationic amino acids (Lys, His, Arg) were selected for the application of nucleic acids recognition, and the DCPs made of Arg gave the best results in terms of DNA complexation and siRNA delivery in live cells. Finally, our most recent achievement is the in situ siRNA-templated polymerization and formation of glyco-peptide DCPs capable of cell-selective siRNA delivery.³⁹

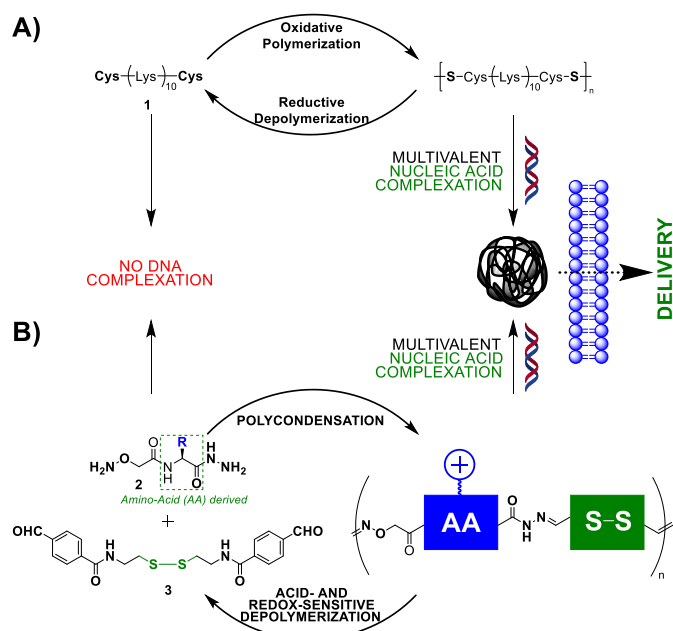


Figure 1. Dynamic covalent polymers endowed with a function of nucleic acid recognition which is encoded by inserted cationic amino acids.

2.3. Peptide-enforced folded DCPs

The group of Montenegro explored peptides as structured scaffolds adopting a helical secondary structure for the construction of gene delivery vectors (Fig. 2A).^{40–42} This programmed folding combined with the capacity to insert modified amino acids bearing reactive hydrazides at precise positions enables generating amphiphiles having separated lipophilic and hydrophilic faces.

On the other hand, peptides can also enforce the folding of DCPs. Following the seminal contribution of Moore and co-workers on folding-driven formation of poly-imines,³¹ the group of Lehn explored poly-acylhydrazone DCPs and demonstrated that a hydrophobically-driven folding process can result in constitutional selection and unusually long DCPs ($M_w \approx 300$ kDa).^{43, 44} They then combining aromatics **4** (carbazole N-functionalized with hexaethylene glycol groups for imparting water solubility) with modified amino acids **5** (C-hydrazide amino acids that can get involved in both imine and acylhydrazone reaction at, respectively, the N- and C-termini) (Fig. 2B).^{45, 46} These “proteoids” form according to a nucleation-elongation polymerization⁴⁷ and have degree of polymerization reaching 60 and $M_w \approx 42$ kDa using a tryptophan-derived amino acid building block, while much shorter DCPs are formed when using a tyrosine-derived building blocks, thereby pointing out the role of the hydrophobic effect that is imparted by the aromatic amino acid side-group in the polymerization process. In the end, this example nicely illustrates the mutual effect of having aromatics and peptides within a single system, by showing how dynamic covalent and supramolecular self-assemblies can influence each other (see section 4 for further information).

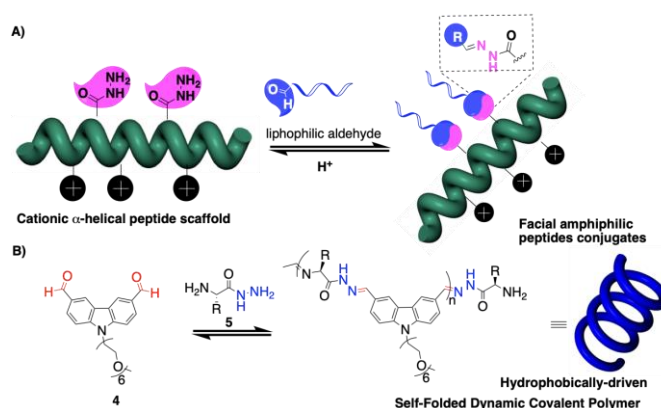


Figure 2. Peptide scaffolds provide facial amphiphiles in laterally-modified dynamic covalent polymers (A), self-folded main-chain dynamic covalent polymers when assisted by the hydrophobic interactions of aromatic groups (B).

3. Supramolecular Polymers made of Aromatic-Peptide Conjugates

3.1. What are supramolecular polymers?

Supramolecular polymers are macromolecular self-assemblies in which the building blocks are held together through non-covalent interactions (e.g. hydrogen bonds, π - π stacking, ion pairing).^{20, 21, 48–50} Like DCPs, and owing to the reversibility of this weak association, supramolecular polymers are dynamic objects capable of constitutional adaptation. This reversible association of monomers endow supramolecular polymers with unique self-healing properties.^{19, 33} On the other hand, the intertwining of supramolecular polymers with the realm of biomolecules can be a fruitful route toward supramolecular biomaterials.¹⁵ In this regard, using bioactive supramolecular polymers, the Stupp group has been recently shown that the dynamics of monomer association within supramolecular polymers plays a key role in the repair of spinal cord injury.⁵¹ Supramolecular polymers can form through different mechanisms,^{52–56} and the pathway taken can have a dramatic impact on their final polymer structures. The isodesmic polymerization has been mentioned above and involves an equal association constant throughout the step-growth polymerization (Fig. 3 A&B). As a result, and following the Carothers' equation, this will limit the degree of polymerization and yield polydisperse supramolecular polymers. Moreover, in these supramolecular polymers that are solely under thermodynamic control, ring-chain equilibria should also be considered as a competitive path.⁵⁶ On the other hand, cooperative polymerization can take place through a nucleation-elongation mechanism,^{47, 57} characterized by a critical elongation concentration – the concentration above which elongation occurs which is inversely proportional to K_e – and a critical elongation temperature T_e ,⁵⁵ which lead to a bimodal mass distribution (monomers and polymers, with little oligomer intermediates), producing longer polymers than those obtained through an isodesmic mechanism (Fig. 3 C-F). In this mechanism that was first exemplified in 2006,⁵⁷ an initial unfavourable nucleation event take place with an association

constant K_n , followed by a more favourable elongation step characterized by K_e ($K_e > K_n$). In certain cooperative systems of higher kinetic stability and displaying fast kinetics of elongation, a seeded supramolecular living polymerization give rise to very long fibres with a very limited length dispersity (Fig. 3 G&H).⁵⁸⁻⁶⁴ Seeding effects originate from a template-accelerated growth that occurs on small aggregate fragments – usually obtained after fragmentation (by sonication) of the nano-assemblies (e.g. fibers, micelles)⁶⁵⁻⁶⁷ – which trigger supramolecular living polymerization by overriding the energy barriers (Fig. 3 H). This methodology enables the programmed assembly of supramolecular block copolymers well-defined in both length and sequence (see section 5.1).⁶⁸ Recent endeavours have reported the photo-control of living polymerization in 2-dimensions.^{69, 70}

A vast category of supramolecular polymers exploit the self-assembly of aromatics through π - π stacking that mainly rest on dispersion interactions.^{71, 72} However, only in cases where additional dipole-dipole interactions take place, a cooperative mechanism can emerge that require long-range attraction forces (typically electrostatics arising from the creation of a macrodipole in the supramolecular polymer like in benzene-1,3,5-tricarboxamides, vide infra).⁵⁴ Thus, the combination of aromatics with peptides capable of partaking in hydrogen bonds represents an interesting approach.

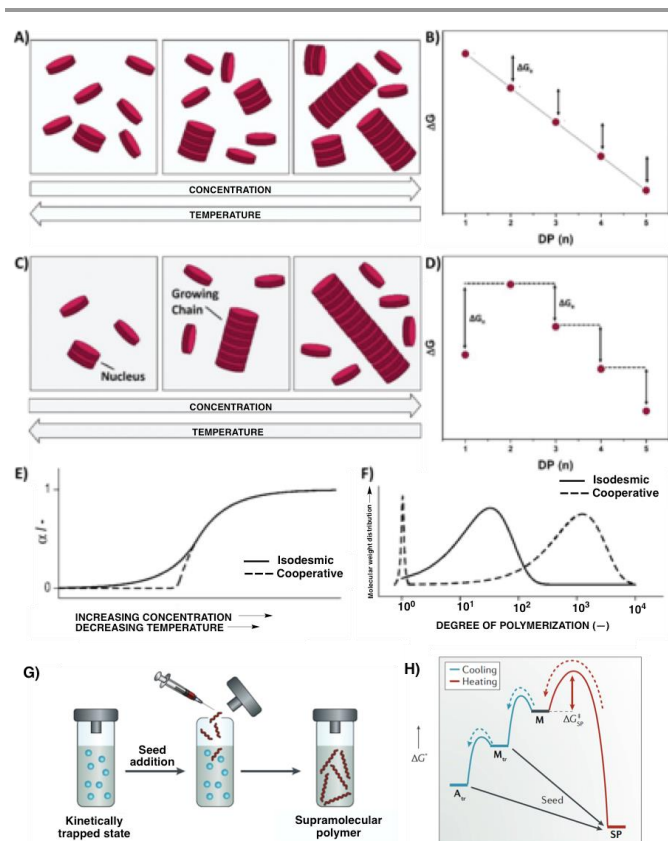


Figure 3. Main features of isodesmic (A, B), cooperative nucleation-elongation (C, D), and living (G, H) supramolecular polymerizations processes. Panels A and C schematically depict how supramolecular polymerization is controlled by concentration and temperature, while panels B and D provide a thermodynamic view of the different steps at play with D representing the case of an uphill process involving unfavoured nuclei. Panels E and F summarize the main differences between isodesmic and cooperative

polymerization processes, the isodesmic supramolecular polymerization continuously yielding small polydisperse polymers as concentration is increased or temperature decreased, and cooperative polymerization yielding larger and less polydisperse polymers only beyond a threshold concentration and below a critical temperature. Panels G and H depict the principle of a seeded supramolecular polymerization, with panel G schematically representing the process involving the addition of seeds onto a solution of a kinetically-trapped monomers, and panel H representing the Gibbs free energy diagram of the nucleation-elongation supramolecular polymerization with the bypass involved in seeded supramolecular polymerization. Adapted from references 52 (permission from the Royal Society of Chemistry), 55 (permission from John Wiley and Sons), and 53 (Copyright 2019 Springer Nature).

3.2. Effect of aromatics on peptide self-assembly

Inspired by the self-assembly of amyloid fibres, a pioneering input from the Gazit group was that a short diphenylalanine can undergo spontaneous self-assembly into tubular⁷³ and spherical⁷⁴ nanostructures in aqueous media.^{75, 76} The group further studied derivatives featuring N-acetyl, C-amide, N-Boc, N-Cbz, and N-Fmoc modifications, and observed marked structural differences in the resulting tubular nano-assemblies. Along with the contributions from other groups, crystallographic analyses reveal that the presence of aromatic groups influence the organization of the self-assembled material in the solid state: while the unmodified PhePhe dipeptide gives discrete, hollow, and well-ordered nanotubes,⁷⁷ extending the repeat to the tripeptide PhePhePhe results in planar nanostructures through β -sheets formation,⁷⁸ and replacing phenylalanine by tyrosine yields microspheres instead.⁷⁹ Adding a Fmoc group at the N-terminus of PhePhe reinforces π - π interactions and yields interlocked anti-parallel β -sheets,⁸⁰ contrary to the acetyl group which lead to a canonical β -sheet structure when placed at the N-terminus (Ac-PhePheF-NH₂).⁸¹ Thus, in addition to providing an extra-stabilization in proteins,⁸² π - π interactions plays also a role in directing the self-assembly of short peptides, as also observed in the early 2000 by the Xu^{83, 84} group.⁸⁵ Indeed, when aromatics are present, very short peptides of 2-3 amino acids can surprisingly lead to the formation of materials such as hydrogels, thereby illustrating their contribution to stabilizing peptide-based self-assemblies.^{86, 87} The properties of these materials depends on the length, composition, and sequence of peptides,⁸⁶ but is also strongly affected by the chirality of the amino acids and by the nature of the aromatic groups.⁸⁸⁻⁹⁶ Such supramolecular self-assembly involves β -sheets formation and different type of arrangement are proposed: parallel, anti-parallel or interlocked anti-parallel (Fig. 4).⁹⁷ However, one caveat to make here for systems combining aromatics and peptides is that the distance between aromatics involved in π - π stacking interactions (3.4 Å) is slightly shorter than the distance separating two peptide strands involved in a β -sheet (\approx 4.8 Å). Therefore, the combination of both interactions requires some structural distortion. Leaders in this area have already reviewed in details the effect of various aromatic groups (Fmoc,⁹⁸ phenyl, naphthalene, pyrene, etc) on the self-assembly of short peptide amphiphiles and the readers are referred to those accounts for comprehensive details and design guidelines that have emerged over the course of these studies.⁹⁹⁻¹⁰³

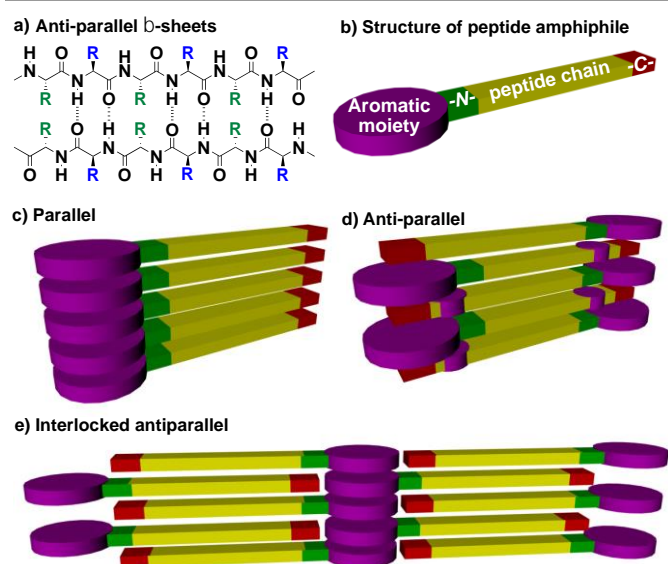


Figure 4. Supramolecular self-assembly of aromatic peptides: a) general structure of anti-parallel β -sheets; b) schematic representation of aromatic peptides with the aromatic group tethered to the N terminal of the peptide chain; possible arrangements of aromatic peptides self-assemblies: c) parallel, d) anti-parallel, e) interlocked anti-parallel.

Aromatics are usually positioned at the N-terminus of peptides and various structural parameters such as the nature of aromatic, structure of spacer, composition and sequence of peptides were explored. Using such aromatic peptides amphiphiles, different types of nanostructures such as spheres, worms, sheets, tapes, fibres/tubes nanostructures and hydrogel networks have been documented from incredibly low-molecular-weight compounds such as Fmoc-F and Fmoc-Y. The role of the aromatic stacking interactions as a driving force for self-assembly has been revealed in several peptide derivatives. For instance, a penta-fluorinated phenyl at the N-terminus of dipeptides was shown to trigger hydrogel formation unlike its non-fluorinated analogue (Fig. 5a).¹⁰⁴ Xu and co-workers reported an interesting example of complementary pentapeptides **A-Py** and **B-Py** that self-assemble through β -sheets in a process driven by the stacking of pyrene groups appended at their C-termini (Fig. 5b).⁸⁵ Interestingly, this happens concomitantly to an α -helix to β -sheet transition in each peptide, shown by circular dichroism (CD) spectroscopy, which depends upon the distance between the aromatic moiety and the corresponding peptides. Last year, Gazit and co-workers reported an interesting dipeptide, Fmoc-Lys(Fmoc)-Asp, bearing two Fmoc groups on the N-terminal Lys, and two hydrophilic carboxylic acid moieties at the C-terminal Asp,¹⁰⁵ which self-assembles in parallel stacks into fibres that lead to a hydrogel at a very low critical gelation concentration (CGC) of 0.002 wt% (Fig. 5c). Very recently, aromatics have also been shown to influence the self-assembly of PhePhe – a well-studied bioinspired prototype of soft materials (Fig. 5d).¹⁰⁶ In this work, the Fernández group functionalized the N terminus of PhePhe with either pyrene or naphthalene groups and found that these aromatics altered the mechanism of self-assembly. While the pyrene peptide conjugate **Py-FF** arranged in parallel β sheets

that are enforced by strong π - π interactions, the naphthalene conjugate **Nap-FF** adopted an antiparallel β sheet organization in H₂O/THF 9/1.

These organization resulted in, respectively, aggregation-caused quenching and aggregation-induced emission of the fluorescence of those conjugates. Interestingly, the self-assembly pathway revealed by variable-temperature studies of UV-Vis spectroscopic data a highly cooperative ($\sigma = 4.5 \cdot 10^{-5}$, see below) supramolecular polymerization for the π -stacked pyrene conjugate and an isodesmic self-assembly for the naphthalene peptide conjugate. Complementary aromatics displaying charge transfer interaction can also be used for the formation of multi-component systems (Fig. 5e).¹⁰⁷ Finally, manipulating the extent of π - π /hydrophobic interactions involving aromatics should then enable modulating the thermodynamic stability of the resulting nanostructure. Indeed, the photo-switching of azobenzenes was shown to enable controlling gel-sol transition with light.¹⁰⁸⁻¹¹⁰

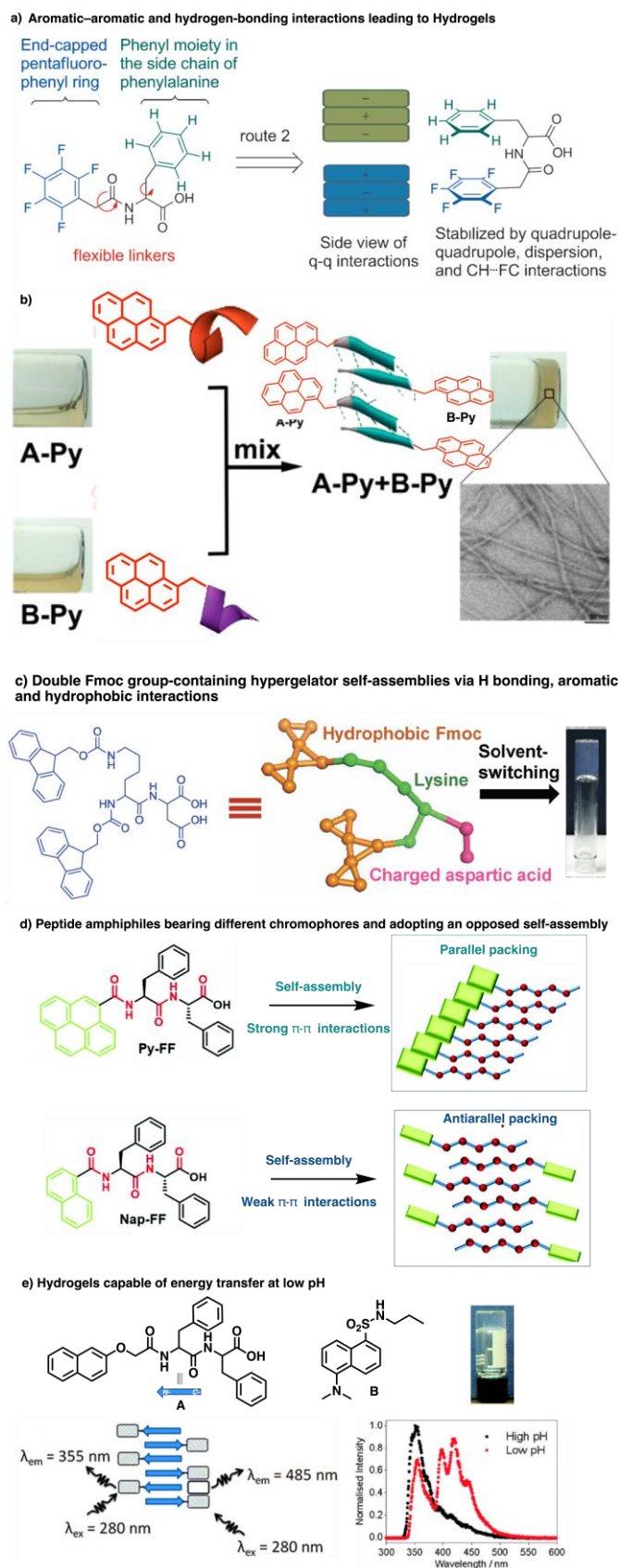


Figure 5. Recent examples of supramolecular polymers made of aromatic peptides: a) hydrogel formation driven by aromatic interactions involving a penta-fluorinated phenyl as N-caps (reproduced from reference 104 with permission from John Wiley and Sons); b) pyrene groups trigger the self-assembly of complementary peptides in β -sheets

(adapted with permission from reference.85 Copyright 2017 American Chemical Society); c) self-complementary Fmoc-Lys(Fmoc)-Asp forms fibres and hydrogel (adapted from reference 105 with permission from John Wiley and Sons); d) the presence of aromatic affects the mode of assembly of PhePhe dipeptides (adapted from reference 106 with permission from the Royal Society of Chemistry); e) self-assembly of aromatic peptides involving complementary donor-acceptor aromatics (adapted from reference 107 with permission from the Royal Society of Chemistry).

Cyclic Peptides (CPs) forms a particular class of compounds capable of self-assembling into columnar nanostructures. These peptides can be obtained by a amide bond cyclization between the N- and the C-termini of a peptide chain (Fig. 6).¹¹¹ Within those CPs, the amide groups are perpendicularly arranged to the plane of the ring, thereby promoting the formation of hydrogen bonds with other cyclic peptides via tubular-assembly. As a result, nanotubes are generated, in which the inner diameter and properties depends on the number and nature of the building blocks.

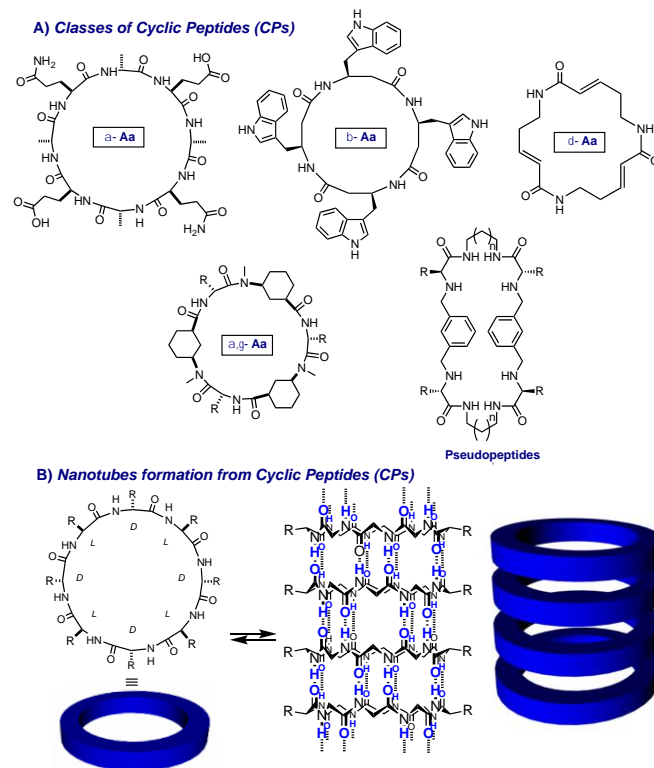


Figure 6. Examples of cyclic peptides (CPs) used for generating nanotubes through supramolecular polymerization: (A) representative structures of cyclic peptides made of α -alt(L,D) residues,¹¹² β -residues,¹¹³ δ -residues,¹¹⁴ α - and γ -residues,¹¹⁵ and cyclic pseudopeptides¹¹⁶; (B) self-assembly of cyclic peptides through β -sheet formation leading to nanotubes.

Initially pioneered by the group of Ghadiri,¹¹² the Granja and Montenegro labs have provided a seminal contribution in the last decade in the synthesis and self-assembly of octameric D/L-alternating cyclic peptide. In particular, they pioneered the use of cyclic γ -amino acids (γ -Aca) in combination with natural α -amino acids of opposite chirality. This combination produces peptides that tend to acquire a flat conformation, which facilitates their supramolecular polymerization. Consequently,

long hollow tubular structures are obtained through the 1D columnar assembly of CPs.¹¹⁷⁻¹²⁰

In order to control the longitudinal growth of the nanotubes, Perrier and co-workers showed the prominent effect of polymers as side-chains of the CPs which limit 2D and 3D assemblies and reinforce the non-covalent associative interactions between CPs by shielding the core from the surrounding water.¹²¹⁻¹²⁶

On the other hand, the use of hydrophobic and aromatic amino acids, well positioned in those cyclic peptides, also participate in their supramolecular polymerization. For instance, pyrenes were reported as promoting the hierarchical supramolecular polymerization of CPs,^{127, 128} favouring fibres and bundles due to the mismatch between β -sheet and π - π stacking that results in interlocking of fibres into bundles.¹²⁹ Controlling the balance of attractive and repulsive forces could grant control over the supramolecular polymerization of CPs. An example was recently reported where a spiropyran photo-switch had been inserted in CPs and afforded fast supramolecular polymerization and depolymerization in response to light irradiation triggering pH changes which modulate coulombic interactions.¹³⁰ Finally, the presence of hydrophobic and aromatic amino acids can be very useful for controlling the 2D growth of CPs. For instance, CPs bearing leucine, phenylalanine and tryptophan in key positions lead to the formation of giant 2D-nanosheets by involving leucine zipper and aromatic stacks in aqueous media (Fig. 7).^{131, 132}

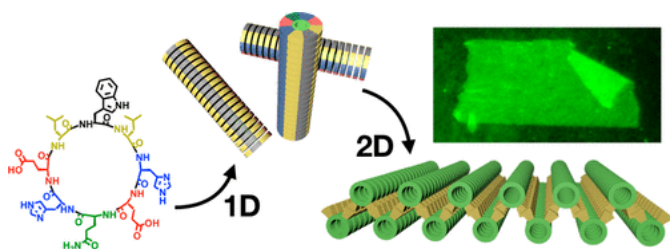


Figure 7. Two-dimensional self-assembly of D/L-alternating cyclic peptides by sequential 1D-to-2D supra- molecular polymerization through leucine zippers and π - π stacks of tryptophan indoles. Reprinted with permission from reference 132. Copyright 2020 American Chemical Society.

A particular class of peptide conjugate that has been extensively studied for their self-assembly propensity is amphiphilic peptides. These peptides are modified with hydrophobic moieties, most often aliphatic chains placed at their N-terminus.¹³³ The group of Stupp pioneered their study, reporting numerous examples of spherical and cylindrical micelles or lamellar structures.¹³³⁻¹³⁵ Like α -helical peptides,¹³⁶ the amphiphilic aromatic β -sheet-forming Glu-(Phe-Glu)_n peptides are capable of self-replication with exponential growth.¹³⁷ Looking at synthetic aromatic-peptide conjugates, Fmoc-VFFAKK is also capable of self-replication and the kinetic control over this process enables producing peptide nanofibers with controlled length and dispersity using a seeded supramolecular polymerization (Fig. 5G&H and *vide infra*), which is of great importance because length distribution determines the mechanical properties (e.g. stiffness) of the resulting hydrogels.¹³⁸ Other examples using for instance Fmoc-

GFFYGHY reported the autonomous growth of hydrogels having emerging esterase-like activity that promotes its auto-catalytic growth.¹³⁹

3.3. Effect of peptides on the supramolecular polymerization of aromatics

Supramolecular polymers involving the self-assembly of aromatics has been a subject of intense effort during the last two decades and several compounds have emerged as leads in this area: benzene-1,3,5-triscarboxamides (BTA),¹⁴⁰ perylene-bisimide (PBI),^{141, 142} triarylamines (TAA),¹⁴³⁻¹⁴⁵ and porphyrins^{60, 64, 146, 147} (Fig. 8).

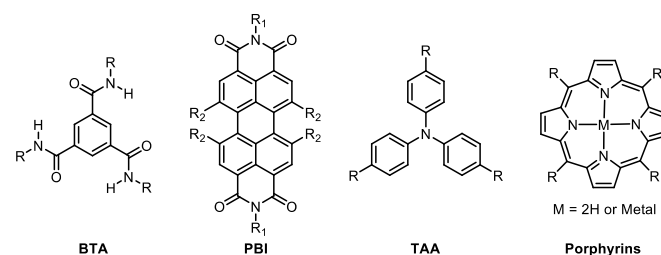


Figure 8. Aromatic cores most commonly used in supramolecular polymers involving poly-association by π - π stacking interactions: benzene-1,3,5-triscarboxamides (BTA), perylene-bisimide (PBI), triarylamines (TAA), and porphyrins.

The group of Meijer pioneered the use of BTAs for making supramolecular polymers. BTAs undergo a cooperative supramolecular polymerization that originates from the subtle combination of π - π stacking interactions between the aromatic cores with hydrogen bonds between the amide groups, resulting in the creation of a strong macrodipole (36 D) due to the enforced rotation out-of-the-plane (45°) of the amide groups within the final helical supramolecular polymer.^{54, 140} BTAs have been extensively studied in nonpolar organic solvents, and numerous derivatives have been reported indicating that the nature of the side chains have a profound impact on the supramolecular polymerization mechanism, going from isodesmic to cooperative polymerization with a wide range of cooperativity factor ($\sigma = K_n/K_e$) ranging from 10^{-1} (weakly cooperative) to 10^{-6} (strongly cooperative).¹⁴⁸ Since their inception, BTAs have been conjugated to peptides, thereby providing four main advantages that are discussed hereafter: i) improving the water-solubility of supramolecular polymers which is a daunting challenge for aromatic-based supramolecular polymers,¹⁴⁹ ii) adding additional non-covalent interactions that may affect the polymerization mechanism, iii) inserting amino acids bringing molecular chirality information that can be transmitted to the supramolecular organization,¹⁵⁰ and iv) introducing functional groups within the final supramolecular polymers in a straightforward and versatile manner.^{16, 151}

Inserting peptides to improve water-solubility. Meijer and co-workers reported in 2010 that flanking the central BTA unit with highly charged peripheral groups – made of a penta-fluorinated L-phenylalanine, an aminobenzoate spacer, and a polycarboxylate ligand complexed to Gd^{III} – enables achieving water-solubility (Fig. 9A, compound 6).^{152, 153} The system

displays a combination of attractive forces (hydrogen bonding, π - π interactions, and hydrophobic effect), along with repulsive electrostatic interactions that frustrates the one-dimensional growth of the supramolecular polymers. The polycarboxylate ligand displays a varying number of negative charges which enable fine-tuning those repulsive forces. The coulombic repulsion was shown to affect the morphology of the resulting nanostructures as well as the mechanism of supramolecular polymerization. While high aspect ratio rod-like aggregates are obtained through a cooperative polymerization in high ionic strength aqueous media, discrete spherical objects were formed when coulombic repulsion dominates at low ionic strength conditions (Fig. 9A). The length and the rigidity of the hydrophobic peptides were found to be critical – only spheres being formed when the penta-fluorinated phenylalanine was replaced by phenylalanine (Fig. 9A, compound **7**). Other examples of BTAs provided by the same group using aliphatic and PEG side-chains have further documented the role of hydrophobic shielding in the cooperative supramolecular polymerization in water, leading to rod-like self-assemblies with nanometer diameters and micrometer lengths (Fig. 9B, compound **8**).¹⁵⁴

Besenius and co-workers followed a different design to achieve supramolecular polymerization in aqueous solutions. They used BTAs conjugated to amphiphilic peptides forming β -sheets, end-capped at their C-terminus with a tetra(ethylene glycol) dendron for water solubility (Fig. 9C, compound **9**). Using a triphenylalanine peptide yields nanorods that are formed through a non-cooperative isodesmic polymerization originating from the steric constraints that grow throughout the polymerization (frustrated growth).¹⁵⁵ The group also developed alternate supramolecular polymers by using complementary peptides of opposite charges, rich in glutamic and lysine amino acids, respectively. At neutral pH, the two peptides interact with each other forming a β -sheet structure reinforced by favourable electrostatic interactions, while at acidic or basic pH, only one species is in a non-ionic form, leading to the formation of homopolymers instead of the alternate supramolecular polymers.¹⁵⁶⁻¹⁵⁸

Other examples have shown that appending peptides can impart water solubility to various aromatic cores that would otherwise not be amenable to supramolecular polymerization in aqueous media. For instance, using C3-symmetric benzotrithiophene functionalized with *L*-phenylalanine peptides, García-Iglesias and co-workers obtained supramolecular fibres that are self-assembled in water through a delicate combination of hydrogen bonding and hydrophobic effects (Fig. 9D, compounds **10** and **11**).¹⁵⁹

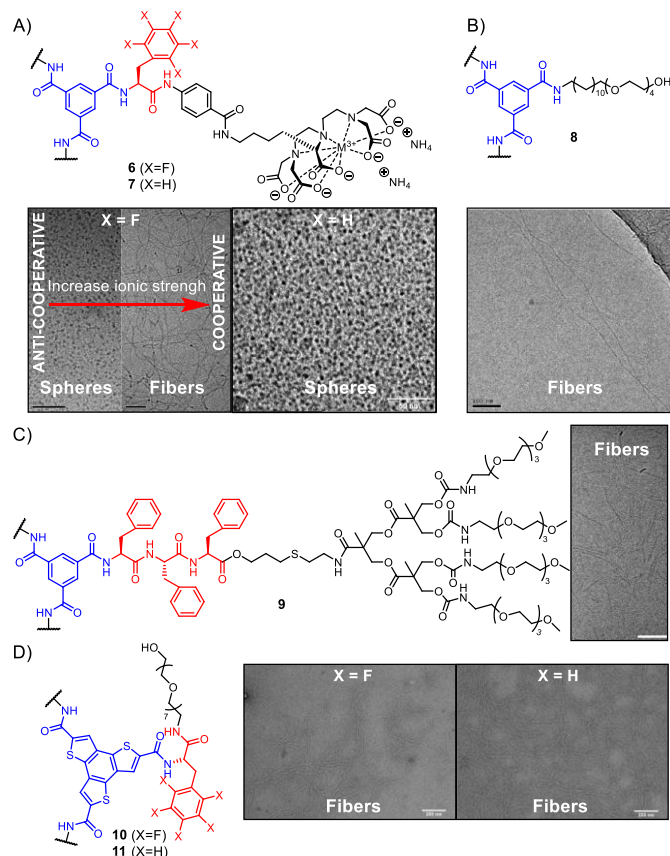


Figure 9. Aromatic-peptide conjugates self-assembling into supramolecular polymers in aqueous media with representative characterization of nanostructures observed by TEM. A) adapted from reference 152 with permission from John Wiley and Sons and reference 153 (Copyright 2010 National Academy of Sciences); B) adapted from reference 154 with permission from the Royal Society of Chemistry; C) adapted from reference 155 with permission from John Wiley and Sons; D) adapted from reference 159 with permission from the Royal Society of Chemistry.

Effect of peptides on the mechanism of supramolecular polymerization. The presence of peptides can have a tremendous effect on the mechanism of supramolecular polymerization as a function of the nature of the (aromatic) side-groups. For instance, in the benzotrithiophene peptide conjugates of García-Iglesias and co-workers, the authors found that the pentafluoro-*L*-phenylalanine side-chain in compound **10** endows an isodesmic self-assembly process dominated by hydrophobic forces, while the *L*-phenylalanine side-chain in compound **11** give rise to a highly cooperative supramolecular polymerization ($\sigma \approx 8 \cdot 10^{-6}$) thanks to a greater contribution of hydrogen bond (Fig. 10A).¹⁵⁹ Yamaguchi and co-workers reported that the compound **12** featuring two pyrenes linked through an alanine-based diamide motif can exist either in a dominant folded state involving intramolecular hydrogen bonds or in an open state involving intermolecular hydrogen bonds, and that only the latter can give rise to a cooperative supramolecular polymerization in low polarity solvents (toluene/chloroform) (Fig. 10B).¹⁶⁰ The retardation of the spontaneous nucleation in the folded state enables seeding to trigger an out-of-equilibrium polymerization. More recently, the group has extended their approach studying the cysteine-

based dimeric diamide **13**, which now shows seeded polymerization in aqueous media (Fig. 10C).¹⁶¹

The Smulders and Stefankiewicz groups used a naphthalene diimide (NDI) flanked with two O-derivatives of *L*-tyrosine (*L*-Tyr(OC(O)C₁₅H₃₁)COOH) to generate soluble self-assemblies in non-polar organic solvent (CHCl₃, MCH) and interestingly found that the solvent affects both the type of objects formed (hydrogen-bonded nanotubes vs. supramolecular polymers) and their mechanisms of formation (isodesmic or cooperative) (Fig. 10D, compound **14**).^{162, 163} These subtle changes are rationalized by differences in solvation effects between J-aggregates (offset face-to-face arrangement of aromatics) and H-aggregates (overlapped arrangement of aromatics). Such differences into competitive pathways of supramolecular polymerization involving either J- or H-aggregates have also been documented in other systems.^{164, 165} Other examples of NDI-peptide conjugates have been reported for the supramolecular polymerization of 1D helical nanostructures in aqueous media¹⁶⁶ and nanotubes,¹⁶⁷ some assemblies even displaying pH-responsiveness due to the presence of ionizable amino acids.¹⁶⁸

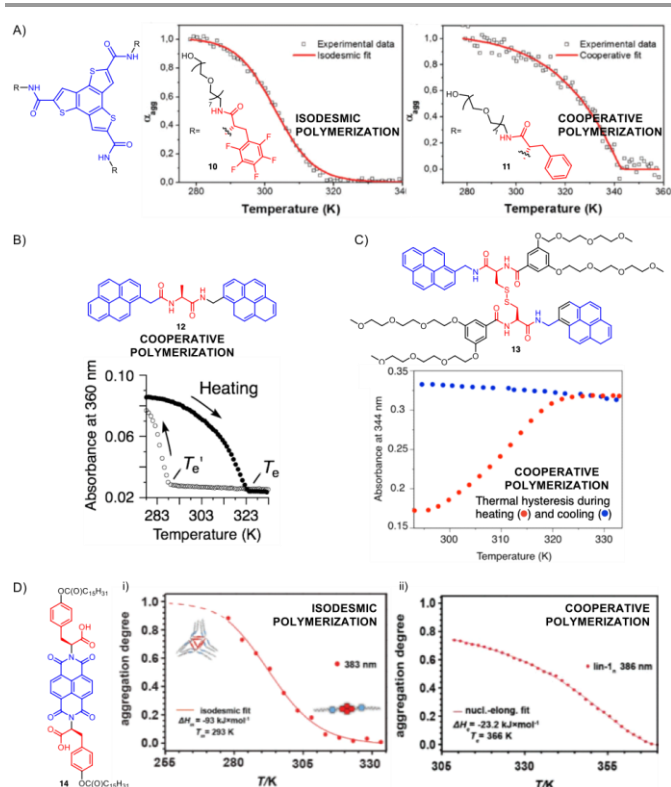


Figure 10. Selected examples showing how peptides can affect the mechanism of supramolecular polymerization. The depicted plots represent the evolution of the degree of aggregation α_{agg} in A) and D), or the evolution of the absorbance in B) and C), as a function of temperature – the sigmoidal or non-sigmoidal changes revealing, respectively, isodesmic or cooperative supramolecular polymerization mechanisms. A) adapted from reference 159 with permission from the Royal Society of Chemistry; B) reproduced from reference 160 with permission from John Wiley and Sons; C) adapted from reference 161 with permission from the Royal Society of Chemistry; D) adapted from reference 162.

Chiral supramolecular polymers. The group of Bouteiller has been particularly active in the investigation of BTA-amino acids

conjugates (Fig. 11A). In 2015, they reported that the presence of α -amino dodecylesters side groups (methionine, norleucine and phenylalanine dodecyl ester) favor the formation of long rods at millimolar concentrations in cyclohexane,¹⁶⁹ and display a strong chiral amplification effect in the helical nanostructure, seen by CD spectroscopy, through the so-called “sergeant-and-soldiers effect” that operate in copolymers made of mixture of chiral and achiral monomers.^{169, 170} Further work on BTA derivatives with valine dodecyl ester revealed a propensity of heterochiral monomers to form long rods while homochiral analogues only formed dimers (Fig. 11B), which can be detected by increases in relative viscosity.¹⁷¹ On the other hand, tryptophan alkyl ester side groups were found to promote supramolecular polymerization through the presence of additional hydrogen bonds involving the indole N-H (Fig. 11C).¹⁷² Small-Angle Neutron Scattering experiments revealed long and rigid one-dimensional cylinders with $L > 1000$ Å and $DP_w > 275$, and circular dichroism showed intense signals that originate from the chiral nanoscale organization of the supramolecular polymers (Fig. 11D).

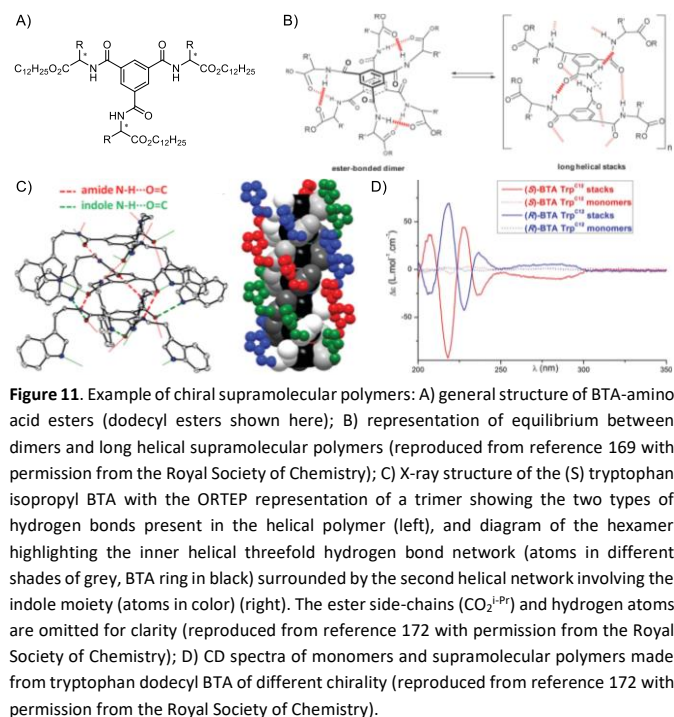


Figure 11. Example of chiral supramolecular polymers: A) general structure of BTA-amino acid esters (dodecyl esters shown here); B) representation of equilibrium between dimers and long helical supramolecular polymers (reproduced from reference 169 with permission from the Royal Society of Chemistry); C) X-ray structure of the (S) tryptophan isopropyl BTA with the ORTEP representation of a trimer showing the two types of hydrogen bonds present in the helical polymer (left), and diagram of the hexamer highlighting the inner helical threefold hydrogen bond network (atoms in different shades of grey, BTA ring in black) surrounded by the second helical network involving the indole moiety (atoms in color) (right). The ester side-chains (CO₂^{i-Pr}) and hydrogen atoms are omitted for clarity (reproduced from reference 172 with permission from the Royal Society of Chemistry); D) CD spectra of monomers and supramolecular polymers made from tryptophan dodecyl BTA of different chirality (reproduced from reference 172 with permission from the Royal Society of Chemistry).

Inserting peptides for achieving functional systems. To illustrate some applications of supramolecular polymers based on aromatic peptide conjugates, we mention hereafter three potential outcomes that have been recently reported.

First, the conjugation with peptides enables improving the water-solubility of aromatic photosensitizers which biological applications are otherwise often hindered by their poor solubility in aqueous media. For instance, porphyrin-peptide (PhePhe) conjugates **15** having a short spacer have been reported to self-assemble into nanodots in aqueous media which, thanks to the peptide-enforced π -stacked arrangement of the chromophores, are active in photothermal therapy (Fig.

12A).¹⁷³ The presence of PhePhe was shown, on porphyrin-peptide conjugates with no spacers, to profoundly impact the morphology of the nanostructures that are formed, yielding fibrils, platelets or nanospheres depending on the solvent composition.¹⁷⁴ The control over the nano-scale organization has been recently exploited to demonstrate, using compound **16**, acid-activated photodynamic therapy (PDT) that originates from an acid-triggered conversion of nanoparticles to nanofibers, the latter having greater PDT activity than the former (Fig. 12B).¹⁷⁵

Secondly, the presence of peptides may also bring responsiveness to supramolecular polymers. For instance, inserting histidines within their BTA-peptide conjugates (BTA-(Phe-His-Phe-His-Phe-X)₃), the group of Besenius was able to tune the pH-switch of supramolecular polymers, allowing the control over their assembly/disassembly in the pH range 5.3–6.0 (Fig. 12C, compounds **17**).¹⁷⁶ Protonation of all low-pKa imidazole groups builds up electrostatic repulsion between monomers and thus triggers depolymerization. A successful application was then shown for the delivery of siRNA. In addition to the histidine-rich core, the design features peripheral primary amines which are protonated at physiological pH and are responsible for siRNA complexation. Acidification during endocytosis triggers depolymerization of the supramolecular polymer vector and thus improves siRNA release.¹⁷⁶ Cationic derivatives of benzotrithiophene peptide conjugates bearing terminal primary amines have been recently described where pH was observed to cause changes, not only switching supramolecular polymerization on and off, but also affecting the mechanism of supramolecular polymerization.¹⁷⁷ In this case, a highly cooperative polymerization ($\sigma = 2.3 \cdot 10^{-5}$) was observed at basic pH (pH = 13) while an isodesmic polymerization was found at lower pH (pH = 7) where amines are protonated and exert electrostatic repulsion. The nature of the aromatic core may also modulate the pH-responsiveness as recently reported by the groups of Besenius and George using different core-substituted NDI derivatives.¹⁶⁸

Thirdly, the ability to self-assemble small molecules into chiral supramolecular polymers opens up applications in different areas. For instance, exploring asymmetric catalysis, the group of Bouteiller and Raynal used chiral BTA ligands for rhodium-catalyzed asymmetric hydrogenation,¹⁷⁸ and hydrosilylation reactions.^{179, 180} Interestingly, the sergeant-and-soldiers principle enables using a ligand-free enantiopure chiral comonomer (down to 0.5 mol%) and an achiral BTA ligand as, respectively, sergeant and soldiers, to achieve the asymmetric hydrogenation with ee up to 90%.^{181, 182} This effect results from the translation of the sergeant-and-soldiers principle to asymmetric catalysis through a chiral amplification that originates from the self-assembly of monomers into helical supramolecular (co)-polymers.^{181, 183} The ability to self-organize aromatics into chiral aggregates may also open applications in the field of organic electronic.¹⁸⁴ In this case, the group of Frauenrath combined peptide with polymer side-chains to organize perylene bisimide, quaterthiophene and other chromophores into chiral nanowires.^{185–187}

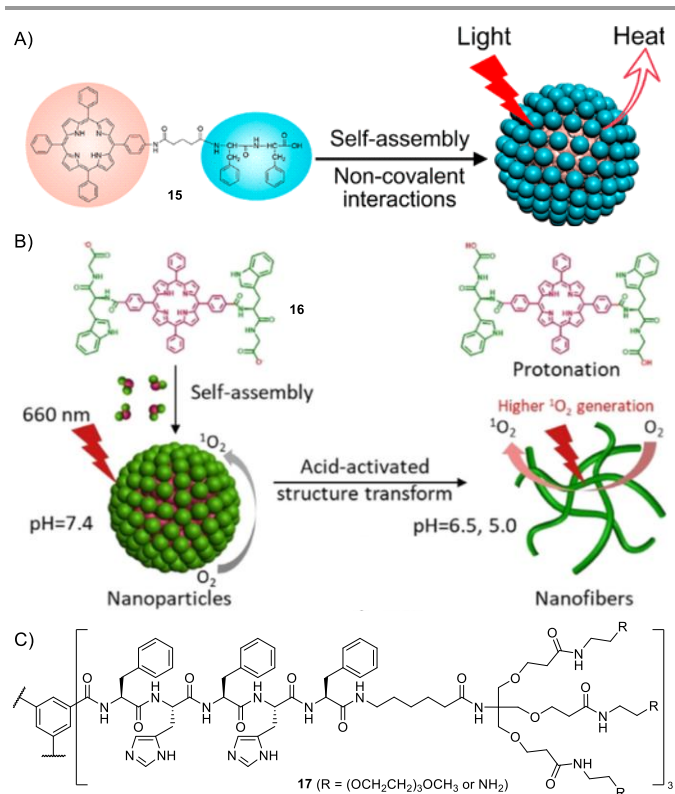


Figure 12. Selected examples of applications using supramolecular polymers decorated with peptides: A) porphyrin-peptide conjugates for photothermal therapy (reprinted with permission from reference 173. Copyright 2017 American Chemical Society); B) acid-activatable porphyrin-peptide conjugates for photodynamic therapy (adapted from reference 175 with permission from John Wiley and Sons); C) molecular structure of BTA-derived monomer leading to pH-switchable supramolecular polymers for siRNA delivery.¹⁷⁶

4. Hierarchical Self-Assembly of Aromatic-Peptide Conjugates through the Combination of Dynamic Covalent and Supramolecular Chemistries

In retrospect, Rideout provided in 1986 a pioneering example of a self-assembling drug where a dynamic covalent bond formation subsequently triggers supramolecular self-assembly in a hierarchical two-step process.¹⁸⁸ In 2010, Ulijn has nicely reviewed the then-growing interests in merging dynamic covalent chemistry and peptide self-assembly.¹⁸⁹ To illustrate recent trends with selected examples, Montenegro and co-workers described the hierarchical self-assembly of micro-fibres from linear peptide amphiphiles using the oxime ligation^{190, 191} and a single covalent connector between a charged peptide head and a lipophilic aliphatic tail,^{192, 193} while Jierry and co-workers reported the protein-induced low-molecular-weight hydrogelator formation through the templated ligation of peptides through a disulphide link.¹⁹⁴ In 2020, George and co-workers reported a very elegant chemically-controlled supramolecular polymerization where a dynamic covalent bond (imine) converts a non-assembling dormant charge-transfer monomer to an activated amphiphile that subsequently undergoes a cooperative supramolecular polymerization.¹⁹⁵ The Ng and Weil groups reported an elaborate system where a

pH-sensitive reversible linkage is connected to a precursor of a self-assembling peptide.¹⁹⁶ The authors showed that the dissociation of the covalent bond at acidic pH triggers the release of the peptide and the formation of self-assembled fibres within live cells.

Beside the hierarchical generation of complex nanostructures from two complementary simple building blocks, there is also a strong interest in understanding the pathways that are taken by more complex systems characterized by the integration of multiple (> 2) building blocks.¹⁹⁷ In this regard, there have been many beautiful results in the last decade of systems combining aromatics with peptides self-assembly. In 2010, while studying artificial self-replicating molecules, the group of Otto came across mechano-sensitive self-replication driven by a complex self-organization process combining a covalent self-assembly with a supramolecular polymerization.¹⁹⁸ The design is based on aromatic-peptide conjugates where the aromatic bears two meta-oriented thiol groups that can further lead to disulphide bond formation and the peptide features alternating hydrophobic and hydrophilic amino acids (Gly-Leu-Lys-Leu-Lys-OH or Gly-Leu-Lys-Phe-Lys-OH) (Fig. 13, compound **18**). The authors found that the corresponding hexamer and heptamer are formed through a sigmoidal growth that is triggered by mechanical forces. Seeding experiments demonstrated self-replication, yielding long fibres of micrometre size. Further analyses by CD spectroscopy and thioflavin T assay confirmed the β -sheet arrangement of the peptides. Overall, these results are interpreted by the disulphide-mediated covalent assembly of aromatic-peptide conjugates that produce rings of different sizes, from which one is prone to nucleation-elongation supramolecular polymerization by π - π stacking and β -sheet formation and emerges by exponential self-replication (Fig. 13).¹⁹⁹⁻²⁰⁴ With the assistance of an appropriate template, it is also possible to down-size the building block to a minimal size that now includes a "peptide" side-group as short as Phe-OH.²⁰⁵ Finally, in a recent work in collaboration with the Huc group, it was shown that low-symmetry foldamers spontaneously emerge from the system when amphiphilic peptides are tethered to the 1,3-dimercaptobenzene aromatic core, thereby documenting a beautiful example of complex self-organization into discrete macromolecules (Fig. 2C).²⁰⁶

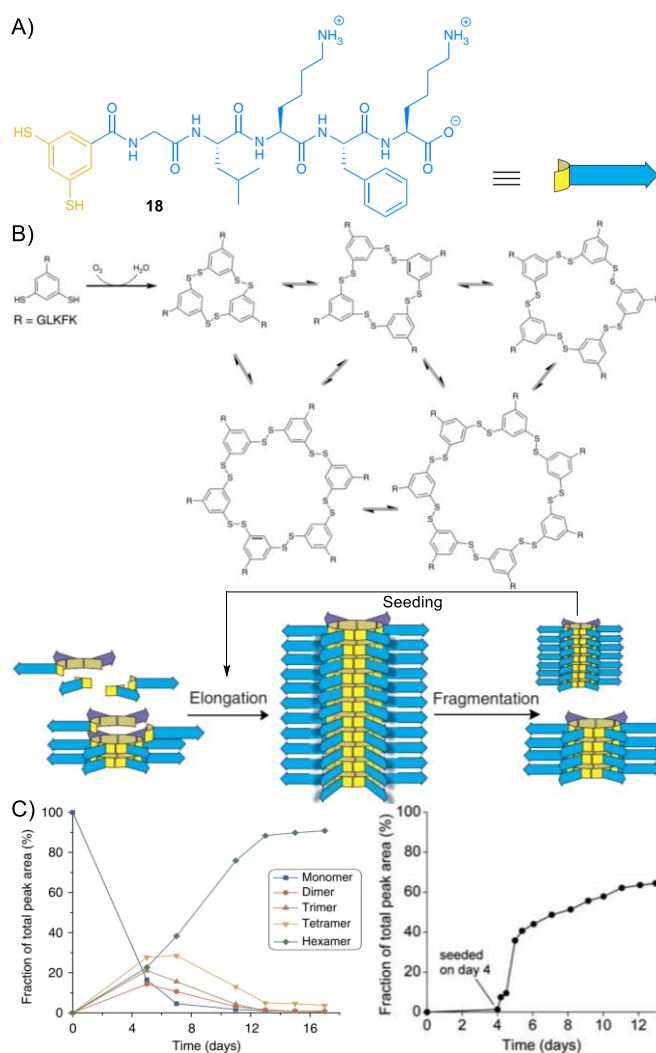


Figure 13. Hierarchical self-organization of aromatic peptide conjugates through disulphide dynamic covalent self-assembly and supramolecular polymerization: A) molecular structure of the building block **18** made of the peptide Gly-Leu-Lys-Phe-Lys tethered to the 1,3-dimercaptobenzene aromatic core; B) schematic representation of its self-assembly at the molecular (top) and supramolecular (bottom) scales upon air oxidation, forming different macrocycles that can undergo supramolecular polymerization; C) representation of the evolution of the constitution of the system showing the amplification of the hexamer (left) and its templated growth in the presence of seeds (right). Adapted from references 198 (Copyright 2010, American Association for the Advancement of Science) and 204.

In 2016, the group of Stupp reported another system of supramolecular polymerization achieved through simultaneous hierarchical covalent and non-covalent self-assembly.²⁰⁷ The building blocks are also made of aromatic peptide conjugates but now the aromatic bears either two reactive aldehyde or amine groups, and the peptides (Val-Glu-Val-Glu-OH) are separated by C_{11} -alkyl spacers (Fig. 14). The mixing of the two complementary building blocks (i.e. bisaldehyde and bisamine) **19** and **20** in 1:1 molar ratio in aqueous solution at pH = 5 triggers imine formation, and the authors observed by cryo-TEM the heterogeneous mixture of one-dimensional structures. In contrast, with the further addition of 2 equivalents of the peptide amphiphile **21** (Dodecyl-Val-Glu-Val-Glu-OH), a hybrid covalent-noncovalent polymer is generated, displaying 1D

structures with precisely defined cylindrical shape and uniform diameter. β -sheet organization of the peptides was evidenced by CD spectroscopy. These results describe an interesting case where covalent and non-covalent processes occur simultaneously and synergistically to trigger the formation of polymers (up to an average molecular weight of 190-250 kDa) following a nucleation-elongation mechanism, which is much higher than for analogous covalent-only polymers having average molecular weights on the order of 14 kDa.¹³³

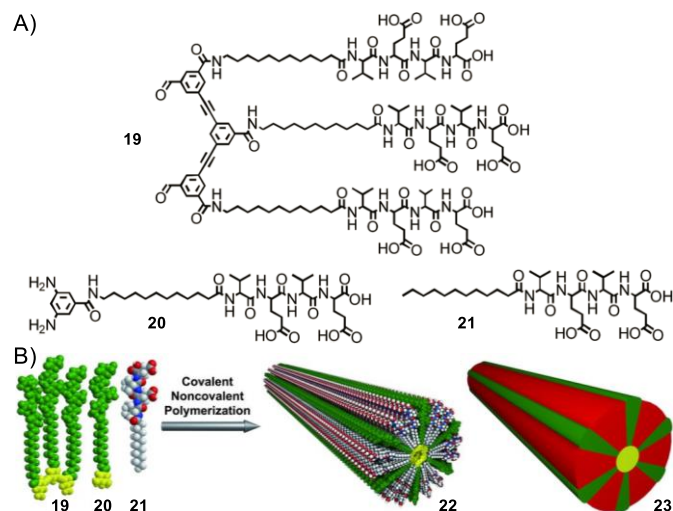


Figure 14. Hierarchical self-organization of amphiphilic aromatic peptide conjugates through imine dynamic covalent self-assembly and supramolecular polymerization: A) molecular structures of the bisaldehyde (**19**), bisamine (**20**) and peptide amphiphile (**21**) building blocks; B) schematic representation of the synergistic process involving the hybrid covalent-supramolecular polymerization of a macrocyclic rosette by mixing monomers **19**, **20**, and **21** in 1:1:2 molar ratio in aqueous solution (pH 5), yielding the 1D fiber assembly **22**. The schematic representation **23** depicts the hybrid covalent-noncovalent polymer with different colors for the covalent (green), dynamic covalent (yellow) and supramolecular (red) interactions at play. Adapted with permission from reference 207 (Copyright 2016, American Association for the Advancement of Science).

In 2017, the group of Lynn reported the modified peptides **24** that undergo both dynamic covalent and supramolecular polymerization driven by β phase formation.²⁰⁸ The system is designed around (Phe)₁₋₂ core with a C-terminal aldehyde and a complementary N-terminal asparagine, and yields mixtures of cyclic and linear oligomers by poly-condensation in acidic acetonitrile, before the appearance of a particle phase and the formation of fibres (Fig. 15). In return, the authors evidenced self-selection and amplification of trimers as a consequence of the emergence of those fibres,^{208, 209} thereby showing an example of adaptive self-assembly with feedback loops linking the emergence and growth of the nanostructure with the selection of dynamic covalent polymers.

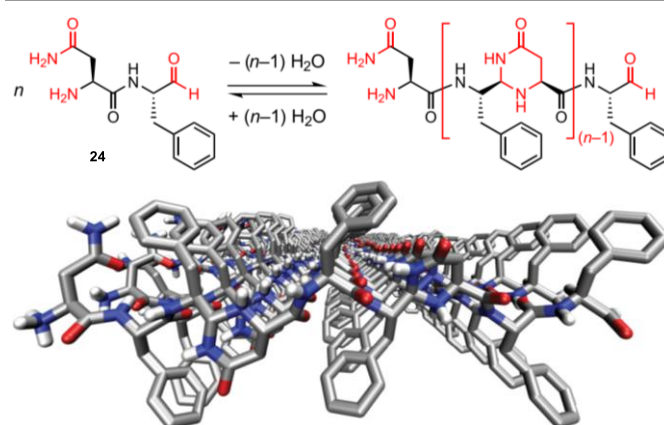


Figure 15. Dynamic covalent polymers that further self-assemble in β -sheets arrangements through supramolecular polymerization. Top: principle of self-condensation polymerization of the peptide **24** (H-Asn-Phe-CHO) that yield oligomers upon formation of N,N-acetal-4-pyrimidinone (py) linkages; bottom: model of the β -sheet assembly of the trimer H-NFFpyNFFpyNFF-CHO generate from H-Asn-Phe-Phe-CHO. Reproduced from reference 208 (Copyright 2017 Springer Nature).

Instead of folding into a repetitive helical polydisperse nanostructure, the groups of Huc and Otto have recently reported a system where the presence of amphiphilic peptides drives the protein-like folding of the system into a low-symmetry monodisperse object (Fig. 16).²⁰⁶ In this case, the presence of charged groups on the phenyl ring of the peptide side groups was found to be critical. In this absence of these charged groups, only tetramers formed from compound **25**. On the other hand, the self-assembly of **26** resulted in mixtures of 9-, 12-, and 13-mers, and **27** and **28** spontaneously yielded, respectively, 23- and 16-mers.

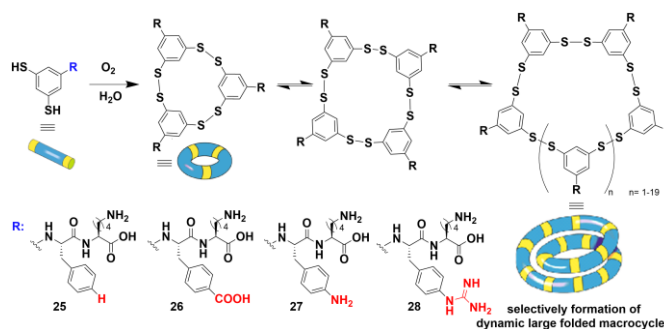


Figure 16. Large folded monodisperse macrocycles formed through hierarchical self-assembly combining dynamic covalent chemistry with supramolecular self-assembly of aromatic peptide conjugates. Adapted from reference 206 (Copyright 2020 Springer Nature).

Finally, it is important to note that the combination of dynamic covalent and supramolecular chemistries also brings an additional reactional responsiveness to the system. The reversible covalent bonds are sensitive to reaction conditions and thus, in addition to the sensitivity of non-covalent interactions to various modulators such as solvent and temperature, such double-dynamic system may display responsiveness to multiple stimuli. For instance, the systems made of disulphides are redox sensitive while those featuring imines or acylhydrazones may be photo-sensitive since those

motifs can be photo-switched.^{210, 211} In this line, the Hamachi group just reported the formation of photo-triggered out-of-equilibrium patterns in hydrogels using photo-responsive nanofibers made of aromatic-peptide acylhydrazone conjugates.²¹²

5. Recent developments

5.1. Multi-component precision polymers

Despite tremendous recent progresses,^{213, 214} synthetic polymers with precise sequence-defined positioning of multiple monomers remain thus far out of reach. Yet, such objects are of great interest as they can be seen as artificial analogues of proteins. Developing processes that grant access to such precision (bio)polymers will open the door to a vast unexplored area from which functional systems will be identified. A strong basis toward this endeavour was made using multicomponent peptide assemblies.^{215, 216}

Using statistically-distributed multi-component dynamic covalent polymers, we have recently shown that multi-components DCPs can display emerging properties with improved cell internalization properties compared to their homomeric counterparts.³⁹ Regarding multi-component supramolecular polymers,^{217, 218} the group of Meijer pioneered the initial investigations on supramolecular copolymers using the BTA-type cooperative supramolecular polymers, studying how the presence of different monomers affect the structure and mechanism of polymerization,²¹⁹ and documenting supramolecular block copolymers that form under thermodynamic control.^{220, 221} The molecular structure of the aromatic core and of the peripheral groups is central here as it affects the propensity to polymerize and therefore the competition between self-polymerization versus copolymerization (Fig. 17). For instance, peptides can be used as side-chains to enforce an alternating organization of the supramolecular polymers dictated through electrostatic attractions.^{156-158, 222}

However, it is the recent discovery of living supramolecular polymerization that is really facilitating the preparation of supramolecular block copolymers, and several examples based on different molecular design have been recently reported by the George,²²³⁻²²⁶ Würthner,²²⁷ and von Delius⁵⁸ groups – all using two-component seeded living polymerization yielding very long fibres with a very limited length dispersity.

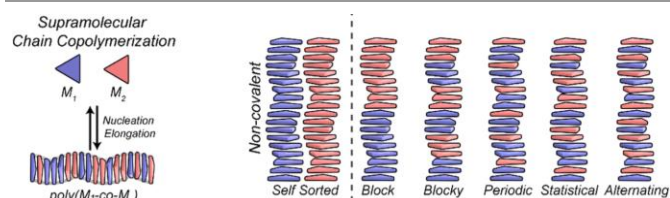


Figure 17. General mechanism of formation and possible organization of two-component supramolecular co-polymers. Reproduced with permission from reference 217 (Copyright 2019 American Chemical Society).

Finally, going towards precision DCPs at one building block resolution will require appropriate techniques to decipher and

read their sequence.²²⁸ Compared to conventional “static” polymers, the unique feature of dynamic polymers (supramolecular polymers and DCPs) is that their sequence is not necessarily only programmed during synthesis but it can also be the result of a spontaneous self-selection enforced by folding, or of an adaptive sequence-selection due to binding to a templating (bio)molecular target.²²⁹ Looking in this direction, we believe the recent discovery reported by the groups of Huc and Otto of a self-folded low-symmetry monodisperse DCP²⁰⁶ represents a milestone that will prompt further the exploration of multi-component DCPs. However, further development of our understanding of complex self-assembly processes leading to multi-component supramolecular polymers is necessary since a designed comonomer can practically turn into a chain capper, a sequester, an intercalator, or a comonomer – understanding how to navigate this fine line is therefore important.²³⁰⁻²³²

5.2. Transient supramolecular polymers

Many biological supramolecular polymers, like actin filaments and microtubules,¹⁴⁹ are temporally expressed, just at the place and for the time their function is needed. Thus, controlling the transient formation of supramolecular polymers has become a current goal of interest in the quest for man-made biomimetic systems.²³³

Supramolecular polymers may feature a diversity of molecular, supramolecular, and nano-scale organizations. However, since the systems are dynamic, interconversion is possible and all the different types of supramolecular polymers may influence each other like in a dynamic constitutional network.^{146, 234-236} Interestingly, the so-called “off-pathway” supramolecular polymers formed under kinetic control may also display distinct and temporally-controlled properties like chiral helical structure²³⁷ or fluorescence output.⁶¹

On the other hand, dissipative self-assemblies that consume a (bio)chemical fuel to sustain the formation of supramolecular polymers which subsequently collapse past its complete consumption also represent a powerful route toward transient materials (Fig. 18).^{238, 239} In this regard, self-assemblies made of peptides are of particular interest since enzymatic²⁴⁰ or non-enzymatic processes (e.g. ester formation/hydrolysis, imine formation, thiol-disulphide exchange/thiol-ester exchange)²⁴¹ can perform transient modifications in aqueous media.²⁴²⁻²⁴⁴ For instance, using aromatic peptide amphiphiles, the group of Ulijn has precisely shown, in pioneering contributions,²⁴⁵⁻²⁴⁸ that protease-catalysed reactions can be used to form self-assembled nanostructures under biocatalytic control. This approach enables moving out-of-equilibrium and controlling the self-assembly pathways and emergence of materials properties in space and time.^{249, 250} The group also studied NDI and 1,8-naphthalimide (NI) amino acid methyl esters that are biocatalytically coupled to amino acid-amides using α -chymotrypsin,^{251, 252} and found nanotubes and nanofibers which life-time is finely dictated by the nature of the amino acids ranging from minutes to hours, with a proof-of-concept showing the transient self-assembly of electronic wires in

aqueous media. The George group reported several examples of dissipative supramolecular polymers using chemical fuels. For instance, a bisfunctionalized NDI compounds was shown to undergo transient helical supramolecular polymerization fuelled by ATP, while the simultaneous presence of alkaline phosphatase (ALP) triggered its depolymerization.²⁵³⁻²⁵⁵ Redox control using $\text{Na}_2\text{S}_2\text{O}_4/\text{O}_2$ ²⁵⁶ over the folding of a NDI-pyrene donor-acceptor complex was also exploited for making supramolecular polymers with low dispersity.²⁵⁷

Here also, the combination of supramolecular and dynamic covalent chemistries is rich in discoveries. The George group recently reported dissipative systems derived from their dormant charge-transfer monomer which turns into an activated amphiphile upon imine formation.²⁵⁸ The growth kinetics of supramolecular polymerization was found to be affected by the presence of inhibitors acting as a direct competitor of the supramolecular polymerization, like ethanol amine or urea/urease which produces ammonia in situ. On the other hand, lipase was found to promote depolymerization. Thus, this work shows that fine control of dynamic covalent self-assemblies may lead to supramolecular polymers with temporal control. Besides imine reactions, disulphides can also be used in dissipative systems. For instance, the Otto group used NaBO_3 and tris(2-carboxyethyl)phosphine (TCEP) to, respectively, oxidize thiols into disulphides and reduce disulphides back into thiols, thus enabling to make self-replicating systems operate out-of-equilibrium.²⁵⁹

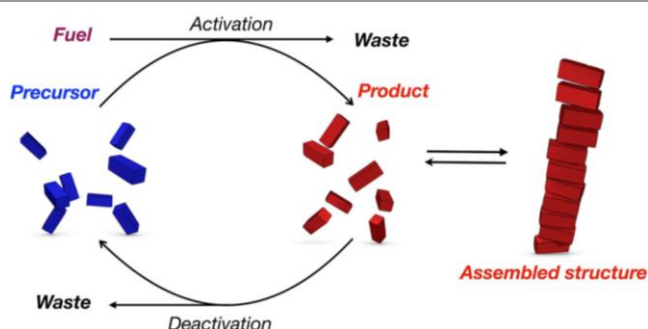


Figure 18. General mechanism representing the transient formation of supramolecular polymers by dissipative self-assembly (Reproduced from reference 243 with permission from John Wiley and Sons).

Achieving a precise control over the kinetic of assembly and disassembly that can be set by molecular engineering for a specific application is an important future line of development. In the longer term, it remains an important challenge to correlate such dissipative self-assembly with a function.

6. Conclusions

This review discussed the recent merging of two areas that previously grew from different communities: peptide-based materials and supramolecular polymers. In this account, we highlighted how modified amino acids and peptides can be inserted into dynamic covalent polymers for bringing functional groups and structured elements within these biomaterials. There is no doubt new applications will be explored using

bioconjugated dynamic covalent polymers. Also, an emerging, yet still challenging, direction is the self-selection of sequence-specific monodisperse dynamic covalent polymers from complex mixtures. In this review, we then described examples showing how β -sheet formation can be assisted by π - π stacking interactions for generating biomaterials such as hydrogels from simple aromatic-peptide conjugates. Conversely, we discussed recent achievements showing how peptide side-groups can influence the supramolecular polymerization of aromatics, enabling water-solubility, affecting their polymerization mechanism, bringing chiral information that can be transmitted to the supramolecular organization, and introducing, in a straightforward manner, reactive groups for developing functional supramolecular polymers. Finally, we highlighted the recent advances on combining dynamic covalent chemistry with the supramolecular polymerization of aromatic-peptide conjugates for obtaining biosupramolecular polymers in a hierarchical manner through complex self-assembly pathways through, for instance self-replication and triggered living polymerization.²⁶⁰ The current endeavours focus on multi-component precision polymers and on the transient expression of supramolecular polymers.

7. Perspectives

Peptide-based systems see continuous and impressive developments as bioinspired soft materials for a wide range of applications (e.g. smart multivalent recognition and delivery, biomimetic catalysis, optic, bioelectronic, biosensing)²⁶¹ and a bright future lies ahead. The combination of peptide self-assembly with the self-assembly of aromatics brings a whole new flavour to the field, where the aromatics can strengthen the peptide-based self-assembly and also bring new function, whereas the peptides can conversely contribute to the self-organization in aqueous media of the aromatic self-assemblies into chiral responsive nano-structures. Furthermore, new methodologies have been recently introduced that further boost the potential of the field: dynamic covalent chemistry and (living) supramolecular polymerization. While the former enables the covalent yet dynamic coupling of aromatics and peptides through covalent bonds that may be addressable, the latter grants access multi-component biosupramolecular polymers by either integrative co-assembly of different building blocks,²¹⁸ kinetic self-sorting in block copolymers,^{227, 262} or sequential seeded-growth.²²³ Also, some of these systems can now form transiently under dissipative conditions. These trends underscore the pursuit toward life-like materials that are self-organized from simple building blocks into well-defined functional architectures through a spontaneous, dynamic, and adaptive hierarchical process, similarly to many examples of biopolymers such as microtubules which are part of the cytoskeleton of cells.¹⁴⁹ Alternatively, there is no doubt that our ability to bring, in a defined order, multiple functions within a single yet multi-responsive chemical entity will unleash new properties, and hopefully technologies, possibly as bioactive molecules, catalysts, and sensors. For instance, the fine control over the complex dynamic self-assembly pathways described

herein will subsequently enable controlling, in space and in time, possibly also as a function of internal or external chemical template,²⁶³ chemical fuel^{152, 239, 264} or a physical effector such as light,²⁶⁵ the dynamic expression of multivalent interactions that is crucial in the well-defined and controllable emergence of many functions (e.g. bioactivity, catalysis). As an illustrative example, one may cite here the contribution of the group of Pal which recently described aromatic peptide–bioglass nanocomposites, with a templated pathway-encoded fine structure, for application as bone scaffolds in tissue engineering.²⁶⁶ Thus, in conjunction with the ability of peptides to generate self-assemblies in complex biological environments,²⁶⁷ it appears clear that peptide-based supramolecular polymers will be central in the future development of supramolecular chemical biology.^{268, 269} However, the achievements described in this review represents the first steps toward this grand objective and many challenges have still to be addressed, for instance looking at the stability and biocompatibility of those complex self-assemblies at low concentration in biological fluids.

Author contributions

All authors discussed the structure of the manuscript and the selection of its content. All authors contributed to drawing illustrations, writing the initial draft, reviewing and editing.

Conflicts of interest

“There are no conflicts to declare”.

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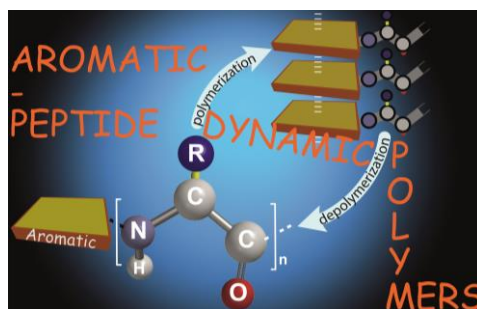
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Table of contents entry



Aromatic-peptide dynamic polymers yield analogues of biomacromolecules and water-soluble chiral supramolecular polymers. The (transient) emergence of multi-component polymers from complex chemical systems will unleash their applications as catalytic and bioactive materials.

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