Supramolecular single-chain polymeric nanoparticles

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Supramolecular Single-Chain Polymeric Nanoparticles

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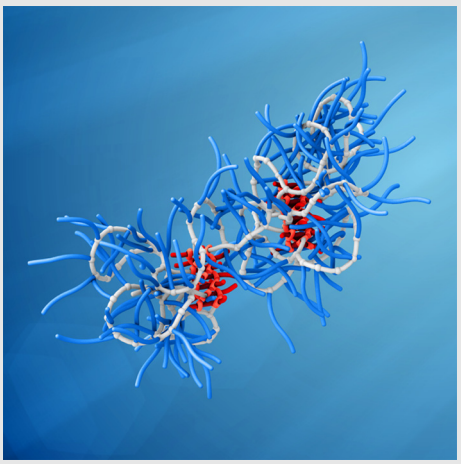
Nature has unparalleled control over the conformation and dynamics of its folded macromolecular structures. Nature's ability to arrange amino acids into a precise spatial organization by way of folding allows proteins to fulfill specific functions in an extremely efficient manner. Chemists and materials scientists have used the delicate structure–function relationships observed in proteins to elucidate nature's design principles. These insights have led to the development of various revolutionary macromolecular architectures, mimicking the structural features of proteins. In this review, we focus on the folding of single polymer chains into well-defined nanoparticles using supramolecular interactions and their possible use as enzyme mimics.



Keywords: **folding polymers, enzyme mimics, supramolecular polymer chemistry, nanoparticle**

Introduction

Mimicking features of enzymes using synthetic macromolecules

Nature's biochemical networks comprise numerous interacting proteins, each with their own specific function. Remarkably though, despite the huge diversity in the shape and functions of proteins, they are based on only 20 different amino acids. Nature's way to create such a wide variety of proteins, based on a limited number of building blocks, lies in its ability to perfectly control the length and sequence of its polypeptides. A specific amino acid sequence can fold into a protein via the formation of directional hydrogen-bonding patterns, such as α helices, turns, and β strands, hereby affording a specific function. In enzymes, which catalyze the biochemical reactions occurring in cells, this results in a well-defined binding groove that not only allows selective substrate binding, but simultaneously lines up the substrate with the enzymatically active site. The combination of these features results in extremely high catalytic activity, selectivity, and specificity. The sophisticated relationship between the structure and function of proteins has been a major source of inspiration to the field of macromolecular science.[1] Attempts to mimic structural features of proteins have led to various revolutionary macromolecular architectures. For example, the hydrophobic pocket of enzymes has been successfully mimicked by incorporating catalytically active groups in the hydrophobic domains of dendrimers, star polymers, micelles, and vesicles (Figure 1a,b).[2–16] Selective catalysts have been obtained via the precise functionalization of well-defined macromolecular architectures, such as

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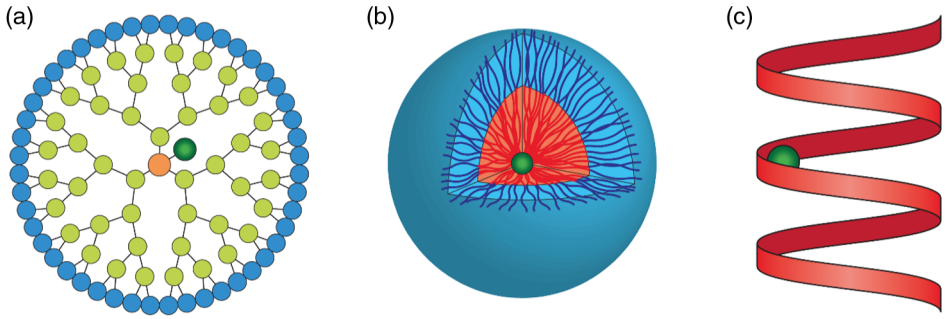

Figure 1 | *Mimicking features of enzymes by incorporating a catalytically active center in synthetic macromolecular architectures such as (a) dendrimers, (b) micelles, and (c) helical polymers.*

chiral dendrimers and helical polymers.[17–34] For example, an achiral catalyst embedded in the well-defined three-dimensional (3D) conformation of a foldamer was shown to successfully perform enantioselective catalysis (Figure 1c).[31]

Collapsing polymers using hydrophobic interactions and intramolecular cross-linking

Apart from hydrogen-bonding interactions, the formation of the 3D structure of proteins is also driven by hydrophobic interactions and disulfide bond formation. These particular driving forces in protein folding have been successfully mimicked by collapsing an individual polymer chain into a so-called single-chain polymeric nanoparticle (SCPN) applying either intramolecular cross-linking reactions or hydrophobic interactions (Figure 2).[35–37] Early examples have predominantly used covalent chemistry to cross-link individual polymer chains intramolecularly. Hereto, click chemistry, radical coupling, dimerization, and cyclization reactions have been used.[38–60] However, the irreversible nature of a covalent bond results in a significant loss of the polymer's dynamics and responsiveness to stimuli. As the fixed nature of such particles contrasts with biological systems, attempts have been made to introduce some reversibility to the systems. This was achieved via the use of dynamic covalent cross-links, using disulfide, hydrazone, enamine, Diels–Alder, or reversible photodimerization chemistry.[61–72] Although the bonds formed using this type of chemistry are, in principle, covalent, they can be broken, reshuffled, and reformed under specific conditions.

Although some proteins do contain dynamic covalent bonds in the form of disulfide bridges, the initial folding of a protein is mainly driven by the hydrophobic effect.[73,74] This dynamic characteristic of proteins can be mimicked with amphiphilic heterograft copolymers. In water, such copolymers, consisting of hydrophobic and hydrophilic grafts, collapse into nanoparticles because of hydrophobic interactions. The polymer's hydrophilic grafts accumulate on the polymer–water interface, whereas the hydrophobic grafts are depleted from the interface, forming a hydrophobic domain.

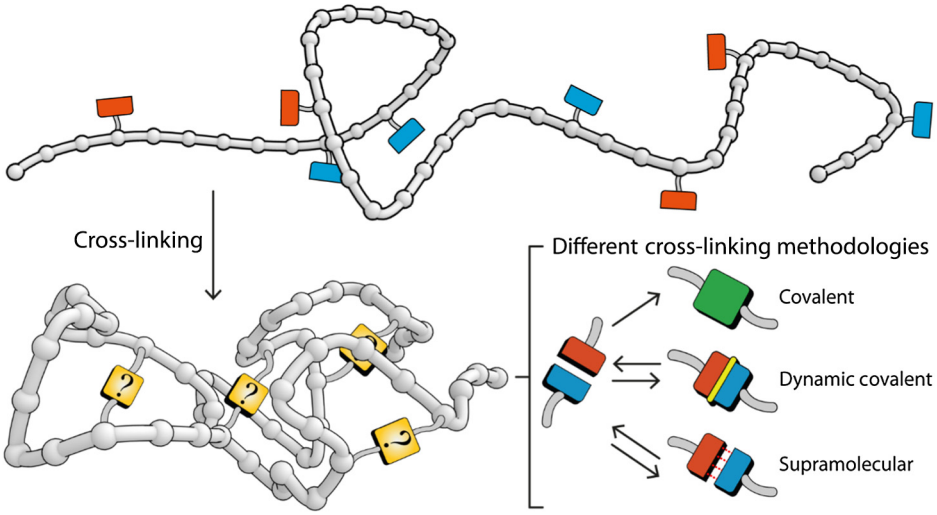

Figure 2 | *Collapse of an individual polymer chain into a single-chain polymeric nanoparticle (SCPN) via various intramolecular cross-linking methodologies.*

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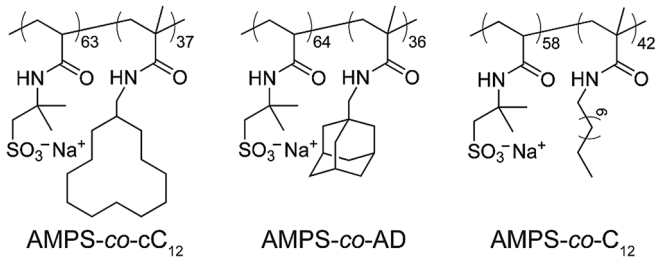

Figure 3 | *Chemical structures of the amphiphilic heterograft copolymers studied by Morishima and co-workers.*[75-77]

Morishima and co-workers[75] were the first, in 1995, to elaborately study the association behavior of random amphiphilic heterograft copolymers. In their pioneering work, 2-acrylamido-2-methyl-1-propanesulfonate (AMPS) was copolymerized with several hydrophobic grafts with a varying hydrophobicity (Figure 3). The copolymers containing *N*-cyclododecyl (cC_{12}) or *N*-(1-adamantyl) (AD) pendants showed a strong tendency to collapse intramolecularly over a wide range of concentrations (<70 mg mL^{-1}). However, the copolymer grafted with (*N*-dodecyl) (C_{12}) only formed SCPNs at much lower concentrations (<2 mg mL^{-1}). At higher concentrations, this copolymer associated into multichain aggregates. In two follow-up studies, the effect of the hydrophobic content and the importance of the sample preparation were carefully investigated for (*N*-dodecyl)-containing copolymers.[76,77] Here, SCPN formation was observed for copolymers with dodecyl incorporations of 30 mol % and lower. At higher dodecyl incorporations (≥40 mol %), the copolymers cluster into kinetically frozen aggregates. The aggregation number of these structures was found to increase as a function of the hydrophobic content of the copolymers.

Terashima and co-workers[78] performed an in-depth study on the association behavior of poly(methyl methacrylate) polymers grafted with poly(ethylene glycol) derivatives and various alkyl groups (Figure 4). It was found that the incorporation percentage of the hydrophobic alkyl pendants controlled the balance between intra- and intermolecular association. Efficient intramolecular collapse of the amphiphilic heterograft copolymers was observed for random copolymers with a hydrophobic content up to 40 mol % (<60 mg mL^{-1}). This upper limit proved to be independent of the structure of the alkyl graft. However, the copolymers containing the more hydrophobic grafts turned out to collapse into more compact structures. The formed nanoparticles were successfully unfolded by elevating the temperature or via the addition of methanol. This highlighted the dynamic and reversible nature of nanoparticles formed via the hydrophobic collapse of polymers.

In several follow-up studies, the behavior of the dodecyl-containing copolymers was further elucidated. Interestingly, these copolymers showed a specific threshold degree of polymerization (DP_{th}).[79-81] Above this DP_{th}, the copolymers collapsed intramolecularly into particles of a certain size. However, below this threshold, shorter copolymers, with the same hydrophobic–hydrophilic balance, associated intermolecularly into multichain aggregates (Figure 5a). Intriguingly, the size of these aggregates was identical to the size of the particles formed by the intramolecular collapse of the long polymer chain (Figure 5b). Moreover, although the size of the multichain aggregates depended on the composition of the copolymers and increased as a function of the hydrophobic content, it was independent of the degree of polymerization ($DP < DP_{th}$). Mixing two different copolymers with distinct compositions resulted in self-sorting of the copolymers into a stable binary mixture.

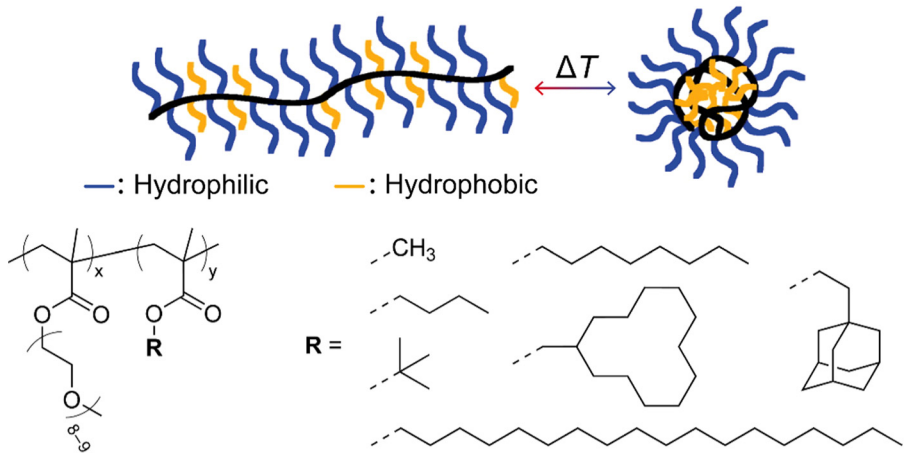

Figure 4 | *Chemical structures of the amphiphilic heterograft copolymers studied by Terashima, Sawamoto et al. Adapted with permission from ref 77. Copyright 2014 American Chemical Society.*

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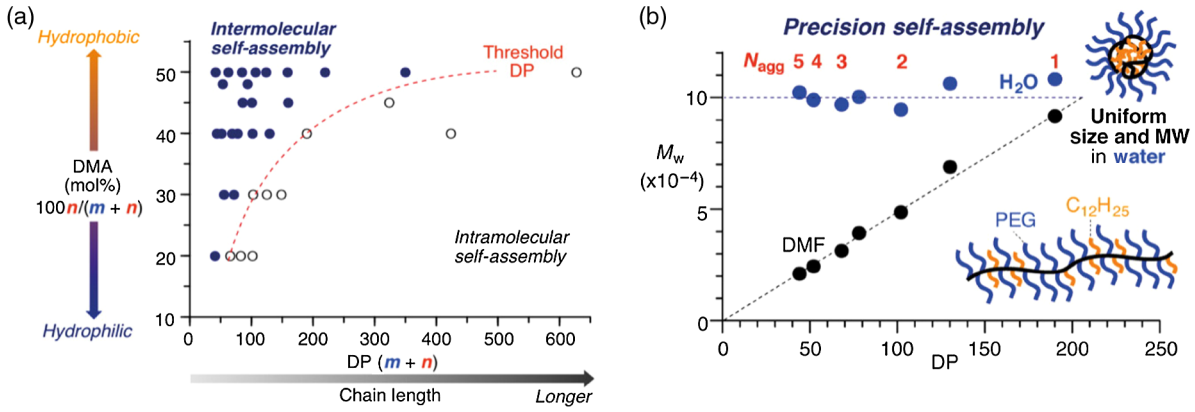

Figure 5 | *(a) The copolymers have a threshold degree of polymerization, which determines whether hydrophobic collapse occurs intra- or intermolecularly. (b) Amphiphilic heterograft copolymers with various degrees of polymerization, but a single composition, form nanoparticles with an almost constant weight-average molecular weight in water. DP, degree of polymerization; DMA, dynamic mechanical analyzer; DMF, dimethylformamide; PEG, poly(ethylene glycol). Adapted with permission from ref 78. Copyright 2016 American Chemical Society.*

Recently, Terashima and co-workers[78] demonstrated that the sequence of the hydrophobic and hydrophilic grafts also impacts the solution behavior of amphiphilic heterograft copolymers. While copolymers with a randomly distributed sequence formed uniform nanoparticles in solution (≤40 mol %), copolymers with a gradient- or block-type architecture associated into multichain aggregates.[78,82,83] Similar results have been obtained for hydrophobically modified polyelectrolytes.[84,85]

Folding polymers via hydrogen-bond-driven dimerization

The precise tertiary structure of folded proteins is not only solely determined by hydrophobic and hydrophilic interactions but also relies on the formation of specific hydrogen bonds. Therefore, the folding of synthetic polymers via hydrophobic as well as hydrogen-bonding interactions is a fascinating route toward rudimentary protein mimics.

Rotello and co-workers[86] were the first, in 1999, to use hydrogen-bonding interactions to fold synthetic polymers in organic media. Hereto, polystyrene was functionalized with diaminotriazine units (Figure 6a). In apolar solvents, the hydrogen-bond–driven dimerization of the self-complementary pendants induced intramolecular folding of the copolymer. Upon the addition of uracil derivatives, the folded structures were either functionalized or unfolded via specific competitive noncovalent interaction.[86–88] Later, Hawker and Kim reintroduced the concept of folding polymers using hydrogen-bond–driven dimerization, by equipping a poly(methyl methacrylate) backbone with self-complementary dendritic bisamides (Figure 6b).[89] The group of Barner–Kowollik used complementary hydrogen-bonding motives for the selective point folding of polymers into loops. The endgroups of a heterotelechelic polymer were functionalized with a cyanuric acid and Hamilton wedge or thymine and diaminopyridine, respectively (Figure 6f,c, respectively).[90,95] In follow-up studies, the orthogonal hydrogen-bonding pairs were combined to create folded ring structures.[91,92] Also, the dimerization between *N*-(6-(3-(2,4-dioxo-3,4-dihydropyrimidin-1(2H)-yl)-propanamido) pyridine-2-yl)undec-10-enamide (Figure 6d), 2-ureido-5-deazapteridines (Figure 6e), and ureido-guanosine and diamino-naphthyridine has been used (Figure 6h).[93,94,99]

In our lab, the first polymeric nanoparticles formed via the dimerization of its hydrogen-bonding pendants were introduced by Foster and Berda in 2009 (Figure 6g).[96,97] Poly(norbornene) and poly(methyl methacrylate) backbones were functionalized with *o*-nitrobenzyl-protected 2-ureido-pyrimidinone (UPy) moieties (10–40 mol %). The folding of those copolymers was impeded by the bulky protecting group preventing the dimerization of the UPy pendants. Upon the removal of the protective groups, via irradiation with UV-A light, the UPy grafts were able to dimerize via quadruple hydrogen-bonding interactions (Figure 7). At low concentrations (≤1 mg mL^{-1}), this dimerization proved to proceed intramolecularly. The accompanying reduction in the copolymer's hydrodynamic volume was successfully detected with size exclusion chromatography.

In an extensive follow-up study, Stals and co-workers[98] investigated the impact of different polymer backbones on their UPy-induced folding behavior. *o*-Nitrobenzyl-protected UPy-motifs were grafted to a poly(acrylate), poly(methacrylate), poly(styrene), and poly(norbornene) backbone via a postfunctionalization approach. Although the copolymer backbones differed in terms of length and rigidity, no significant difference in their folding behavior was observed by size-exclusion chromatography and dynamic light scattering. However, it

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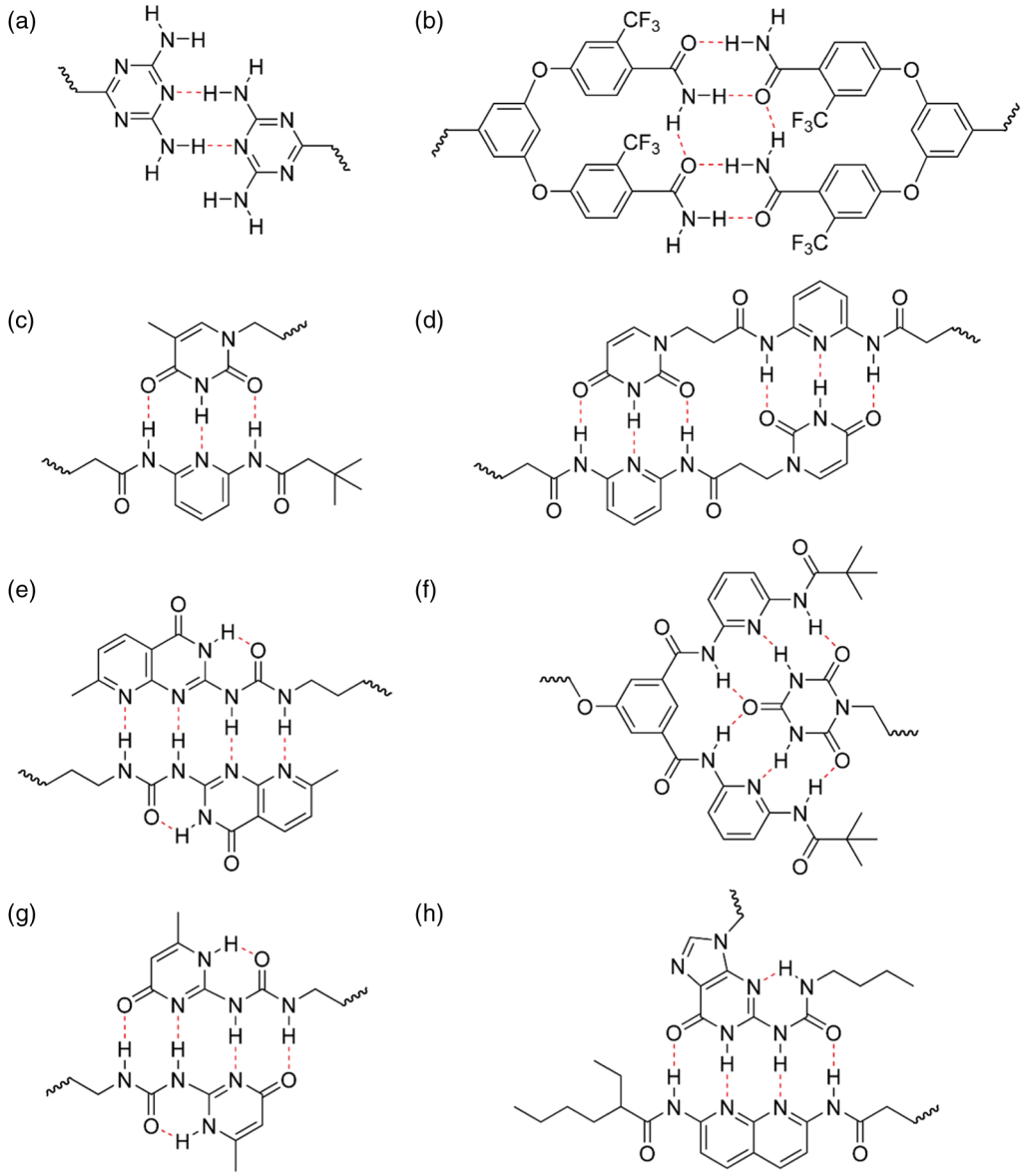

Figure 6 | *The structures of the hydrogen-bonding motifs used to fold synthetic polymers in organic media: (a) Rotello and co-workers,[86-88] (b) Kim and co-workers,[89] (c) Barner-Kowollik and co-workers,[90-92] (d) Xin and co-workers,[93] (e) Du and co-workers,[94] (f) Barner-Kowollik and co-workers,[90-92,95] (g) Meijer and co-workers,[96-98] and (h) Romulus and Weck[99]*

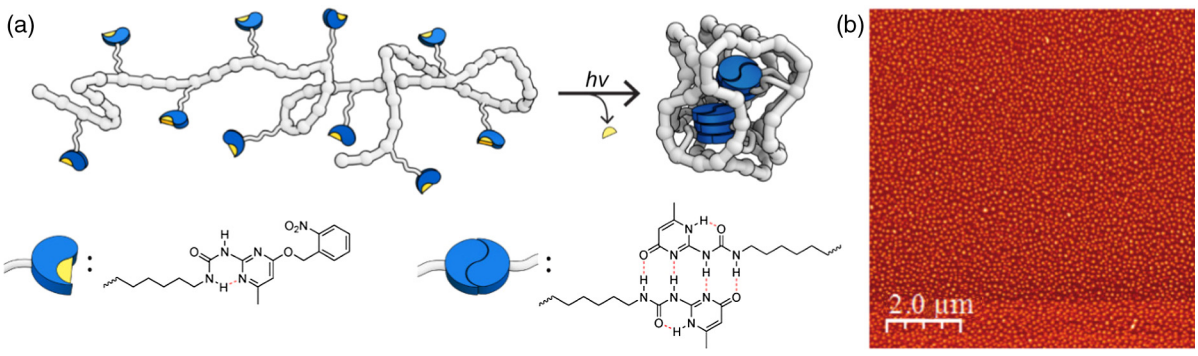

Figure 7 | *(a) Schematic representation of polymer folding induced by the deprotection of its 2-ureido-pyrimidinone (UPy) pendants. (b) Atomic force microscopy image of the folded polymer structures on mica.[96-98] Adapted with permission from ref 95. Copyright 2009 American Chemical Society.*

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was found that the solvent choice does play a crucial role in the formation of stably folded nanoparticles. Although well-defined SCPNs were formed in tetrahydrofuran (THF), the use of more apolar solvents, such as chloroform, lead to interpolymer aggregation. Apparently, solvents that strongly promote the formation of hydrogen bonds also increase the interpolymer interactions.

In addition to hydrogen-bonding supramolecular interaction, a wide variety of other supramolecular interactions has been explored to fold synthetic polymers. The use of host–guest chemistry employing cyclodextrin,[100–103] crown ethers,[104] cucurbituril,[105,106] and calix[4]pyrroles was reported by multiple groups.[107] In addition, the groups of Rotello and Weck used π-stacking interactions between homo- and heteroaromatic pendants for the reversible folding of copolymers, while O'Reilly and co-workers[108–111] used ionic interactions. Recently, Artar,[112,113] Cai,[114–116] Pomposo,[117–119] Lemcoff,[120–122] Barner-Kowollik,[123–125] Zimmerman,[126] and others have been using a wide variety of metal–ligand complexations to collapse polymer chains.[127–133]

Folding using directional supramolecular motifs in organic media

In addition to dimerizable groups, our lab has also focused on moieties that self-assemble into one-dimensional supramolecular fibers.[134] Especially, the benzene-1,3,5-tricarboxamide (BTA) moiety and its derivatives have been studied extensively.[135] The inherent ability of BTAs to self-assemble into helical supramolecular polymers—stabilized by 3-fold hydrogen-bonding—makes them suitable to structure a polymer in solution (Figure 8). The formation of this helical internal structure can be monitored using circular dichroism (CD) spectroscopy. Therefore, the use of BTAs to induce the folding of polymers into structured nanoparticles can be probed in more detail.

Mes and co-workers[136] were the first to demonstrate the BTA-driven folding of polymers in organic media. Hereto, *o*-nitrobenzyl–protected BTAs were attached to a poly(isobornyl methacrylate) via a postfunctionalization approach. The presence of the bulky protective group, attached to one of the BTA's amide groups, successfully impeded the BTA-driven folding of the copolymers. A step-wise removal of the photo-labile protecting groups, via the irradiation with UV-A light, allowed the copolymer to fold in a step-wise manner. CD spectroscopy showed that the BTAs did still self-assemble into their typical helical stacks when grafted to a polymer backbone.

The BTA-driven folding of polymers in organic media was further elucidated by Hosono and co-workers.[137] ABA-type triblock architectures with an intriguing "Soldier–Sergeant–Soldiers" design were synthesized (Figure 8). Although the two outer blocks of the polymers contained achiral derivatives of the BTA, the middle block was functionalized with chiral BTA grafts. The anticipated transfer of chirality from the chiral sergeants in the middle block to the achiral soldiers in the outer block proved to be minimal. Therefore, it was concluded that a folded polymer chain does not contain a single chiral BTA stack, but must be composed of multiple, segregated stacks.

Ogura and co-workers[138] investigated the importance of the copolymer's sequence distribution. Hereto, 2-ethylhexyl methacrylate was copolymerized with a BTA-functionalized methacrylate to form copolymers with either a random, a gradient, or a bidirectional gradient distribution of the grafts. Surprisingly, the temperature-dependent self-assembly of the BTA pendants proved to be independent of their sequence distribution. However, while the random sequence had the

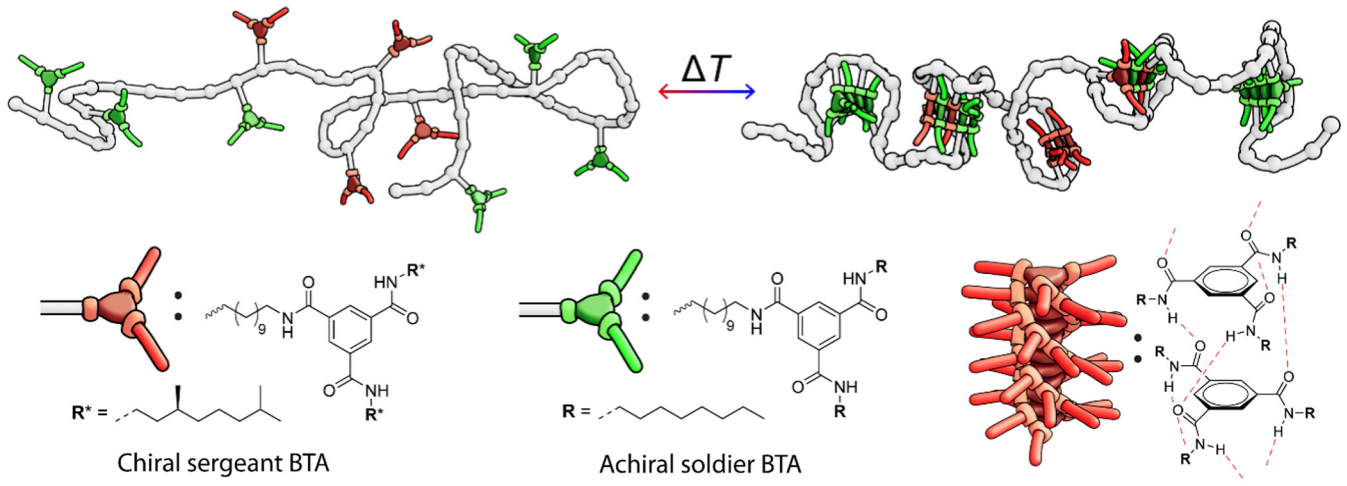

Figure 8 | *Schematic representation of a "Soldier–Sergeant–Soldiers" ABA-type triblock copolymer and its folding into multiple segregated stacks. BTA, benzene-1,3,5-tricarboxamide.*[137]

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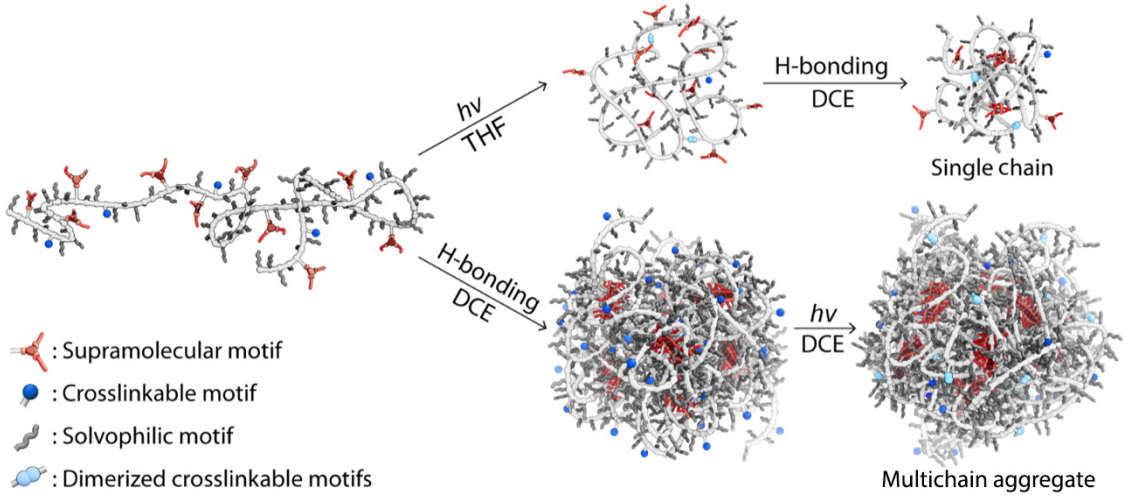

Figure 9 | *Schematic representation of the two pathways applied to fold and cross-link the copolymers. In the first pathway (top), the coumarin pendants are first dimerized with UV-A light in THF (a solvent that prevents hydrogen bonding), followed by redissolving the particles in 1,2-dichloroethane (*DCE*), a solvent that promotes hydrogen bonding. In the second pathway (bottom), the benzene-1,3,5-tricarboxamide pendants are aggregated in DCE, after which the coumarin pendants are dimerized with UV-A light.*[139]

tendency to fold intramolecularly, the two gradient architectures proved to aggregate intermolecularly.

Recently, we explored the effect of structural constraints induced by covalent cross-links between coumarin pendants on the hydrogen-bond–driven folding of such copolymers.[139] Two different folding pathways were compared (Figure 9). In one case, the coumarin pendants were first covalently cross-linked within the copolymers in a solvent, which prevents hydrogen bonding, after which hydrogen bonding is activated, inducing folding of the copolymer. In the other case, the hydrogen-bonding interactions between tethered BTAs were induced prior to covalent cross-linking of the coumarin pendants. The results showed that, as in nature, the order of events matters greatly and determines the outcome. Although the first pathway resulted in SCPNs, the other procedure led to cross-linked multichain aggregates showing a fundamentally different response to changes in temperature.

Hosono and co-workers[140] were the first to successfully combine the UPy- and BTA-driven folding into a single polymer. ABA-type triblock copolymers were prepared with the middle-block-containing BTAs and the two outer blocks *o*-nitrobenzyl protected UPy groups (Figure 10). These complex copolymers were folded in an orthogonal step-wise manner. First, the self-assembly of the BTAs was induced by lowering the temperature of the solution. Subsequently, the UPy groups were deprotected photochemically to induce their dimerization. In a follow-up study, the order of the blocks was inverted to BAB.[141] The BAB-type triblock copolymers were found to fold into a slightly less compact nanoparticle than the ABA-type triblock copolymers. The difference was attributed to the BTAs having a larger tendency to form multiple segregated domains when located in the outer blocks.[137] Altintas and co-workers[142] reported the orthogonal folding of ABC-type triblock copolymers. Here, the middle block contained BTAs, but the A and C blocks were functionalized with Hamilton wedges and cyanuric acid derivatives, respectively.[142] These examples show that the complexity and specificity of a SCPN's internal structure can be tuned by using multiple orthogonal supramolecular motifs.

In addition to hydrogen-bonding interactions, π-stacking also was used to fold polymers into SCPNs.[143] Gillissen and co-workers used ring-opening metathesis to synthesize poly(norbornene) polymers grafted with 5–10 mol % of 3,3′-bis(acylamino)-2,2′-bipyridine-substituted BTAs. The copolymers were shown to fold intramolecularly in mixtures of THF and methylcyclohexane. Interestingly, concentration-dependent, dynamic light-scattering experiments showed that the intermolecular interactions between copolymers decreased for increasing BiPy–BTA incorporations. It was hypothesized that higher BiPy–BTA incorporations resulted in a stronger propensity to form a defined internal structure. Embedding the discotics in a more stable structure simultaneously prevented them from interacting intermolecularly.

Folding using directional supramolecular motifs in aqueous media

In 2011, Terashima and co-workers[144] were the first to successfully modify the designs used in organic media to enable BTA-driven polymer folding in aqueous media.

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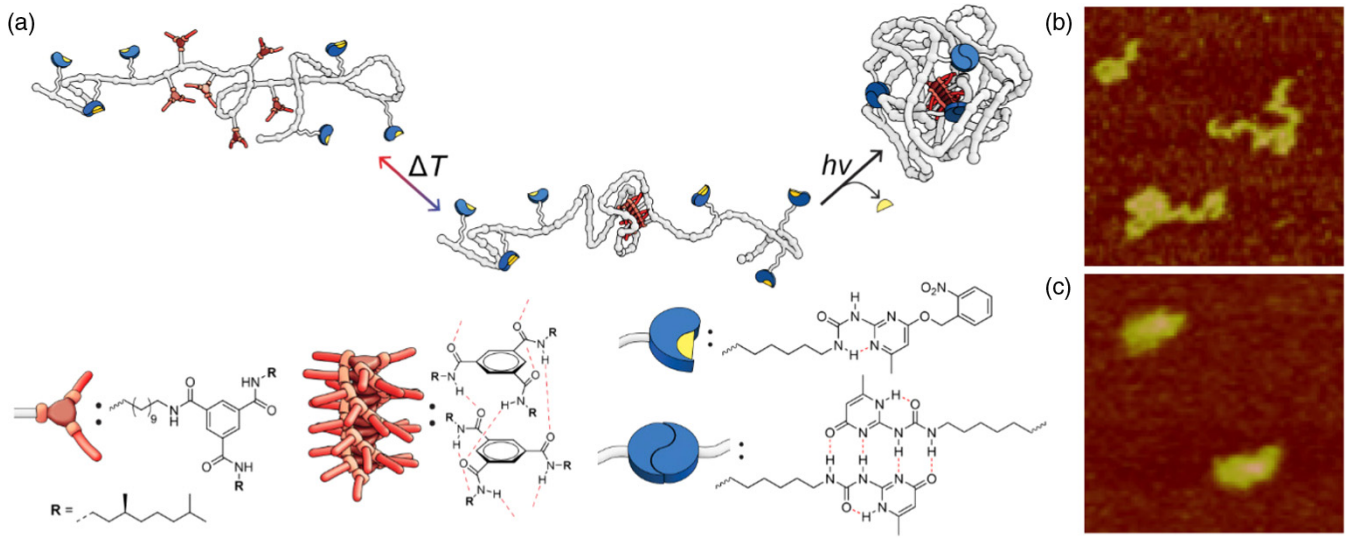

Figure 10 | *(a) Schematic representation of the sequential orthogonal folding of an ABA-type triblock copolymer. Atomic force microscopy images of the partly folded (b) and fully folded (c) single-chain polymeric nanoparticles. Adapted with permission from ref 136. Copyright 2009 American Chemical Society.*

Water solubility was introduced to the systems by attaching hydrophilic poly(ethylene glycol) methyl ether grafts to the poly(methacrylate)-based polymers. When dissolving these amphiphilic heterograft copolymers in water, the hydrophobic nature of the BTAs induced the hydrophobic collapse of the copolymer. CD spectroscopy was used to show that the BTAs still self-assembled into their typical helical supramolecular structures. Therefore, it was concluded that the polymeric nanoparticles possessed a well-defined, structured interior.

The impact of the formation of such an internal structure on the overall conformation of the copolymer was further elucidated by Gillissen et al.[145] and Stals et al.[146] They used a chiral BTA-functionalized methacrylate that was randomly copolymerized with poly(ethylene glycol) methyl ether methacrylate in a 1:9 ratio with varying degrees of polymerization (DP = 100–450) (Figure 11). The extent of BTA self-assembly was carefully controlled by varying the temperature of the solution and/or via the addition of a cosolvent that disrupted the BTA-stack's stabilizing hydrogen bonds (e.g., isopropanol). Using

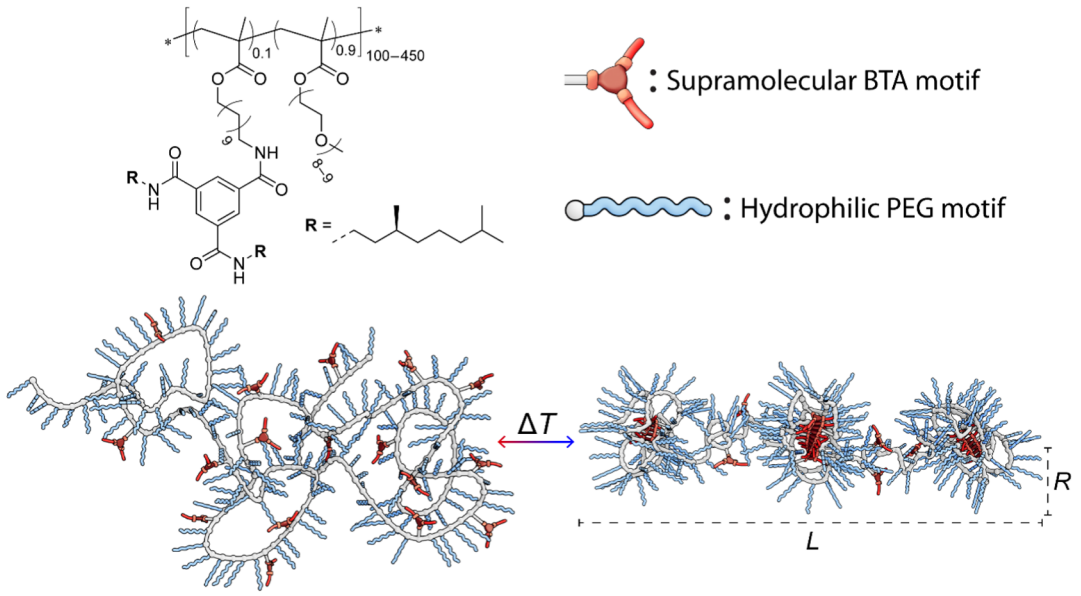

Figure 11 | *Schematic representation of the folding of amphiphilic heterograft copolymers into asymmetric nanoparticles with a constant cross-sectional radius (R) and a varying length (L). PEG, poly(ethylene glycol).*[145,146]

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small-angle neutron-scattering experiments, it was shown that an individual polymer folds into an asymmetrically shaped nanoparticle that shows a constant cross-sectional radius of ca. 3 nm, but increases in length with increasing DP. Interestingly, upon self-assembling the BTA grafts, the length increased, whereas it decreased upon their dissociation. Therefore, it was concluded that the formation of an internal structure influences the global conformation of the polymer. It was hypothesized that the amphiphilic heterograft copolymers fold into several segregated hydrophobic domains along the backbone, adopting an elongated overall conformation.[146] Similar polymer conformations have been suggested in molecular simulations by Pomposo et al.[147] and in experimental work by Terashima, Sawamoto, and co-workers.[148]

Recently, we investigated the effect of the copolymer composition on the association behavior of amphiphilic copolymers in solution.[149] A family of amphiphilic, heterograft copolymers containing hydrophilic, hydrophobic, and supramolecular units based on Jeffamine M-1000, dodecylamine, and BTA motifs, respectively, was prepared via a postfunctionalization approach. Relatively small changes in the polymer's graft composition proved to strongly affect the intra- versus intermolecular assembly processes. Thus, the intra- and intermolecular self-assembly pathways can be directed by carefully tuning the copolymer's hydrophilic–hydrophobic balance (Figure 12).

In a follow-up study, the effect of the geometry of the water-soluble grafts on the supramolecular folding of amphiphilic heterograft copolymers was investigated.[150] Hereto, the linear poly(ethylene glycol) pendants normally used to convey water compatibility were partially substituted with branched analogues. The results showed that even though branching of the hydrophilic pendants does affect the local structure of the folded copolymer, it does not influence the very compact spherical conformation and single-chain character of the folded copolymers in solution.

Also in aqueous media, π-stacking was used to fold amphiphilic heterograft copolymers into SCPNs.[151] To this end, hydrophilic heterograft copolymers containing structuring, chiral 3,3′-bis(acylamino)-2,2′-bipyridine-substituted BTAs units were prepared via ring-opening metathesis polymerization. The results showed that the folding of the copolymer required an optimal balance between the conformational freedom of the polymer's backbone and the stability of the π-stacked units. Small-angle X-ray–scattering experiments showed that the shape of the SCPNs is controlled by the formation of a chiral internal secondary structure.

Functional folded polymers

The collapse of amphiphilic heterograft copolymers into nanoparticles involves the association of the hydrophobic pendants into a shielded hydrophobic domain. The unique character of these shielded domains, with respect to their environment, can be utilized for the encapsulation and the controlled release of hydrophobic molecules such as chiral amino acids, peptides, vitamins, and drug molecules.[152–161] The incorporation of gadolinium ions, gallium atoms, or fluorescent groups have allowed SCPNs to be used as contrast agents in magnetic resonance and fluorescent imaging.[40,143,159,160,162–170]

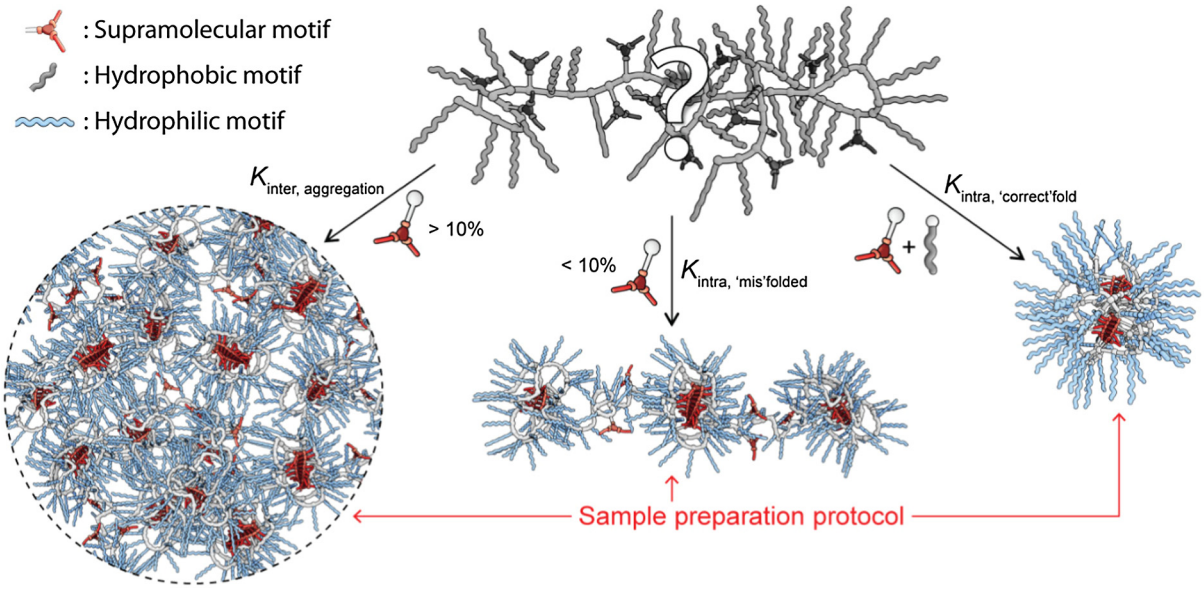

Figure 12 | *Schematic representation of the effect of the polymer's graft composition on the different inter- and intramolecular self-assembly pathways of supramolecular amphiphilic heterograft copolymers.*[149]

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Furthermore, the interior of collapsed polymers has been successfully used for the synthesis of nanoparticles and polymers.[71,119,171–175]

If the hydrophobic collapse of a polymer occurs intramolecularly, the structure of the formed nanoparticle is directly related to its macromolecular design. Therefore, careful synthetic design can be used to place specific functional groups in close proximity to each other. Following this concept, various rudimentary enzyme mimics have been synthesized by equipping the polymers with catalytically active groups.[176–178] Via the incorporation of Cu, Pd, Ti, Pt, Rh, and Ir ions, a wide variety of click, coupling, reduction, and oxidation reactions have been successfully performed albeit predominantly in organic media.[57,117,121,124–126,129–131] Terashima and co-workers[144] copolymerized BTA and oligo(ethylene glycol) methyl ether derivatives with triphenylphosphine ligands to bind ruthenium ions. The resulting system proved to efficiently catalyze the transfer hydrogenation reaction of ketones. Similar copolymers were also able to facilitate the oxidation of secondary alcohols into their corresponding ketones.[113] These systems showed to be highly selective toward more hydrophobic substrates. More hydrophobic substrates resulted in a higher local concentration of the substrate around the catalytic center, leading to increased reaction rates. Surprisingly, the incorporation of hydrophobic BTA pendants was not essential for an efficient catalysis.[112] Apparently, the catalytically active groups are also sufficiently shielded from the aqueous environment by a polymer backbone containing dodecyl pendants as the hydrophobic graft. Following these concepts, the hydrophobic pocket of foldable amphiphilic heterograft copolymer was used to shield L-proline groups.[179,180] Hereby, a suitable environment was created for the catalysis of aldol reactions in water. Remarkably, the presence of a structured interior, formed by BTA aggregation, was crucial for catalytic activity and selectivity. Detailed studies were performed on analogous copolymers in which the proline was replaced by a TEMPO spin label to elucidate the origin of this remarkable finding.[181] Electron paramagnetic resonance measurements revealed that the local polymer backbone dynamics were unaffected by the presence of the structuring BTA units. In contrast, Overhauser dynamic nuclear polarization measurements, which probe the local water translational diffusion dynamics within 0.5–1 nm of the tethered TEMPO labels, indicated that the water retardation inside the SCPNs was affected by the structure of the interior. In fact, a higher water retardation was found for the BTA-comprising copolymers. In enzymes, it is well known that the properties of hydration water—both its structure and dynamics—plays a dominant role in enzyme catalysis.[182–185] SCPNs with a structured interior show water retardation similar to that found for surface water in enzymes. As a result, these experiments show that SCPNs with structured interiors show surface hydration properties resembling those of enzymes.

Liu et al.[186] introduced a modular postfunctionalization approach to synthesize amphiphilic poly(acrylamide) polymers equipped with copper- or palladium-binding ligands (Figure 13). Upon the complexation of the two different metals, azide–alkyne cycloadditions and depropargylation reactions were accelerated, respectively. Functionalization of a polymer with a porphyrin motif enabled the photo-induced production of singlet oxygen. The generated singlet oxygen was used to cleave an amino-acrylate linker, releasing a drug mimic from the nanoparticle. Interestingly, the catalytic reactions were performed in phosphate buffer at a physiological pH. Later, the catalytic activity of the SCPNs was

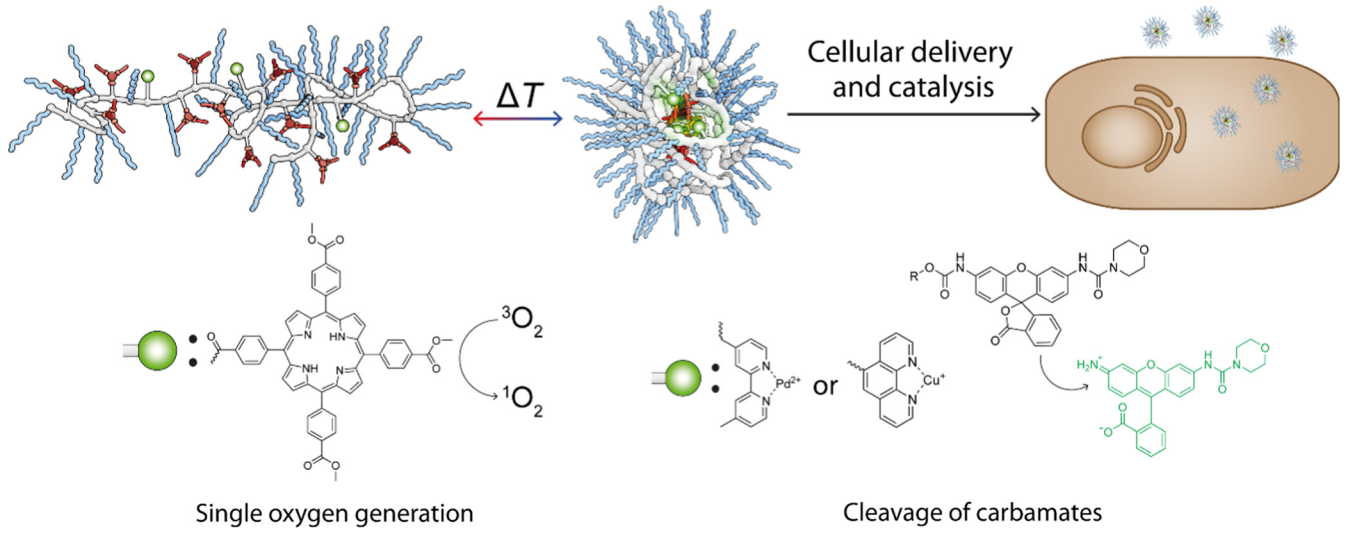

Figure 13 | *Schematic representation of the folding of catalytically active copolymers, its cellular delivery, and catalysis.*[186–188]

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studied at both the ensemble and individual level using single-molecule fluorescence microscopy.[187]

Recently, Liu et al.[188] showed that depropargylations were also possible using folded copolymers comprising Cu(I) and Pd(II) complexes in the presence of HeLa cells (Figure 13). Three different cellular compartments were selectively targeted by means of using different delivery strategies. The polymeric particles proved to be nontoxic to the cells and their catalytic functions were retained in the complex media, although at a lower efficiency compared with in vitro studies. However, inside the HeLa cells, the catalytic activity of the SCPNs was lost, indicating that the design of the SCPNs needs further improvement to have more stable catalysts available. Zimmerman and co-workers[189] took a next step by successfully using catalytically active nanoparticles in both bacterial and mammalian cells. Poly(norbornene) polymers were functionalized with imidazolium groups and α-amino acids, to provide water solubility and to form reactive copper complexes, respectively. These particles proved to be excellent catalysts for the copper-catalyzed alkyne–azide cycloaddition in living cells. Finally, Wong and co-workers[190] showed that SCPNs consisting of oligo(ethylene glycol) methyl ether derivatives in combination with various hydrophobic and amine groups exhibit excellent antimicrobial activity.

Conclusion and Outlook

The folding of amphiphilic heterograft copolymers has proven to be a fascinating approach to obtaining structured nanoparticles. The modular nature of this approach allows such synthetic macromolecular architectures to fulfill diverse functions. However, in order to further improve the diversity, efficiency, and specificity of such functional structures, more insight into the structure–function relationship is crucial. In water, such copolymers, consisting of hydrophobic and hydrophilic grafts, collapse into nanoparticles because of solvophobic interactions. The polymer's hydrophilic grafts accumulate on the polymer–water interface, whereas the hydrophobic grafts are depleted from the interface, forming a hydrophobic domain. However, if an excessive part of the hydrophobic elements of an amphiphilic heterograft copolymer remains exposed to the solvent, interparticle aggregation is promoted in a concentration-dependent manner. While the intramolecular collapse of an amphiphilic heterograft copolymer is energetically most favorable at low concentration, its intermolecular aggregation into oligomeric or large amorphous structures is facilitated at high concentration. Therefore, in close resemblance to proteins, the intramolecular folding of amphiphilic heterograft copolymer results in a metastable state, while intermolecular aggregation is thermodynamically more favorable.[191–193] However, at a given concentration, the tendency of an amphiphilic heterograft copolymer to assemble either intra- or intermolecularly is predominantly controlled by its hydrophilic–hydrophobic balance. This balance appears to be extremely delicate and depends strongly on the copolymer's hydrophobic content, which seems to be related to the degree of incorporation of the hydrophobic pendants as well as the size, number of carbon atoms, of these pendants. In addition, the equilibrium between intra- and intermolecular assembly can be affected by the addition of additives. While the addition of a good cosolvent might enhance the single-chain character of an amphiphilic heterograft copolymer in solution, the addition of a sufficient amount of "free" hydrophobic dye or substrate promotes the formation of multichain aggregates. As a result of this continuous competition between the intra- and intermolecular association of the copolymer, the folding and characterization of supramolecular amphiphilic heterograft copolymers into SCPNs are far from trivial.

Due to the strong concentration-dependence of a polymer's single-chain character, the synthesis of SCPNs is typically restricted to very dilute polymer solutions. This severely limits the scalability of their synthesis, and thus their potential application at large scales. Recently, researchers started to tackle this crucial challenge, but the number of successful approaches is still limited.[194–197] In terms of characterization, a wide variety of different techniques have been employed to study the behavior of such foldable polymers.[198] However, most of them are only capable of providing circumstantial evidence of a particle's single-chain character. The only way to unambiguously determine whether a nanoparticle is folded intramolecularly, and not a small multichain aggregate, is via the determination of the mass of the nanoparticle in solution. Static-scattering techniques, such as static light scattering and small-angle X-ray or neutron scattering, are ideally suited for this purpose, yet, not commonly implemented in the SCPN field.

By developing a diverse toolbox to fold synthetic polymers using supramolecular interactions, we are gradually gaining insight into the design principles controlling the intra- and intermolecular self-assembly pathways. Hence, we can slowly start to focus on further improving the specificity of the folded structures. As described in this review, this can be achieved by carefully tuning the components and composition of copolymers with a random sequence. However, the intricate designs and structures of nature's folded architectures are typically formed by the folding of perfectly defined amino acid sequences. Therefore, one could argue that the sequence, molar mass dispersity, and molecular weight of a synthetic polymer should matter. However, to mimic nature's ability to fold a perfectly defined polymer in an unambiguous structure, a highly specific network of interactions is required. In the absence of such specificity,

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the system will not have a clear energy minimum and will therefore still be able to adopt a large number of different conformations. Currently, we lack the ability to introduce this required complexity in a purely synthetic system, especially if it must remain soluble in solution. Nevertheless, pioneering work by Zuckermann and co-workers[199] using polypeptoids demonstrated that predicted hydrophilic–hydrophobic sequences show a much more defined collapse compared to a random sequence. However, in addition to the major synthetic challenges lying ahead, the folding of sequence-controlled structures will pose a massive challenge for detailed characterizations. The current disperse systems are already at the limit of what we can investigate.[198] Therefore, intriguing polymer designs in combination with new characterization methodologies have to be developed to determine which sequence results in a better folded nanoparticle.

Finally, as described in this review, the unique nature of folded supramolecular amphiphilic heterograft copolymers is ideally suited for a wide variety of applications, such as drug delivery, sensing, imaging, and catalysis.[160,178,200,201] While the single-chain character might not be essential for all of these different applications, a detailed insight into the functional nanoparticle's structure will be crucial for the optimization of its function. To this end, a major benefit of the SCPN approach is that, in contrast to multichain nanoparticles, the final structure of an individually folded copolymer is directly related to the composition of the copolymer. Therefore, modifications in the copolymer's design are directly influencing the performance of the particle. This could be especially interesting in order to control the direct surrounding of a catalytic group. Such a modular platform, able to catalyze a wide variety of different reactions, is especially interesting in combination with the first biocompatible SCPNs that are currently being developed. One day, rudimentary enzyme mimics might be able to participate seamlessly in nature's multicomponent networks, replacing missing or malfunctioning enzymes.

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