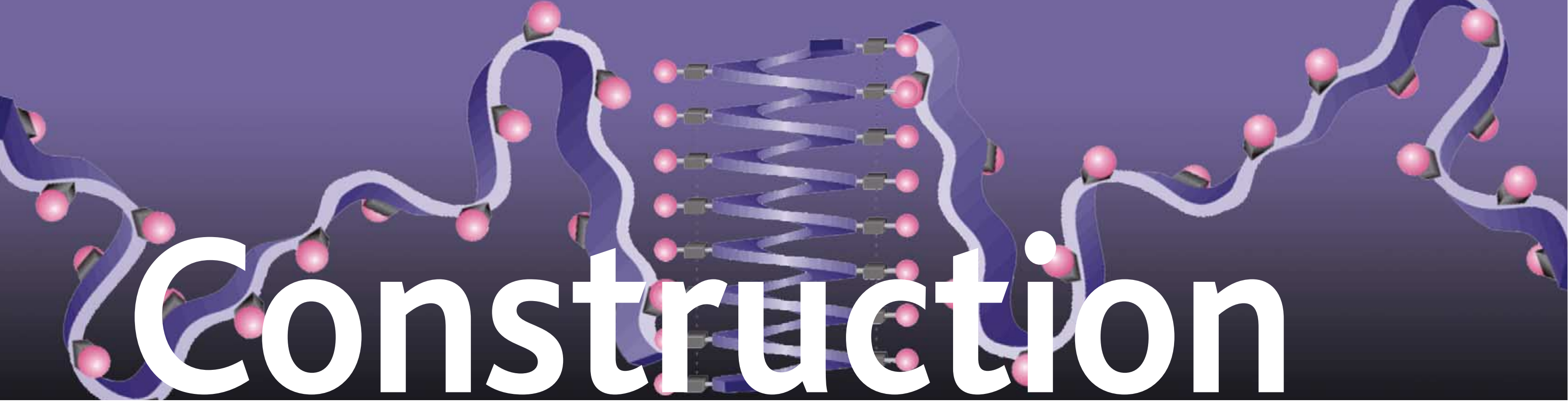

Construction with macromolecules

by Stefan Hecht

The generation of nanosized features via the bottom-up organization of individual atoms and molecules represents one of the most rapidly emerging fields in modern science and technology. In order to gain general and modular access to nanostructures, a construction kit consisting of molecular building blocks with defined nanoscale dimensions, shape, and functionality is required. While nature has developed a hierarchical strategy to construct sophisticated and complex nanostructures, chemistry is just starting to explore artificial macromolecules as a means to synthesize specific nano-objects. In this review, recent advances in achieving control over conformation within macromolecules and the interconnection of conformationally defined subunits by either covalent bonds or self-assembly are discussed in analogy to natural structure evolution.

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Structures of various shapes and functions found in nature are compelling for their beauty and diversity, as well as inspiring for the design of new architectures. In proteins – the principal machinery of life – structure, and thus function, is generated using a hierarchical construction plan. At the primary structure level, different amino acid monomers are covalently connected to yield the desired peptide sequence. At the next stage, regions of this strand are folded into well-defined chain conformations, using noncovalent interactions within the strand and with the environment, giving rise to secondary structures such as helices and sheets. The tertiary structure involves the relative arrangement of secondary structure motifs within the same strand, for instance by introducing specific turns. In more complex proteins, several of these subunits assemble into a quaternary structure held together by multiple noncovalent interactions. Although scientists constantly gain more insight into these astonishingly complex processes, many mysteries, including the folding problem, remain.

When comparing natural and artificial macromolecular systems, it becomes apparent that although polymer chemistry is frequently considered a mature discipline, many features prominent in biological systems are absent in their synthetic counterparts. While polymer science has made tremendous progress over the last half century in controlling primary structure by developing controlled/living

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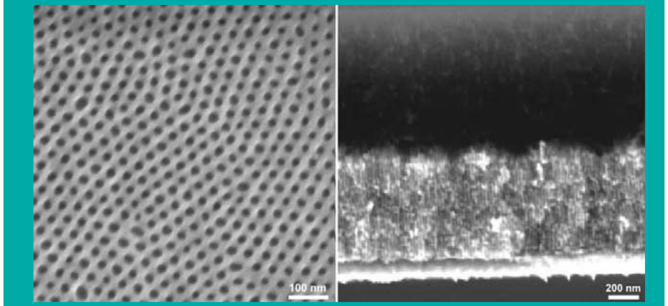
Polymer-based nanofabrication

Block copolymer self-assembly

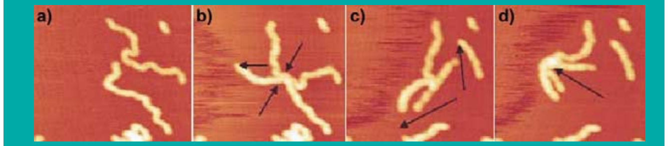
Phase separation of block copolymers enables the preparation of nanostructures on a large surface area with control over the vertical (film thickness) and horizontal (block length) dimensions of the features. Since part of the chemically different, segregated areas can be transformed into inorganic materials, this method allows for the versatile creation of ultrahigh-density nanowire arrays[55-57]. This method is being explored for commercial applications, for example in metal-oxide-semiconductor (MOS) capacitors.



(Left) Template: Atomic force microscope (AFM) image showing a hexagonal array of holes within a polystyrene matrix obtained by microphase separation and selective removal of poly(methyl methacrylate) cylinders. (Right) Nanowire array: scanning electron micrograph of a fracture surface of Co nanowires grown half way within the template by electrodeposition. (Courtesy of the University of Massachusetts, Amherst.)

Highly branched dendritic polymers

Increasing steric congestion because of continuing branching from a spherical or cylindrical core molecule leads to globule- or rod-like objects with tunable nanoscale dimensions. Perhaps the most flexible synthesis of spherical nano-objects allows for modular tuning of dimensions as well as the chemical composition of inner and outer compartments[58]. Nanocylinders based on dendronized polymers have been imaged, manipulated, and used for AFM-controlled synthesis of nano-objects[59].



AFM images showing the covalent connection of two individual dendronized polymer chains by photocrosslinking of peripheral azide groups: (a) imaging; (b) moving and connecting; (c) cutting; and (d) moving sequence. (Courtesy of Jürgen P. Rabe, Humboldt-Universität Berlin, Germany.)

polymerization processes, hierarchical structural organization of conformationally defined macromolecules using concepts from the emerging field of supramolecular chemistry has only recently begun.

Synthetic macromolecules display a diverse chemistry ranging from pure hydrocarbons and typical organic compositions to other main group and transition metal containing polymers. While almost any functional group can be incorporated into a polymer, structure and hence shape and function of the entire system are usually poorly controlled. What is polymer synthesis able to achieve today, and which are the important contributions to structural control?

Controlled/living polymerization techniques involving cationic, radical, anionic, and transition-metal-mediated (ring opening) polymerization processes have allowed a high level of control over chain length and distribution. Perhaps more importantly, these advanced synthetic protocols have enabled the preparation of copolymers consisting of connected blocks with defined length and chemical composition. In recent years, such block copolymers have enjoyed much attention because of their ability to form nanostructures based on phase separation of their chemically different blocks[1-3]. Control over branching in polymers represents another important aspect that allows for the synthesis of nano-objects with tailored shapes and functionalities, most prominently exemplified by discrete dendrimers with hyperbranched polymers representing their less perfect counterparts[4,5]. The use of both block copolymers and dendritic polymers for the generation of nanostructures is highlighted in the textbox (see left). From a critical standpoint, and with an admiration of nature's approach, it becomes apparent that polymer synthesis has mostly impacted the primary structure level. What about higher organizational levels?

Within the last few years, a conscious effort has been made to design macromolecules with specific shapes (mostly spherical and cylindrical geometries), defined nanoscale dimensions, and tailored interior and exterior functionalities. Such macromolecular building blocks will play a key role in nanofabrication as top-down and bottom-up approaches merge[6,7]. Several design concepts have been developed to synthesize desired nano-objects, with most making use of directed and nondirected noncovalent interactions. For example, macromolecules with stable secondary structures in

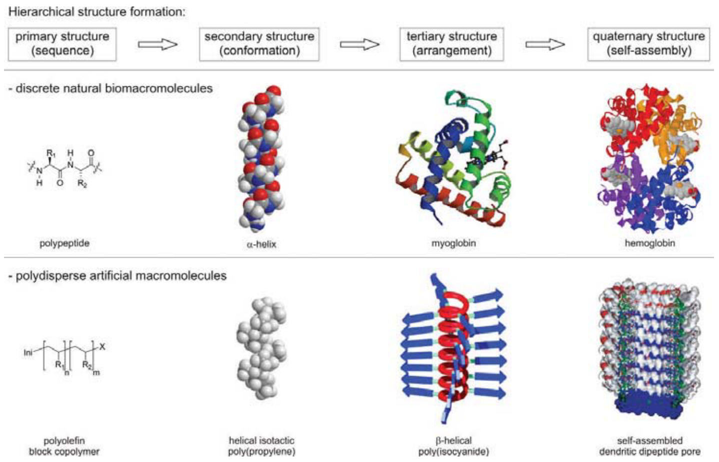


Fig. 1 Consecutive organizational levels in natural and synthetic nanoconstruction using macromolecules. (Reproduced in part with permission from[32] © 2001 AAAS. Reproduced in part with permission from[39].)

solution, or 'foldamers', have received increasing attention on the one hand[8,9], while on the other, supramolecular polymers based on strong intermolecular interactions such as quadruple hydrogen bonding have been developed[10,11]. It turns out that a combination of covalent and noncovalent synthesis is best suited to the preparation of shape-persistent objects of finite dimension in the nanosize range[12]. Detailed structural analysis of the prepared molecular-scale objects has become possible with modern physical tools such as atomic force microscopy (AFM)[13,14] as well as scanning and transmission electron microscopies (SEM and TEM, respectively). These and other tools have been used not only to image but also to manipulate such nano-objects[15].

In this review, selected outstanding examples of higher-level structural control using *macromolecular* building blocks are presented with reference to the natural structural hierarchy outlined above (Fig. 1). Of course, this article reflects my own viewpoint and is by no means comprehensive. However, I hope to spark interest in this exciting field and provoke discussion about the challenges at this dynamic frontier of polymer chemistry.

Controlling chain conformation: the secondary structure level

In general, there are two ways to design macromolecules with defined secondary structures, one involving bonding and steric constraints between adjacent repeat units and the other arising from tunable noncovalent interactions between (non)adjacent repeat units. In the former of these two extreme cases, the macromolecule has a permanently fixed structure, while in the latter the macromolecule adopts its global equilibrium structure. During the last decade, the synthesis and investigation of discrete oligomers (and sometimes polymers) adopting well-defined conformations that give rise to a stable secondary structure in solution have become increasingly popular. This field of foldamer research has been excellently reviewed by Moore and coworkers and the reader is strongly encouraged to consult their inspiring and comprehensive article[9]. With regard to polydisperse macromolecules, synthesis has provided significant contributions to influence secondary structure since, in addition to polymer composition, length, and distribution, it dictates some crucial parameters such as regio- and stereochemical connectivity. In particular, control over tacticity represents the classical approach to affect the structure of a given polymer. In this section, polymers with stable helical secondary structures are discussed, as the helix represents by far the most frequently occurring folding motif in natural as well as in synthetic macromolecules.

Helical biopolymers, such as the polypeptide α-helix[16] or DNA double helix[17], inspired synthetic polymer chemists in the second half of the last century. Beside the preparation and investigation of various polypeptides, Natta's synthesis of isotactic polypropylene[18] marks the first truly synthetic structural mimic of helical biopolymers. Since then, a multitude of different helical polymers has been prepared[19,20]. Helical polymers can be divided into two classes depending on their helix inversion barrier (Fig. 2, top). In solution at room temperature, stiff helical polymers having helix inversion barriers greater than 20 kcal/mol exist as stable helices, while more flexible helical polymers exist as dynamic polymer chains in which helix reversals move along the backbone. Depending on the stability of the helix, its twist sense can be biased using either asymmetric polymerization processes or chiral side/main chains. Stiff helical polymers can be prepared in their enriched/pure enantiomeric form from achiral monomers using chiral catalysts that induce only one handedness during the polymerization process. In dynamic helical polymers, excess helicity is most frequently introduced with the aid of chiral monomers. An intriguing aspect here is concerned with the induction and amplification of chirality in such systems[21]. Stiff helices are typically realized using backbones with restricted rotation because of (hyper)conjugation and strong steric repulsion between bulky substituents. This class is exemplified by polyisocyanides carrying bulky side chains pioneered by Drenth and Nolte[22]. Dynamic helices, such as isotactic polypropylene, display only slightly hindered rotation along their backbones. Important representatives of this class are polyisocyanates, which have received significant attention recently because of Green's elegant work[23] on chirality transfer from chiral monomers, so called 'sergeants', to the helical polymer backbone, mainly consisting of achiral monomers or 'soldiers'.

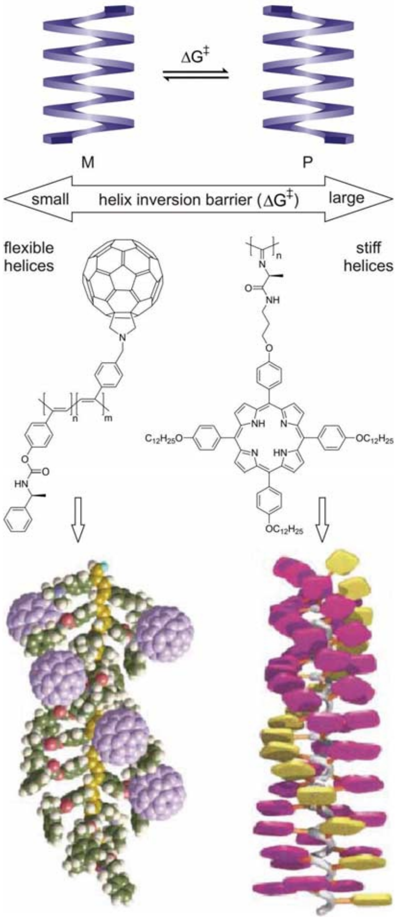


Fig. 2 Polymers adopting a helical secondary structure can be divided into rigid and flexible helices, depending on their helix inversion barrier. For example, Yashima's C_{60}-containing poly(phenylacetylene)s are rather flexible[24], while Rowan's porphyrin-substituted poly(isocyanide)s are fairly rigid[25]. (Reproduced in part with permission from[24,25]. © 2002, 2003 Wiley-VCH.)

Two more recent examples of flexible and stiff helical polymers with incorporated functional moieties are briefly discussed here. Yashima and coworkers have arranged fullerenes in a helical array using a polyphenylacetylene backbone (Fig. 2, left)[24]. Copolymerization of C_{60}-containing monomers with chiral phenylacetylene monomers leads to polymers that exhibit induced circular dichroism (CD) at low temperatures and, indeed, show left-handed structures in AFM analysis. Such materials promise interesting optoelectronic properties; however, the challenge remains to increase the helix inversion barrier by introducing even bulkier side chains without losing polymerization activity.

The groups of Rowan, Nolte, and Scolaro have prepared porphyrin-appended polyisocyanides in which the chromophores are aligned in stacks parallel to the helix axis (Fig. 2, right)[25]. Ni-catalyzed polymerization of amino-acid-derived porphyrin monomers gives polymers with degrees of polymerization around 830 and exceptionally high molecular weights exceeding 1 x 10^6 Da, as determined by AFM analysis. Optical spectroscopy reveals extensive electronic coupling over 25 porphyrin chromophores. In this case, the helicity of the polyisocyanide derivative remains, even at elevated temperatures.

Apart from the helix motif, polymer backbones adopting sheet-like conformations have also been explored. In analogy with natural and synthetic β-strands, these structures are based on multiple hydrogen-bonding interactions[26]. Another means to restrict accessible conformation and select specific structures is ring formation. Large synthetic macrocycles have been the subject of intense investigation over the past decade[27-29] and, in many cases, can be considered shape-persistent. Furthermore, by means of cofacial aggregation, these cyclic objects can be used to build up tubes[12,30], while barrels can be derived from aggregation of suitably substituted rods[12,31].

From these examples, it is apparent that stable secondary structures of various kinds are becoming more and more accessible to synthetic polymer chemists, but what about their relative orientation within a given macromolecule?

Controlling covalent connections: tertiary structure level

At the next hierarchical level, regions with defined secondary structures within the same macromolecule have to be arranged and oriented with respect to each other. The term ‘tyligomer’[9] has been coined for such intramolecular collections of foldamers. It should be emphasized that although multicompartmentalization can be achieved by means of phase segregation in block copolymers, the individual microdomains do not exist in well-defined conformations and the associated length-scale is usually in the tens of nanometer size range. If looking critically at the rational covalent connection of clearly defined secondary structure elements within a given synthetic macromolecule, only a few examples exist.

The most striking example is an artificial β-sheet helix reported by Nolte’s group (Fig. 3)[32]. Their unique design makes use of β-strand-like di- and tripeptide side chains that extend radially outward from the central polyisocyanide helix and form β-sheets running parallel to the helical axis. The hydrogen bonding rigidifies the helical backbone significantly so that an unprecedented persistence length in the range of 70 nm can be reached, as elucidated by AFM measurements[33]. Remarkably, the hydrogen-bonding stabilization remains intact even in water. Molecular modeling suggests that a dipeptide side chain comprised of alanine residues with opposite stereochemistry, i.e. L and D, leads to diminished steric repulsion between methyl groups in adjacent repeat units as compared with its L,L-diastereomer. Indeed, in contrast to the L,L-monomer, the L,D-isocyanide can be polymerized even in the absence of a Ni catalyst by the simple addition of acid to yield extremely long polymers extending up to 13 μm[32,33]. Monitoring the polymerization by CD spectroscopy reveals the cooperative folding of peptide side chains into a helical conformation. This helix-templated, multistrand sheet motif represents a unique tertiary structure without precedent in nature. Nolte’s group has also incorporated this structural element into block copolymers, for instance to create giant vesicles and helical superstructures[34]. To the best of my knowledge, no other notable examples exist that organize several secondary structural motifs within the same macromolecule by means of covalent bonds. But what about using noncovalent interactions as a glue?

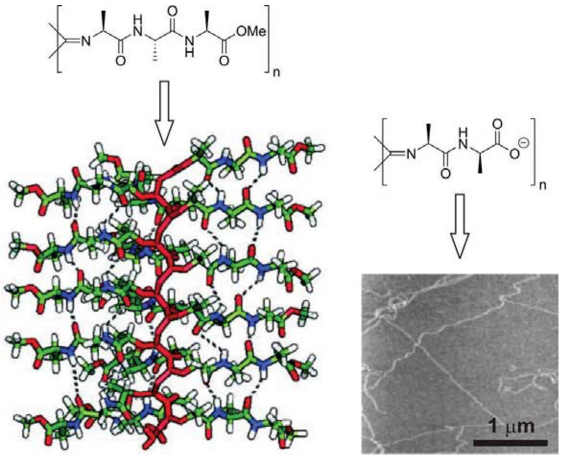


Fig. 3 Nolte’s β-helices based on polyisocyanides carrying peptide side chains: (left) structural model showing the helical polyisocyanide backbone (red) and the β-sheet-type hydrogen-bonding interactions between the tripeptide fragments; and (right) AFM image of individual polymer chains extending over several micrometers[32]. (Reproduced in part with permission from[32]. © 2001 AAAS.)

Controlling self-assembly: tertiary and quaternary structure levels

While the controlled, covalent connection of secondary structural elements is rather poorly explored, self-assembly between such subunits to achieve higher organizational levels seems more common. Here, the analogy to nature’s structural hierarchy becomes less clearly defined since, in these cases, the tertiary level is neglected and truly only a ‘pseudo-quaternary’ stage is reached. Self-assembly offers the important advantage that it allows the generation of defect-free, periodic structures from readily accessible molecular building blocks without the need of elaborate syntheses but with the drawback of limited predictability[35].

Perhaps the most impressive body of work in this context is by Percec and coworkers, who have created sophisticated self-assembled nano-objects founded on their systematic studies of the aggregation behavior of a large number of dendrons. Their approach is based on the equilibrium conformation of certain dendrons that gives rise to either conical- or wedge-shaped macromolecular amphiphiles (Fig. 4, top)[36,37]. In analogy with virus assembly in nature, cones self-assemble into spherical objects while wedges form cylinders. Since functionalization is readily introduced at the dendron’s focal point, this strategy leads to encapsulation and has been used to generate self-assembled, insulated wires (Fig. 4, center)[38]. For this purpose, several π-electron donors and acceptors were attached to fluorinated gallate moieties and the self-assembly, which yields either donor, acceptor, or donor-acceptor columns, investigated. X-ray diffraction (XRD), nuclear magnetic resonance (NMR), and other techniques elucidated the supramolecular organization of π-π stacked aromatics into helical columns. The materials generated in this way display high charge carrier mobilities of up to 10^{-3} cm^2/Vs in the liquid crystalline state, which represents an improvement of three to five orders of magnitude over the amorphous state and points to potential applications in organic electronics. In more recent work, the same group has created synthetic pores of tunable diameter by placing dipeptide fragments at the dendron's focal point (Fig. 4, bottom)[39]. In the solvent cyclohexane, which preferentially solvates the nonpolar corona of the amphiphile, hydrogen bonding between the dipeptides causes aggregation. Self-assembly into a pore-like geometry is dictated by the steric demands of the dendrons, which below a certain temperature (42°C) adopt the desired all-*trans* conformation, and the stereochemistry of the amino acid residues, which mediate hydrogen bonding. While the self-assembly process could be elucidated using optical spectroscopies (ultraviolet/visible and CD) and NMR, the hollow cylindrical geometry is confirmed by powder XRD and AFM. Preliminary measurements indicate proton transport activity across phospholipid bilayers. Related approaches leading to pore formation and transmembrane transport activity by the groups of Ghadiri[30] and Matile[31] should also be mentioned.

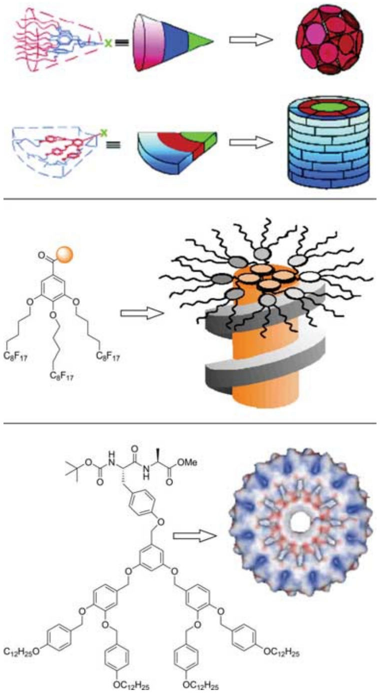


Fig. 4 Percec's self-assembly of conformationally defined dendritic building blocks: (top) shape control[37] (reproduced in part with permission from[37] © 2004 American Chemical Society); (center) insulated nanowires using aromatic stacking interactions between focal electron donors/acceptors[38]; and (bottom) nanopores with tunable dimensions based on hydrogen-bonded dipeptide cores[39] (reproduced in part with permission from[38,39]).

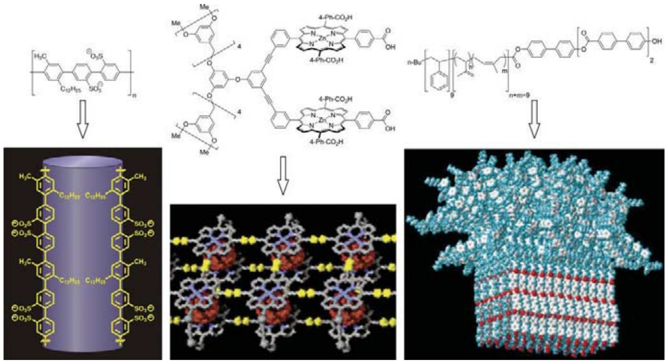


Fig. 5 Nanoscale objects formed by self-assembly of polymeric building blocks: (left) Wegner's cylindrical micelles from anionic poly(para-phenylene) amphiphiles[40]; (center) Aida's peapods from C_{60} inclusion complexes of dendritic bisporphyrin clips organized by hydrogen-bonding carboxylic acid groups[41]; and (right) Stupp's mushrooms composed of miniaturized triblock copolymers[42]. (Reproduced in part with permission from[41]. © 2003 American Chemical Society. Reproduced in part with permission from[42] © 1997 AAAS.)

Several alternative objects have been generated successfully by self-assembly, and some representative examples are illustrated in Fig. 5. For example, Wegner and coworkers have used a multitude of scattering techniques to demonstrate aggregation of ionic poly(*para*-phenylene) amphiphiles into cylindrical micelles with constant radii and aggregation numbers (Fig. 5, left)[40]. Nanosized peapods, leading to a defined array of fullerenes, have been created by Aida's group using hydrogen-bonding-mediated self-assembly of dendronized bisporphyrin clips (Fig. 5, center)[41]. Mushroom-shaped objects have been prepared by Stupp's group using self-assembly of miniaturized triblock copolymers containing an aggregation-inducing biphenyl-type mesogen (Fig. 5, right)[42]. These examples underline the enormous utility of self-assembly in generating nanosized objects of various shapes and tunable dimensions; however, what about stabilizing these often fragile structures?

Covalent stabilization of equilibrium structures

While processes driven and directed by noncovalent interactions offer the advantage of reversibility and, therefore, more or less error-free structure formation, covalent bonds can be very useful to fix such equilibrium structures permanently. It should be noted that the task of covalent stabilization without structural distortion, in other words the ideal topochemical reaction, is by no means trivial. In the context of polymer synthesis, regioselective crosslinking has proven a beneficial concept[43]. Using this approach, two-dimensional sheets[44], spherical nanoparticles[45], and hollow nanocapsules[46] among others have been synthesized.

In the context of locking polymers adopting a well-defined secondary structure, Hecht and Khan recently reported an approach to access tubular architectures based on hollow, helically folding polymers (Fig. 6)[47]. They synthesized amphiphilic poly(*meta*-phenylene ethynylene)s[48] resembling Moore's solvophobically driven foldamer family[49], and equipped the polymeric analogs with photocrosslinkable double bonds in the form of cinnamates[47]. The cooperative folding process into a helical secondary structure is followed by successful covalent intramolecular stabilization using irradiation at high dilution. In principle, this approach enables the design of organic nanotubes[12] with defined dimensions and regiospecific functionalization. In this context, the impressive work of Stupp's group on peptide nanofibers, based on the crosslinking of self-assembled peptide amphiphiles containing cysteine residues, should also be mentioned[50,51].

In certain cases, the crosslinked structure does not resemble its precursor and represents a completely new entity. In these cases, covalent bonds establish certain connectivities within a given macromolecule that can render the intramolecular crosslinking reaction highly regiospecific. Such a crosslinking reaction is usually referred to as an annellation. Two impressive examples that have allowed the construction of flat, shape-persistent, two-dimensional nano-objects include Müllen's extended graphite disks[52] and Osuka's gigantic porphyrin tapes[53]. In both cases, more flexible, three-dimensional precursors are initially prepared and subsequently frozen into a permanent conformation by multiple intramolecular carbon-carbon bond-forming reactions.

It should be emphasized that, while permanent integrity of the structure certainly has its merits, the reversibility of structural transitions as the result of changes in the environment can also be advantageous and enable the design of responsive or 'smart' materials.

Future perspectives

From the highlighted examples, it becomes apparent that more and more sophisticated synthetic schemes exist that allow the construction of nanosized structures using macromolecular building blocks. In addition to broadening the scope of this synthetic approach further, more suitable methods of characterizing the prepared objects at the ensemble as well as single-molecule level have to be developed. The experimental merging of microscopy and spectroscopy to push both space and time resolution, which would allow an unprecedented insight into elementary processes on the nanoscale, certainly poses one of the most fundamental quests. But also rational manipulation techniques have to be further developed to enable integration of the prepared nano-objects into actual devices.

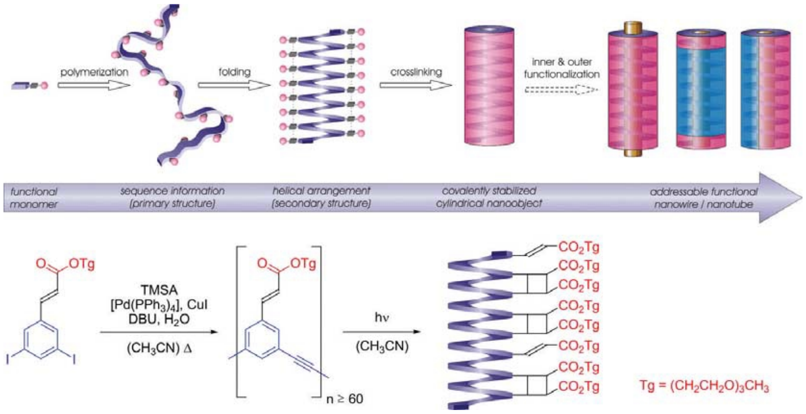


Fig. 6 Organic nanotubes by intramolecular crosslinking of helically folded polymers: (top) schematic representation; and (bottom) chemistry involving poly(meta-phenylene-ethynylene)s containing photocrosslinkable cinnamate groups[47].

From a more applied standpoint, the contact problem, i.e. the connection of the macroscopic (top down) and the molecular (bottom up) worlds, and the design of highly parallel nanofabrication processes constitute two important challenges in moving from nanoscience toward nanotechnology. But what are the next steps to be taken by synthetic polymer chemists?

In addition to continuous exploration of catalysis to develop improved and novel controlled/living polymerization systems, modern methodologies including solid-phase-supported synthesis as well as highly efficient coupling methodologies and activation schemes need to be implemented in order to prepare (practically) monodisperse macromolecules with high sequence variation. Furthermore, fruitful elements of supramolecular chemistry, such as recognition sites and various topologies as well as (externally) switchable units, have to be incorporated to render synthetic macromolecules highly functional. In many of these aspects, nature serves as an inspiring muse and demonstrates that 'atomic assemblers'[54] are not necessary to create functional objects on the nanometer scale. If the synthetic polymer chemistry community continues to learn nature's lessons and remains open to cross-disciplinary fertilization, it will certainly play a key role in future technologies. MT

Acknowledgments

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