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A SUPRAMOLECULAR APPROACH TO MACROMOLECULAR SELF-ASSEMBLY: CYCLODEXTRIN HOST/GUEST COMPLEXES

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1.1 INTRODUCTION

Macromolecular self-assembly is one of the key research areas in contemporary polymer science. Because complex macromolecular architectures have a significant effect on self-assembly behavior, tremendous effort has been made in the synthesis of well-defined complex macromolecular architectures [1]. The versatility of polymeric materials, such as indicated by polymer functionality, polymer composition, and polymer topology, enables the formation of materials for a broad range of applications, including hybrid materials [2], biomedical materials [3], drug/gene delivery [4], supersoft elastomers [5], and microelectronic materials [6]. In order to obtain well-defined structures, synthetic techniques are required that can provide precise control over the material properties of these structures. Among the polymerization techniques that have proved to be powerful tools for the synthesis of well-defined polymers are reversible-deactivation radical polymerization approaches, such as nitroxide-mediated radical polymerization (NMP) [7], atom transfer radical polymerization (ATRP) [8], and reversible addition-fragmentation

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chain transfer (RAFT) polymerization [9]. Especially their convenient handling and tolerance toward functional groups have led to a plethora of novel materials with precision-designed properties. Furthermore, the introduction of modular ligation chemistry has provided the opportunity to synthesize complex building blocks and architectures in a precise and efficient manner and again with high functional group tolerance [10]. Several modular ligation reactions are widely utilized in that regard, such as copper(I)-catalyzed azide-alkyne cycloaddition (CuAAc) [11], Diels–Alder reactions [12], and thiol-ene reactions [13]. Thus perfectly suited tools for the formation of materials for macromolecular self-assembly are currently available [14].

The introduction of the concept of supramolecular chemistry has influenced the entire field of chemistry significantly. Especially polymer science and the formation of complex macromolecular architectures have benefited from supramolecular chemistry [15]. New types of macromolecular architectures based on supramolecular bonds are now continually being investigated and higher level complex self-assemblies of macromolecules governed by supramolecular interactions have been formed. Several types of supramolecular interactions are used in polymer science such as hydrogen bonding [16], metal complexes [17], and inclusion complexes [18]. One of the frequently employed supramolecular motifs is cyclodextrin (CD), which forms inclusion complexes with hydrophobic guest molecules in aqueous solution. This property has been exploited readily in polymer chemistry and materials science for various applications, such as drug delivery [19], nanostructures [18b,20], supramolecular polymers [21], self-healing materials [22], amphiphiles [23], hydrogels [24], bioactive materials [25], or in polymerization reactions [26].

The incorporation of CD-based supramolecular chemistry has proved to be an elegant way for the formation of complex macromolecular architectures [14c,24a]. Reversible-deactivation radical polymerization and modular ligation techniques have emerged as effective tools for the synthesis of CD and guest functionalized building blocks. Taking the overall goal of macromolecular self-assembly into account, these building blocks can be considered as the primary structure specifying which blocks are guest and which are host functionalized. The formation of the direct supramolecular host/guest complexes can be considered the secondary structure leading to complex macromolecular architectures. The next level is the assembly of the supramolecularly formed macromolecules into higher aggregates/self-assemblies—the tertiary structure. Thus several levels of molecular complexity are available via the combination of CD host/guest chemistry and polymeric building blocks (Figure 1.1) [18a].

An interesting feature of polymer architectures governed by supramolecular interactions is modularity. The formation of a variety of architectures can be achieved by a small number of initial building blocks much like modularity in modular ligation chemistry. Thus structure–property relationships are accessible via a small amount of reactions compared to traditional material formation. Furthermore, the dynamic nature of the supramolecular bonds affords the opportunity to study systems in the bound as well as the unbound state or to dynamically change the properties of the

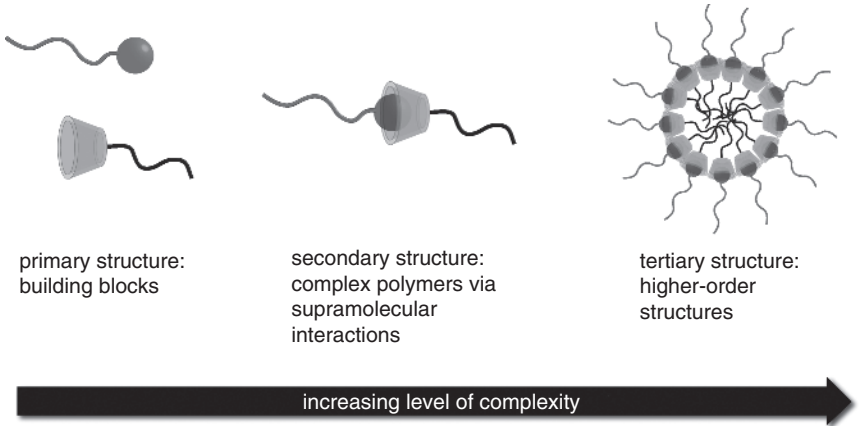

Figure 1.1 Overview over the different levels of complexity enabled via the combination of CD host/guest chemistry and macromolecular structures.

materials via external stimuli or addition of materials with competing supramolecular interactions. Especially in the case of CD host/guest chemistry, a broad range of stimuli-responsive host/guest pairs is available. Combined with stimuli-responsive polymers an extraordinary amount of combinations, and thus materials with unique properties, is accessible.

1.2 SYNTHETIC APPROACHES TO HOST/GUEST FUNCTIONALIZED BUILDING BLOCKS

1.2.1 CD Functionalization

CDs are oligosaccharides and thus contain a significant number of hydroxyl groups that can be utilized for functionalization. Hence selectivity of CD functionalization reactions is a major issue. The primary hydroxyls at C-6 are more reactive due to less steric hindrance, while the secondary hydroxyls at C-2 or C-3 are less reactive. The difference in reactivity gives the opportunity to obtain selectivity with regard to the addressed face of the CD and can be tuned with reaction conditions [27]. The selectivity toward the number of functionalized hydroxyl function remains much more challenging, yet the optimization of reaction conditions has led to several effective protocols to yield—mostly—mono functionalized CDs.

Mono tosyl CDs are the most utilized building blocks because they are readily converted into a variety of useful reactants (Figure 1.2). Several methods have been described for the synthesis of mono tosylated CDs at C-6. The most convenient route for α-CD and β-CD utilizes tosylchloride in aqueous NaOH [28], while another convenient method toward mono tosyl β-CD makes use of 1-(*p*-toluenesulfonyl)imidazole instead of tosylchloride [29]. For γ-CD, a synthesis with triisopropylphenylsulfonyl chloride has been reported in order to form a γ-CD

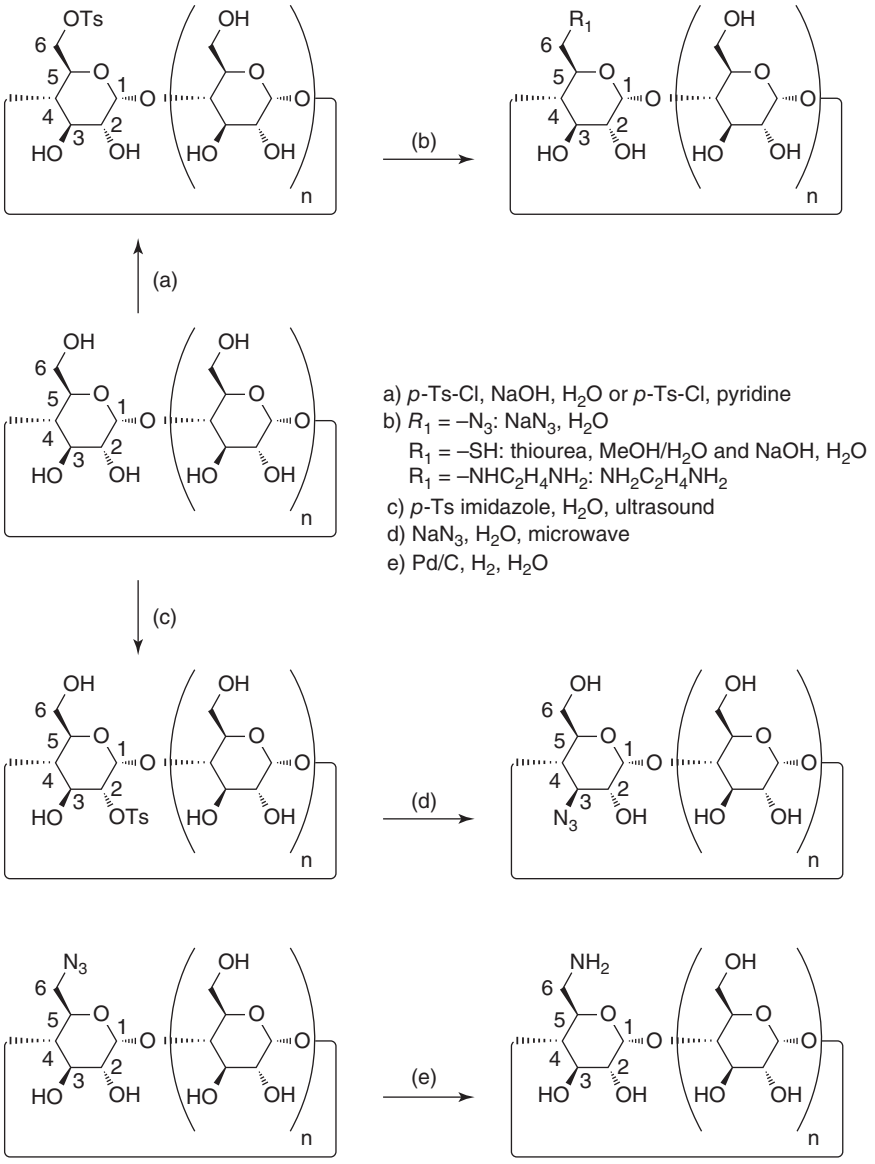

Figure 1.2 Synthesis of various mono functionalized CD derivatives [14c]. Reprinted from [14c]. Copyright 2014, with permission from Elsevier.

derivative with single leaving group [30]. Furthermore, all CD mono tosylates are available via tosylation in pyridine as well [31]. Starting from mono tosylated CD or CDs with similar leaving groups, several useful building blocks are accessible. A nucleophilic substitution with sodium azide leads to the corresponding azides that are

suitable for click reactions [31], namely CuAAc. After methyl ether protection, the mono tosylates can be converted into mono alkynes via sodium propargylate, which is the complementary building block for CuAAc in addition to the well-known CD azides [32]. The azides can be further converted to amines via reduction, for example, via hydrogenolysis [31b,33] or Staudinger reduction [31a]. Another possibility to obtain mono amine functionalized CD is the substitution of the mono tosylate with an excess of a suitable diamine [34]. A thiol functionalization is amenable via substitution with thiourea and subsequent hydrolysis [35], which opens up access to thiol-ene click chemistry [36]. Less frequently utilized are C-2 or C-3 substituted CD derivatives, which is most likely due to the inconvenient and tedious synthesis of pure mono functionalized derivatives. Nevertheless, several reports on the synthesis exist [10]. Having several hydroxyl groups, CDs are, in principle, targets for esterification or etherification reactions as well, yet the selectivity in ester/ether functionalization reactions is usually low. Either full conversions of the hydroxyl groups are desired or—in the case of lower targeted substitution grades—complicated purification methods are required in order to obtain pure products. Nevertheless, the broad range of different mono functionalizations of CDs allows for the incorporation into polymers either pre- or post-polymerization. Several examples for CD functionalized polymerization mediators—the pre-polymerization incorporation—are described in the literature, for example, for NMP [37], ATRP [38], and RAFT [39]. Furthermore, post-polymerization conjugations are described as well, for example, after ATRP [38a] or RAFT polymerization [40].

1.2.2 Suitable Guest Groups

Besides functionalization with CDs, guest moieties have to be incorporated in order to form supramolecular host/guest complexes. The common guest groups do not possess a similar multifunctionality as CDs, which makes the pre- or post-polymerization functionalization straightforward. Common routes include esterification, amide formation, or several types of modular ligation reaction.

One of the most interesting features of CD complexes is their response to external stimuli, that is, the complex dissociates and/or associates reversibly due to external stimuli. The stimuli response that all guests share is temperature, namely at higher temperatures the complexes dissociate due to the usually negative association enthalpy (Figure 1.3a) [41]. A further frequently utilized stimulus is redox response based on the ferrocene/CD pair. Oxidation of ferrocene to ferrocenium leads to an increase in size that ultimately leads to complex dissociation, since the ferrocenium cation does not fit into the β-CD cavity (Figure 1.3b) [42]. Furthermore, after reduction, complexation is observed again, which can be followed via cyclovoltammetry [43]. Complexation of phenolphthalein derivatives with β-CD leads to a color change at basic pH from pink to colorless (Figure 1.3c). The lactone ring of phenophthalein forms again at higher pH due to association with β-CD, which forces the molecule into the sterically more compact structure [44]. Very recently, Harada *et al*. showed metal–ion responsive complexation based on bipyridine ligands and iron (II) or copper (II) ions (Figure 1.3d). While bipyridines are complexed with

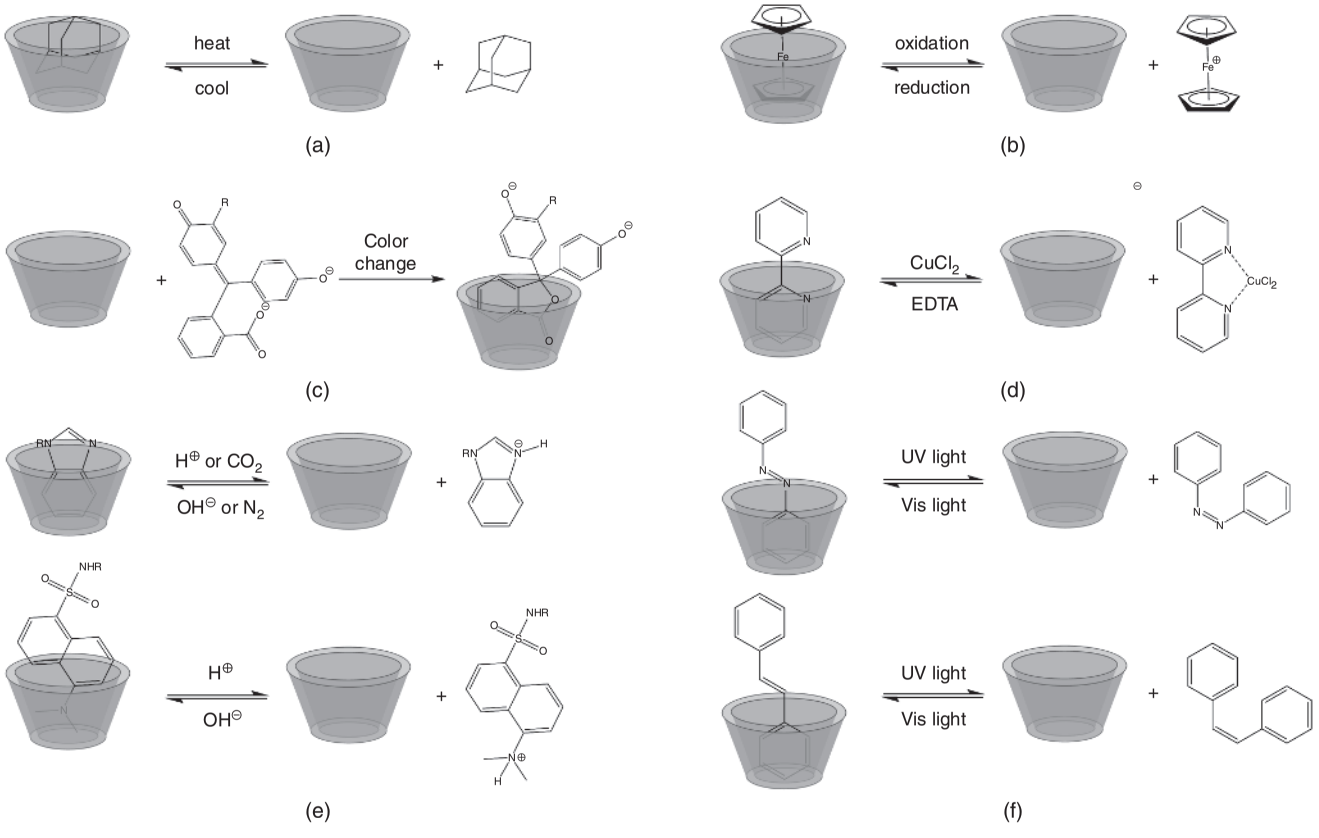

Figure 1.3 Stimuli-responsive host/guest complexation based on β-CD: (a) Thermoresponsive adamantyl complex, (b) redox-responsive ferrocene complex, (c) color changing phenolphthalein complex, (d) metal–ion-responsive bipyridine complex, (e) pH-responsive benzimidazole or dansyl complexes, and (f) light-responsive azobenzene or stilbene complexes.

β-CD in metal-ion free solutions, bipyridine/metal ion complex formation leads to an increase in size of the guest moieties and thus to decomplexation of the CD/bipyridine complex [45]. Recently, pH responsive complexes were introduced. For example, the benzimidazole/β-CD pair shows complexation/decomplexation depending on the apparent pH (Figure 1.3e) [46]. A further development of benzimidazole pH response is protonation in CO_2 enriched aqueous solution. The increased size of the protonated benzimidazole molecule leads to decomplexation, yielding a CO_2 responsive host/guest complex [47]. Dansyl groups show pH responsive complexation with β-CD as well; namely at pH below 4 the complexation is not favored [48]. A very beneficial stimulus is light as it can be controlled spatially and temporarily in a precise way. Common light responsive guest groups that lead to decomplexation upon light irradiation are azobenzenes or stilbenes. UV irradiation induces an isomerization from the thermodynamically more stable *trans* conformation to the *cis* conformation that exhibits lower complexation constants due to steric hindrance (Figure 1.3f). The situation can be reversed via irradiation with visible light, where a re-isomerization takes place and the complexes can form again. A rather biochemical stimulus is enzymatic degradation of CDs that leads to disassembly of the complexes as well, yet in an irreversible fashion [49].

1.3 SUPRAMOLECULAR CD SELF-ASSEMBLIES

After successful formation of building blocks, as described above, supramolecular interactions can be utilized to connect different building blocks in order to obtain complex architectures. Taking the manifold types of guest molecules with their various types of stimuli-responsive complexation into account, a broad range of material properties is accessible. Furthermore, the utilization of different polymer types leads to arguably unlimited possible combinations and more stimuli responses, when stimuli-responsive polymers are incorporated. In the following, several types of CD self-assemblies are presented, such as block copolymers, star polymers, and polymer brushes, leading to single macromolecules connected in a supramolecular way (Figure 1.4). CD complexes have been employed to obtain materials with special polymer functionality, polymer composition, and polymer topology. Polymer functionalities can be obtained via reversible-deactivation radical polymerization of CD and guest functionalized mediators or via modular ligation techniques. Various polymer compositions are available via CD and guest units between blocks in order to obtain supramolecular block copolymers. Complex topologies can be formed via more complex building blocks, such as multi-guest and/or CD functional building species. Complex macromolecular architectures governed by CD complexes can be constructed step by step: the polymer functionality gives rise to more complex compositions or topologies—from the primary structure to the secondary structure.

1.3.1 Linear Polymers

Linear block copolymers are a frequently studied class of CD-based macromolecular architectures. The formation of AB block copolymers is straightforward as only

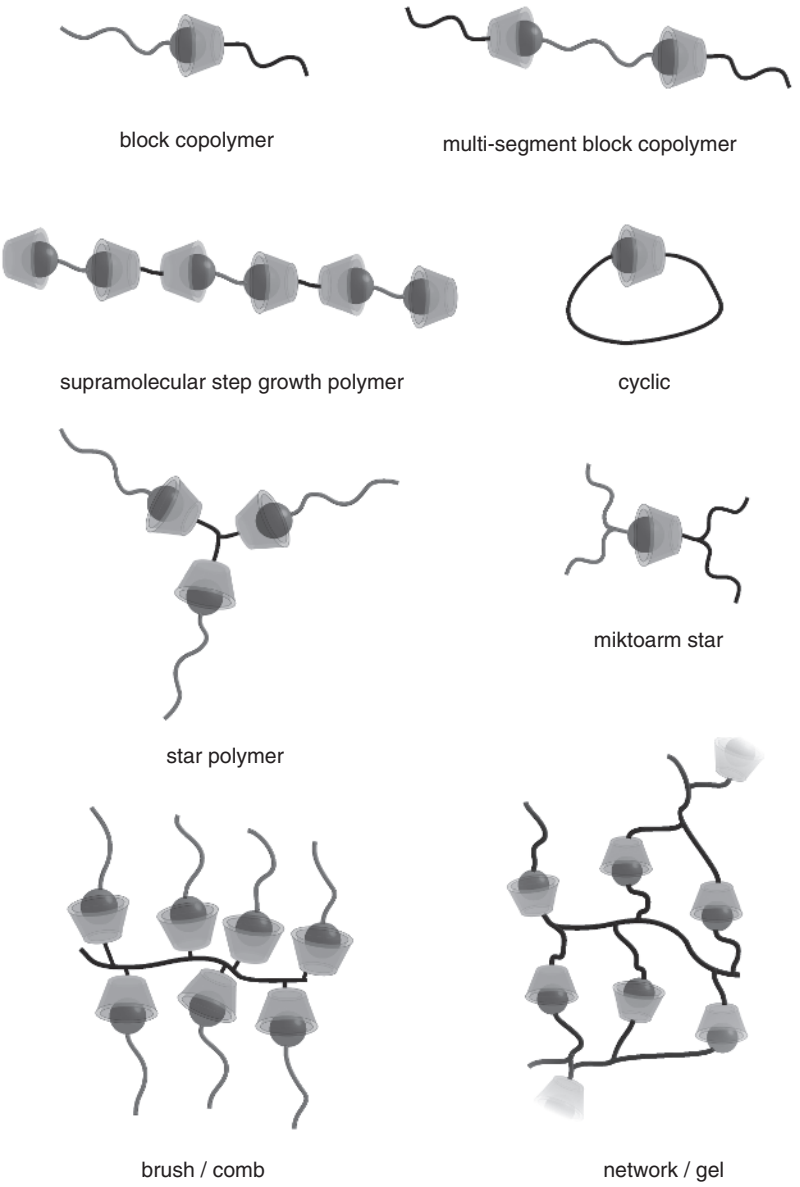

Figure 1.4 Overview of complex macromolecular architectures formed via CD host/guest complexes.

two homo polymers with guest and CD end-group, respectively, are needed. Higher block copolymers are accessible via the introduction of double functionalized middle blocks. The borderline case for higher block copolymers would be supramolecular polymers that are formed from multi-host/guest functionalized building blocks in a supramolecular step growth polymerization mechanism. The degree of polymerization is directly correlated with the number of host–guest complexes formed. This type of linear polymer is based on a step growth reaction approach. Guest and host moieties are combined in an AB- or AA/BB-type fashion to obtain supramolecular polymers.

As described in Section 1.2.3, stimuli-responsive complexation is well known with CDs, and in the following several examples of block copolymers with stimuli-responsive linkage are described. Furthermore, the respective blocks allow the incorporation of additional stimuli response, and in combination, a broad range of multi-stimuli-responsive materials is accessible, giving the opportunity to tailor the polymeric material with regard to application.

1.3.1.1 Diblock Copolymers The first example of CD-based block copolymers was described in 2008 by Zhang *et al*. (refer to Figure 1.5a) [39b]. A CD functionalized poly(4-vinylpyridine) (P4VP) and an adamantyl functionalized

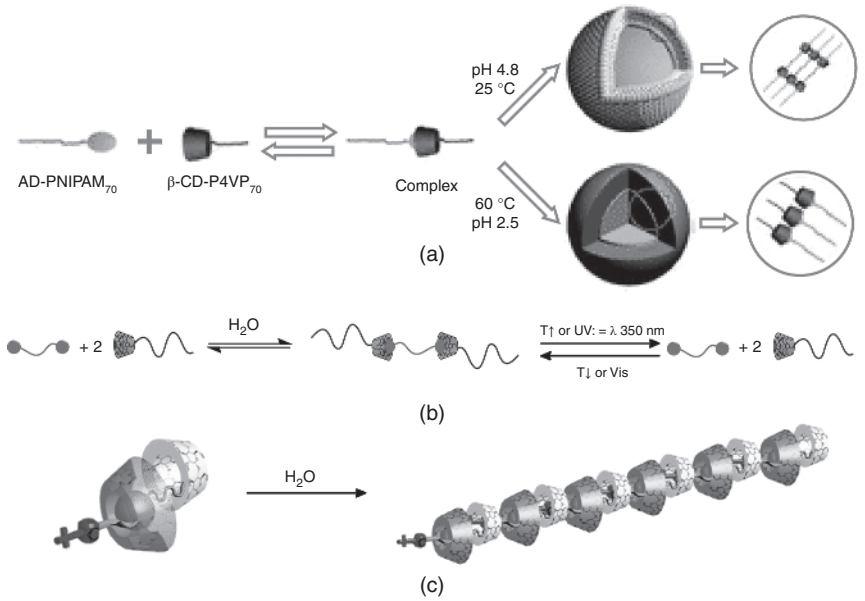

Figure 1.5 (a) Formation of a supramolecular double stimuli responsive diblock copolymer based on P4VP and PNIPAM [39b] (Reproduced from [38b] with permission of The Royal Society of Chemistry), (b) formation of an ABA triblock copolymer with temperature- and light-responsive block junctions [40b] (Adapted with permission from [39b]. Copyright 2013 American Chemical Society), and (c) formation of an AB monomer (α-CD-adamantyl/β-CD-cinnamoyl) based supramolecular alternating α-CD/β-CD copolymer [50] (Adapted with permission from [49]. Copyright 2013 American Chemical Society).

poly(*N*-isopropylacrylamide) (PNIPAM) block were synthesized via RAFT polymerization. The block copolymer was formed via supramolecular host/guest complexation and proved to be pH- and thermoresponsive, which was utilized for stimulus-induced micellization that was investigated via dynamic light scattering (DLS), static light scattering (SLS), fluorescence measurements, and transmission electron microscopy (TEM). The most frequently utilized guest moiety is adamantyl, yet it only provides a temperature responsive connection [40b]. Other examples of diblock copolymers based on CD/adamantyl complexation include poly(2-methyl oxazoline)-*b*-PNIPAM [38b], poly(*N*,*N*-dimethylaminoethyl methacrylate)-*b*-PNIPAM (PDMAEMA-*b*-PNIPAM) [38a], and poly(methyl methacrylate)-*b*-poly(hydroxyethyl acrylate) (PMMA-*b*-PHEA) [36]. A voltage/redox responsive block copolymer was presented by Yin *et al*., where a ferrocene functionalized poly(ethylene glycol) (PEG) was connected to a β-CD functionalized poly(styrene) (PS) [51]. Vesicles were formed that were prone to disruption by an application of external current and small molecule release was probed. More recently, Yuan *et al*. presented a block copolymer of poly(lactic acid) (PLA) and PEG [52]. A pH sensitive block copolymer amphiphile was formed by He *et al*. [46]. Benzimidazole functionalized poly(ε-caprolactone) (PCL) was connected to β-CD functionalized Dextran and utilized as biodegradable drug delivery vehicle upon micelle formation in neutral aqueous solution. Drug release of Doxorubicin was studied and was supported by the difference of intra and extra cellular pH. A CO_2 responsive AB block copolymer was described by Zhao *et al*. (refer to Figure 1.8a) [47]. A β-CD functionalized Dextran was coupled to a benzimidazole functionalized poly(L-valine) in dimethylsulfoxide. Addition of water led to the formation of nanostructures depending on the degree of polymerization (DP) of the poly(L-valine) block. Vesicles were obtained for similar DP of dextran and poly(L-valine), while fiber-like structures were obtained for higher DPs of poly(L-valine). A photoresponsive block copolymer was described by Yuan *et al*. (refer to Figure 1.8b) [53]. The supramolecular block copolymer was based on PCL-*b*-poly(acrylic acid) (PCL-*b*-PAA) with azobenzene and α-CD end-groups, respectively. In aqueous solution nanotubes were formed that were disassembled upon UV irradiation. Furthermore, Rhodamine B was released from the nano tubes via light irradiation.

1.3.1.2 Higher Order Block Copolymers While diblock copolymers are described frequently, multi-block copolymers are underrepresented so far. Our team prepared an ABA triblock copolymer based on β-CD featuring thermoresponsive and light responsive connections, namely adamantyl or azobenzene guests (refer to Figure 1.5b) [40b]. Poly(*N*,*N*-dimethylacrylamide) (PDMA) and poly(*N*,*N*-diethylacrylamide) (PDEA) middle blocks were connected with biocompatible poly(*N*-2-hydroxypropyl methacrylamide) (PHPMA) outer blocks. The block formation and dissociation upon external stimuli was investigated via DLS and nuclear Overhauser enhancement spectroscopy (NOESY). Furthermore, the temperature-induced aggregation due to thermoresponsive PDEA blocks was studied via temperature sequenced DLS and turbidimetry showing a two-stage aggregation.

Another example of supramolecular ABA block copolymers was described by Zhang *et al*. [54]. PS with an adamantyl group on one end and an azobenzene group on the other end were complexed with β-CD functionalized PEG. Vesicles were formed in aqueous solution, characterized via TEM and DLS. The response of the vesicles to photo irradiation was probed as well, indicating a change in morphology toward micelles. A pH/CO_2 responsive ABC block copolymer was described by Yuan *et al*. [55]. RAFT-derived PNIPAM was subjected to aminolysis in order to obtain thiol functionalized PNIPAM. Furthermore, methacrylate and adamantyl functional hetero telechelic PCL and β-CD end-functionalized PDMAEMA were connected in one pot via a combination of a thiol-ene reaction and supramolecular complexation. Vesicles with variable size, depending on CO_2 or N_2 stimulation, were obtained via the pH responsive PDMAEMA. Furthermore, these vesicles could be transformed into micelles via heating due to the collapse of the PNIPAM block.

1.3.1.3 Supramolecular Step Growth Polymers An alternative to linear polymers based on supramolecular CD interactions is based on a step polymerization analogue [21a,56]. Host and/or guest functionalized small molecules are joined, leading to a polymer formed by multiple host/guest complexes. Either an AB or an AA/BB approach is utilized to form such polymers. Harada *et al*. utilized an α-CD functionalized with a cinnamoyl group as an AB monomer to form supramolecular polymers in the fashion of a daisy chain [57]. An AA/BB approach was undertaken by the same group [58]. A double adamantyl functionalized molecule was complexed with a β-CD dimer. Depending on the rigidity of the spacer between the adamantyl moieties, cycles, or linear polymers were obtained. The combination of different CDs was probed by Harada *et al*. as well, utilizing the strong complexations between the pairs of α-CD/cinnamoyl and β-CD/adamantyl, such as the combination of an α-CD/adamantyl and a β-CD/cinnamoyl based linker (refer to Figure 1.5c) [50]. Ritter *et al*. presented a linear supramolecular polymer based on a PDMS backbone and β-CD/adamantyl or ferrocene complexation that showed redox response [59]. A ternary supramolecular polymer was described by Liu *et al*. A naphthol functionalized β-CD was combined with an adamantyl-viologen dilinker and cucurbit[8]uril [60]. The β-CD complexes with the adamantyl moiety, while the cucurbit[8]uril complexes with the viologen and naphthol units. Thus a supramolecular polymer is formed via the utilization of two host/guest complex systems. A similar approach was performed by Zhang *et al*. [61]. Metal-complexes were utilized in the formation of supramolecular polymers as well: Tian *et al*. utilized a pyridine functionalized β-CD and a double azobenzene end-functionalized linker molecule [62]. The azobenzene functionalized linker was complexed by two pyridine containing β-CD units. Addition of a Pd (II) ethylenediamine salt led to polymer formation as the β-CD units were linked via metal-complex formation of two pyridines and a Pd (II) complex. The formation of the poly(pseudorotaxane) was evidenced by atomic-force microscopy (AFM) and NOESY. Zhang *et al*. presented a tripeptide (Phe-Gly-Gly) functionalized with an azobenzene that was complexed with cucurbit[8]uril in the ratio 2:1, which led to dimerization via complexation of two phenylalanine units [61]. The exposed azobenzenes were complexed with a β-CD dilinker, ultimately

forming a supramolecular polymer. A difunctional β-CD molecule and a cationic difunctional ferrocene molecule were utilized in an AA/BB fashion to obtain redox responsive supramolecular polymers that show interesting gene vector abilities [63]. Tian *et al*. reported a photoresponsive supramolecular polymer based on γ-CD [64]. Two coumarin units were connected by a viologen unit. After addition of γ-CD in water, a ternary complex of two coumarin units originating from two different linker molecules and γ-CD was formed. Thus a step growth polymer was achieved, linked by plain γ-CD molecules. Furthermore, the coumarin units could be photo dimerized inside of the γ-CD cavity to obtain covalently bound polymers with threaded γ-CDs. A similar approach was performed by Ma *et al*. [65]. A viologen functionalized coumarin was complexed by a bis-sulfonatocalix[4]arene, which prefers the complexation of the viologen unit. Addition of γ-CD leads to the complexation of two respective coumarin units, forming a supramolecular polymer. As evidenced by TEM and DLS, the supramolecular polymer formed several hundred nanometer long fibers in solution. An interesting structure was presented by Sollogoub *et al*. who reported supramolecular polymers of α-CD azides in the solid state [66]. While α-CD C-6 mono azides lead to single-strand supramolecular polymers due to complexation of the azide by another α-CD, double azide functionalized α-CD showed higher interactions. In addition to the primary interaction, namely the complex formation of the azide and an α-CD, an azido–azido dipolar interaction is evident. Furthermore, a tertiary interaction—namely an azido hydrogen bonding —takes place. In sum, the contributions from the different interactions led to hierarchical supramolecular polymers that show a helical morphology.

1.3.2 Branched Polymers

Branched architectures have attracted significant attention in recent years. Especially the area of hydrogels has been investigated extensively, for example, with regard to their mechanical properties, stimuli response, and self-healing. As CD complexes are an ideal system for aqueous environments, prospective applications in biomedical sciences have driven progress in this field. Less pronounced branched structures are star polymers with a dominant quantity of examples of CD centered star polymers. Compared to the manifold examples of CD centered star polymers, significantly fewer reports on star architectures driven by CD host/guest complexes have been described in the literature. Nevertheless, several examples were described so far, especially with regard to stimuli responsive structures. Furthermore, supramolecular brush polymers have been added more recently to the portfolio of CD-based branched architectures.

1.3.2.1 Hydrogels By far the most studied type of CD-based branched architectures are hydrogels [24a,67], yet mostly free radical polymerization is utilized to synthesize the utilized building blocks or the branching points are distributed randomly, as in the case of α-CD/PEG crystallization driven networks [68]. A few examples utilize controlled radical polymerization techniques to obtain well-defined multiple host/guest containing polymers. Hetzer *et al*. utilized a trifunctional β-CD linker and double adamantyl end-functionalized PDMA to obtain networks

[69]. Depending on CD/guest ratios, chain length, and concentration, increasing viscosities were determined via rheological investigations. Addition of free CD or competing guest molecules led to a significant decrease in viscosity. Redox responsive networks were described by Zhang *et al*. [70] as well as Yuan *et al*. [71]. The former utilized two- or three-fold β-CD linker molecules and ferrocene functionalized PEI. The latter formed a hydrogel from β-CD and ferrocene functionalized PDMA. Photoresponsive hydrogels were described by Wang *et al*. [72]. A difunctional β-CD linker with disulfide connection was utilized to form a network with a copolymer of NIPAM and an azobenzene monomer. Thus a redox and light responsive hydrogel was formed.

1.3.2.2 Star Polymers An important type of branched architecture is the star polymer. Very frequently described are CD centered star polymers that utilize the high functionality density of CD in order to form a star core [14c,73]. In contrast, CD host/guest complexes have been employed less frequently for the formation of star polymers. Wenz *et al*. described a connection of both approaches, namely α-CD centered PMMA stars were threaded onto PEG in a rotaxane fashion with large stopper molecules [74]. Similarly Yui *et al*. investigated α-CD/PEG rotaxanes with PLA grafted α-CD [75]. A sliding rotaxane brush example was provided by Gao *et al*. [76]. An α-CD threaded PEG backbone was stoppered with β-CD. The CDs were functionalized with azides via esterification with an azide functionalized acid chloride. Subsequently, alkyne functionalized PEGs and alkyne functionalized palmitic acid (C16) were attached via CuAAc forming sliding brushes with tunable amphiphilicity. A β-CD centered PNIPAM star was synthesized by Li *et al*. [77]. Addition of a multiadamantyl functionalized PEG star led to the formation of a supramolecular multi block star polymer. Furthermore, heating above the cloud point of the PNIPAM blocks resulted in hydrogel formation.

In the area of mere star architectures driven by CD host/guest complexes, our team reported the formation of three-arm star polymers via supramolecular interactions of adamantyl end-functionalized PDMA or PDEA and a β-CD trilinker (refer to Figure 1.6a) [78]. The formation of supramolecular star polymers was probed via DLS and rotating frame nuclear Overhauser effect spectroscopy (ROESY) as well as turbidimetry measurements in the case of PDEA arms. Another three-arm star polymer was described by Wu *et al*. that connected guest functionalized oligo ethylene glycol dendrimers to a β-CD trilinker [81]. A significant effect of dendrimer generation, dendrimer end-group (ethyl or methyl), and ratio of different dendrimer types (with ethyl or methyl end group) on the thermoresponse of the supramolecular star polymers was measured. The effect of thermally induced decomposition of the supramolecular complexes as well as the effect of salt concentration on the thermoresponsive behavior was investigated, too. More complex AB_2 and A_2B_2 miktoarm star polymers were described by us (refer to Figure 1.6a) [79, 80]. Adamantyl mid functionalized and β-CD end-functionalized or adamantyl mid and β-CD mid functionalized polymers were utilized, respectively. Again, turbidimetry, DLS, and NOESY/ROESY were utilized to characterize the complexes. Similarly important is the investigation of temperature-induced micellization caused by

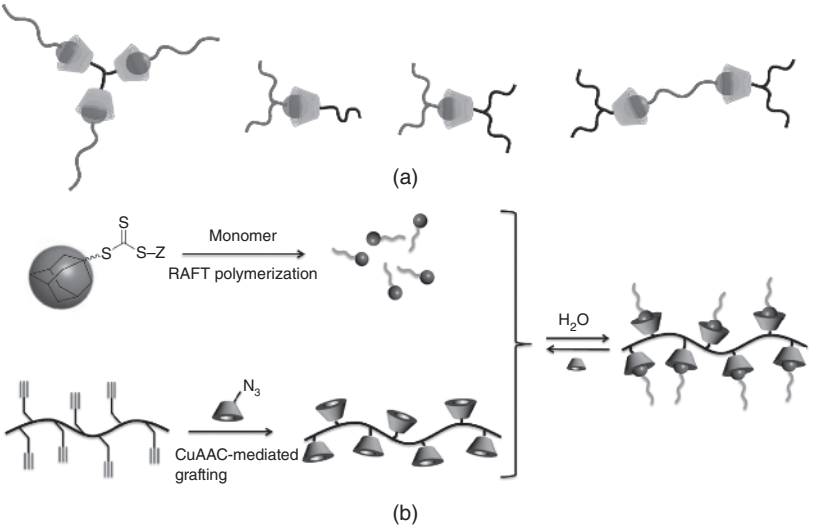

Figure 1.6 (a) Various supramolecular star architectures from left to right: Three arm stars [78], A_2B miktoarm stars [79], A_2B_2 miktoarm stars [80], and H-shape stars [80]. (b) Supramolecular brush formation via adamantyl end-functionalized PAA and CD conjugated poly(acrylate) [40a]. Reproduced from [39a] with permission of The Royal Society of Chemistry. (*See color insert for color representation of this figure*).

thermoresponsive PDEA blocks. A two-stage aggregation was detected, which was attributed to initial micelle formation close to the cloud point of the thermoresponsive block, followed by aggregation upon further heating of the complexes, which is a behavior well known in literature [38a,82]. An AB_4 miktoarm star polymer was described by Allcock *et al*. [83]. Four poly(oligo ethyleneglycol methacrylate) (POEGMA) arms were grafted from β-CD and an adamantyl end-functionalized poly(bis-(trifluoroethoxy)phosphazene) was added. Micelle formation was evident and characterized via DLS, TEM, and AFM. Even more complexity was obtained by Zhu *et al*., who described an ABC miktoarm star polymer based on several functionalization reactions of β-CD [84]. Mono azido functionalized β-CD was mono tosylated. An alkyne functionalized PEG was attached via CuAAc and the remaining tosylate substituted with an azide. Subsequently, an ATRP initiator was incorporated via another CuAAc and DMAEMA was grafted from the β-CD core via ATRP. Then, adamantyl end-functionalized PMMA was connected to the two arm β-CD core via supramolecular interactions to afford an ABC miktoarm star polymer that formed micelles in aqueous solution due to the hydrophobic PMMA block.

The utilization of double end-functionalized polymers gives the opportunity to form more complex structures. Schmidt *et al*. described the formation of H-shape star block copolymers via double guest functionalized middle blocks and mid β-CD functionalized outer blocks [80]. Again, DLS, NOESY, and temperature-induced micellization were investigated, with results in line with previous observations, namely an aggregation that proceeds in two stages with small micelles at lower temperatures and

agglomeration at higher temperatures. Doubly guest functionalized PEG and β-CD centered PNIPAM four-arm star polymers were utilized by Li *et al*. [85]. The formation of the dumbbell-shaped architecture was proved via NOESY and turbidimetry. Subsequently, the authors exchanged the middle PEG block with double adamantyl functionalized poly(propylenegylcol) (PPG), leading to a system with two different thermoresponsive polymers [82]. The temperature-dependent aggregation was studied in detail via DLS, NMR, fluorescence measurements, AFM, and TEM. In cold water, dumbbell-shaped copolymers were obtained. At temperatures over 8°C, micelle formation was observed, whereas micelle destabilization and aggregation was the case above 22°C.

Another type of branched star-like structures utilizes less well defined cores. A spherical core moiety is grafted with CD molecules and subsequently guest functionalized polymers are attached in a supramolecular fashion. In that regard mostly inorganic core material has been used so far, such as SiO_2 nanoparticles [86], CdS quantum dots [87], and gold nano particles [88]. Several guest/CD pairs were exploited to equip the formed hybrid stars with stimuli-responsive properties, such as light response [39a,87a,88b] or redox response [87b]. Furthermore, thermoresponsive blocks were added in several cases for temperature-induced hydrogelation in order to form hybrid hydrogels [87]. Polyhedral oligomeric silsesquioxane was decorated with β-CD by Li *et al*. [89]. The amphiphilic molecule self-assembled into nanospheres in aqueous solution and azobenzene end-functionalized PEG-*b*-PDMAEMA was added to form supramolecular complexes. The light-responsive azobenzene/CD complexation allowed for the formation or dissociation of the polymer shell, while the size of the micelles could be tuned via pH. Chen *et al*. presented a supramolecular star polymer generated via a combination of CD-based host/guest chemistry and a protein [90]. Concavalin A (ConA) was utilized as a core that interacts with mannopyranoside. Furthermore, a mannopyranoside/β-CD functionalized dilinker was synthesized and the complex association between ConA and the mannopyranoside was investigated via isothermal titration calorimetry. Further recognition was found when an adamantyl end-functionalized PEG was added. The CD/guest interaction led to the formation of a supramolecular four-arm star polymer. Again, isothermal titration calorimetry was performed to study the complexation. Addition of α-CD led to the formation of hydrogels via α-CD/PEG complex formation. Ritter *et al*. combined CD end-functionalized hyperbranched polyglycerols with azobenzene end-functionalized PNIPAM [91].

1.3.2.3 Brush Polymers Bottle brush polymers are another type of branched architectures that have found CD-based supramolecular analogues. Two major factors have to be considered in the formation of brush polymers. First, the formation has to be via a grafting-to approach, which results from the supramolecular nature of the grafting. Thus one has to decide whether the CD units should be bound to the backbone or as end groups of the grafts. Second, the grafting density depends strongly on the steric hindrance induced by large CD molecules. Furthermore, the grafting density depends on the association constants of the utilized CD/guest pair. Bernard *et al*. formed

supramolecular brushes of adamantyl functionalized PAA and a poly(acrylate) backbone with adjacent CD units that were attached via CuAAc (refer to Figure 1.6b) [40a]. DLS and NOESY were utilized to prove the complex formation. The group of Ritter in cooperation with our team described the formation of a supramolecular brush polymer that shows changes in optical properties upon complex and thus brush formation [44a]. A CD end-functionalized PDEA was added to phenolphthalein functionalized PDMA. Phenolphthalein—a well-known pH indicator —changes its color from pink to colorless at pH > 8.4 via the opening of its lactone-group. In the presence of β-CD, the lactone ring reforms—even at higher pH—due to the formation of a host/guest complex that forces the molecule into the sterically more compact lactonoid structure. The complex formation could be followed via DLS, NOESY, and UV-VIS. Furthermore, the complex formation was visible to the naked eye. Redox-responsive brush polymers were described by Ritter *et al*. [43] as well as by Yuan *et al*. [92]. The former utilized a ferrocene functionalized acrylamide and DMA derived copolymers in conjunction with CD end-functionalized PDEA. The redox response of the formed supramolecular brushes was probed via cyclovoltammetry. Yuan *et al*. utilized PEG-*b*-poly(glycidyl methacrylate) (PEG-*b*-PGMA) that was reacted with mono thiol functionalized β-CD to obtain a β-CD functionalized block [92]. Moreover, ferrocene end-functionalized PCL was utilized to form supramolecular brush copolymers, which was probed via NOESY and UV-Vis. Self-assembly into micelles was investigated via TEM and DLS also with regard to an electrochemical redox response. Further, Yuan *et al*. prepared a photoresponsive brush polymer [93]. Ethyl cellulose was grafted with PCL and CD was conjugated to the PCL end-groups. The supramolecular brush was formed via addition of azobenzene functionalized PEG. In aqueous solution micelles formed with hydrophobic ethyl cellulose core and PEG corona. The structures were studied via TEM and DLS also with regard to their photoresponse. A rather rare polymer type was utilized by Allcock who utilized poly(phosphazene) with multiple β-CD grafts and formed brush polymers with adamantyl end-functionalized poly(phosphazene) [83].

A supramolecular dendronized polymer brush was described by Zhang *et al*. [81]. Adamantyl functionalized oligo ethylene glycol dendrons were attached onto a CD functionalized backbone and the thermoresponsive behavior was studied. A broad range of LCSTs from 34°C to 56°C was accessible via changes in dendrimer generation or hydrophobicity of dendrimer end groups. The dehydration and collapse of the oligo ethylene glycol chains leads to disassembly of the host/guest complexes as indicated by NMR and isothermal titration calorimetry data. Frey *et al*. studied the brush formation of CD functionalized PHPMA with adamantyl functionalized PEG-*b*-hyperbranched poly(glycerol) [94]. The efficiency of supramolecular brush polymer formation was studied in detail via ITC and DOSY. It was evidenced that the association constants depend strongly on the degree of branching of the poly(glycerol) block as well as the presence and the length of introduced PEG spacers. Nevertheless, the association constants have a final value independent of the degree of branching already at moderate molecular weights of the poly(glycerol) block.

1.3.3 Cyclic Polymer Architectures

Rather uncommon structures are cyclic polymers with a supramolecular CD-based ring closure. Harada *et al*. showed a CD-based macrocycle based on the PEG platform with azobenzene guests that showed the ring opening depending on temperature and light irradiation [95]. Recently Willenbacher *et al*. presented a β−CD/adamantane based macrocycle utilizing RAFT derived polymers [96]. Although only PDMA was probed in the present study, a broad range of polymer macrocycles is, in principle, available via utilization of different water soluble monomers and RAFT polymerization. The ring formation was proved via NOESY, DLS, and diffusion-ordered NMR spectroscopy (DOSY). Furthermore, the temperature response of the ring closure was probed.

1.4 HIGHER ORDER ASSEMBLIES OF CD-BASED POLYMER ARCHITECTURES TOWARD NANOSTRUCTURES

A variety of supramolecular-based macromolecular architectures has been described so far, as shown in the previous section. Starting from various building blocks—the primary structure—different assemblies were obtained—the secondary structure. Yet the obtained assemblies can be considered as single macromolecules if strong association is operational. The next step to more complex materials would be an assembly of CD host/guest bound macromolecules forming a tertiary structure. Ultimately, these ensembles of CD complex governed macromolecules yield a higher molecular level of complexity and a new level of properties as well. Again, a broad range of stimuli responsive CD/guest pairs and polymers is available rising the opportunity to form a significant amount of novel materials. Technically hydrogels belong to this category as well and the reader is referred to Section 1.3.2.1 for a brief description.

1.4.1 Micelles/Core-Shell Particles

The simplest higher order structures are micelles or core-shell particles. In the same way as covalently bound polymers, amphiphilic supramolecular block copolymers can be utilized to form micelles. As micelles are of particular interest in drug delivery, in that delivery of hydrophobic drugs/cargoes, supramolecular block copolymers, are the object of research to perform drug delivery tasks. Especially when triggered release of drug cargo is considered, stimuli-responsive block connections or stimuli-responsive blocks seem to be a tool of choice.

Zhang *et al*. described a supramolecular connected micelle in 2008 [39b]. The adamantyl/β-CD interaction was utilized to form a diblock copolymer of P4VP and PNIPAM that was able to form micelles upon pH or temperature stimuli. Similar strategies have been employed for a variety of supramolecular diblock copolymers [36,38a,46]. Micelles were also formed from supramolecular—mainly miktoarm—star polymers, such as a hydrophilic β-CD centered four-arm POEGMA complexed with a hydrophobic adamantyl

end-functionalized P(bis-(trifluoroethoxy)phosphazene) [83]. Another example is a β-CD conjugated with PEG and PDMAEMA that was complexed with an adamantyl end-functionalized PMMA yielding an amphiphilic structure [84]. A micelle-forming brush copolymer was described by Yuan *et al*., who utilized ferrocene end-functionalized PCL as hydrophobic and biodegradable block and a PEG-*b*-PGMA block conjugated with β-CD, yielding redox-responsive micelles [92]. Micelles were also formed from PCL grafted ethyl cellulose with attached β-CD that was complexed with azobenzene end-functionalized PEG [93]. A β-CD centered seven-arm poly(L-glutamic acid) with the drug c*is*-dichlorodiamine platinum (II) attached to the arms was described by Liu *et al*. [99]. Furthermore, supramolecular complexes with adamantyl functionalized PEG were formed. The formed supramolecular miktoarm star polymers assembled into micelles that were capable of drug release. A brush polymer forming micelles has been described by Jiang as well (refer to Figure 1.7a) [97]. A poly(*N*-vinyl-2-pyrrolidone) copolymerized with β-CD containing monomers was grafted with adamantyl end-functionalized PCL. Characterization via TEM, DLS, and AFM revealed multicore micelles in the case of preparation under nonequilibrium conditions, whereas usual core-shell micelles were obtained under equilibrium conditions. Li *et al*. utilized *O*-isopropylidenation of several hydroxyl groups in α-CD or β-CD in order to protect the hydroxyl groups as acetals and alter the properties of the molecules [100]. Furthermore, α-CD or β-CD polymers were formed by means of epichlorohydrin-induced polycondensation under basic conditions in water and the obtained polymeric hydroxyls could be converted into acetals as well. In the case of acetalated poly(β-CD), addition of an adamantyl functionalized PEG led to the formation of micelles or cylindrical assemblies in water, which could be controlled via the PEG/poly(β-CD) ratio. Due to the acid labile acetal protection, the assemblies showed a pH-dependent disintegration. The

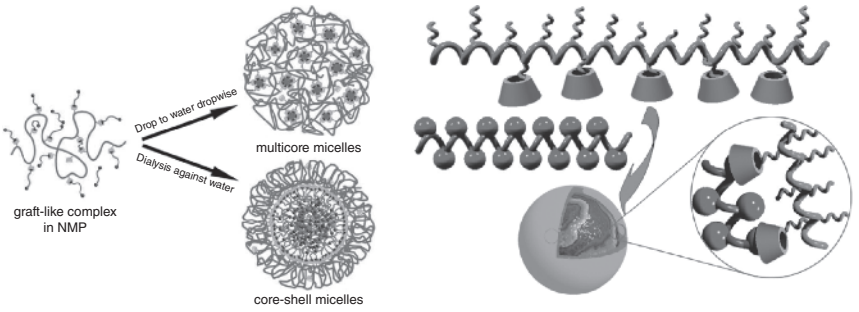

Figure 1.7 (a) Formation of micelles based on poly(*N*-vinyl-2-pyrrolidone) with β-CD side chains and adamantyl end-functionalized PCL leading to different micelle architectures depending on the preparation technique [97] (Reproduced from [96] with permission of John Wiley and Sons) and (b) formation of micelles based on β-CD conjugated poly(ethylene imine) and poly(β-benzyl-L-aspartate) [98] (Reproduced with permission from [97]. Copyright 2010 American Chemical Society). (*See color insert for color representation of this figure*).

rate of hydrolysis was controlled via the degree of acetylation. A micellar aggregate was described by Jiang *et al*., too [101]. A poly(methacrylate) with β-CD in the side chains was complexed with a copolymer of poly(*tert*-butyl acrylate) (PTBA) and an adamantyl containing monomer. The hydrophobic adamantyl containing PTBA block formed the core that was bound to the shell-forming hydrophilic CD containing block via supramolecular interactions. Furthermore, the shells were cross-linked and the core removed in order to obtain β-CD containing nanocages and the surface of the micelles/nanocages could be modified via guest addition, for example, cationic or anionic adamantyl derivatives. A similar approach was described by Ma *et al*. (refer to Figure 1.7b) [98]. A β-CD conjugated poly(ethylene imine) (PEI) was combined with a poly(β-benzyl-L-aspartate) and core-shell particles were formed via the dialysis method, leading to a complex formation of the benzyl groups and β-CD. Furthermore, drug-loading/release was studied as well as plasmid DNA (pDNA) loading and delivery *in vitro*.

1.4.2 Vesicles

More complex macromolecular assemblies are vesicles. While micelles have two interfaces, namely the interface between the blocks and the interface shell/solvent, vesicles have three interfaces, namely the interface between the blocks and the interface between inner shell/solvent and the interface between outer shell/solvent. Thus supramolecular-based vesicles are less frequently described in the literature. Nevertheless, vesicles are very well suited for cargo delivery/release, especially of hydrophilic molecules, and thus are an important target structure for polymer chemists.

Vesicles were described for several systems, such as the supramolecular diblock copolymer. A β-CD functionalized PS and a ferrocene functionalized PEG were utilized to form vesicles that could be disrupted via a redox stimulus [51]. A supramolecular diblock copolymer of β-CD functionalized dextran and benzimidazole functionalized poly(L-valine) formed vesicles for similar DP of dextran

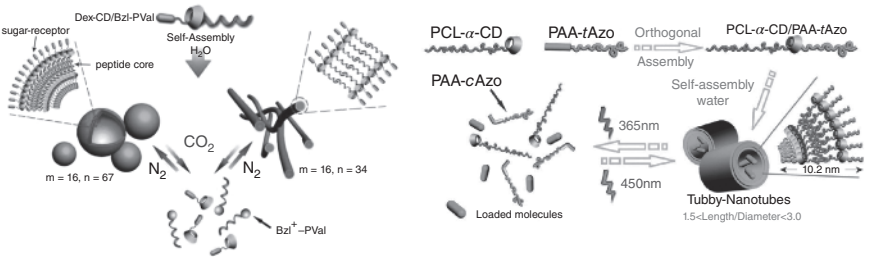

Figure 1.8 (a) Formation of pH/CO_2 responsive vesicles or fibers based on β-CD/benzimidazole interactions [47] (Reprinted with permission from [46]. Copyright 2014 American Chemical Society) and (b) formation of supramolecular light-responsive nanotubes based on azobenzene/α-CD interactions [53] (Reproduced from [52] with permission of The Royal Society of Chemistry). (*See color insert for color representation of this figure*).

and poly(L-valine), while fiber-like structures were obtained for higher DPs of poly(L-valine) (refer to Figure 1.8a) [47]. Jiang *et al*. prepared vesicles with doubly β-CD end-functionalized poly(ether imide) [102]. Furthermore, the inner and outer surface could be modified via host/guest complexes with adamantyl functionalized PEG. Li *et al*. presented recently a β-CD fully functionalized at C-6 with hydrophobic ortho esters that formed vesicles or spherical nanoparticles after complexation with adamantyl end-functionalized PEG [103]. The size and morphology of the aggregates could be adjusted via the chain lengths of pendant aliphatic chains attached to the ortho esters and feed ratio of the components. Furthermore, the surface of the aggregates could be modified via addition of ionic guest compounds as shown via zeta potential measurements. Due to the incorporation of acid labile ortho esters, the aggregates were dePEGylated at pH of 7.4 and finally disassembled completely at pH 6.4. Yan *et al*. presented a Janus-type hyperbranched polymer [104]. A β-CD centered hyperbranched polyglycerol and a hyperbranched poly(3-ethyl-3-oxetanemethanol) with an azobenzene at the apex were complexed via azobenzene/β-CD host/guest interaction. The complex formed vesicles in aqueous solution that could be disassembled into unimers after irradiation with UV light. The example of an ABA block copolymer with a hetero bifunctional middle block by Zhang *et al*. makes use of a PS with an adamantyl group on one end and an azobenzene group on the other end [54]. Complexation with β-CD functionalized PEG leads to vesicles, yet the morphology changes upon light irradiation due to the change in the block composition from ABA to AB after dissociation of the azobenzene/β-CD complexes. Another system that transforms from vesicles to micelles after application of an external stimulus—namely temperature—consists of a PNIPAM-*b*-PCL that is connected to PDMAEMA via adamantyl/β-CD interaction [55]. While the vesicle size could be tuned via CO_2 or N_2 pressure, the change in morphology toward micelles could be achieved via heating and collapse of the PNIAPM block. Ravoo *et al*. formed vesicles of hydrophobically decorated β-CD and added adamantyl functionalized maltose or lactose to modify the surface of the vesicles [105]. Furthermore, addition of ConA or peanut agglutinin led to agglutination of the vesicles due to interactions with either the lactose or maltose units on the surface of the vesicles.

1.4.3 Nanotubes and Fibers

Compared to the isotropic morphologies of micelles and vesicles, anisotropic structures like nanotubes and fibers are much more difficult to achieve. Therefore examples in the literature are rare. One example was described in Sections 1.3.11 and 1.4.2, fibers of a dextran and poly(L-valine) supramolecular block copolymer were obtained for high DPs of poly(L-valine) (refer to Figure 1.8a) [47]. Another example was described earlier as well, where nanoparticles of acetalated β-CD derived from an emulsion method lead to cyclindrical assemblies in water after addition of adamantyl end-functionalized PEG [100]. A photoresponsive example was reported by Yuan *et al*. (refer to Figure 1.8b). Supramolecular nanotubes with a length of 220 nm and a diameter of 90 nm were obtained from a block copolymer of

azobenzene end-functionalized PCL and α-CD end-functionalized PAA [53]. The light-responsive linkage could be exploited for the triggered release of Rhodamine B.

1.4.4 Nanoparticles and Hybrid Materials

The formation of nano particles via supramolecular interactions requires the careful adjustment of the utilized building blocks, yet significant potential toward applications like drug-delivery exists for supramolecular CD-based nanoparticles. Furthermore, the combination of polymer-based CD host/guest chemistry with biological motifs or inorganic materials, such as DNA and metal oxide nanoparticles, has found increasing interest in the last years. Thus a broad range of materials with enhanced or novel properties is available, especially when the stimuli-responsive nature of several CD complex types is taken into account.

Recently, Huskens *et al*. described a supramolecular nanoparticle that does not rely on the amphiphilicity of the employed polymers [106]. Poly(isobutyl-*alt*-maleic acid) was grafted with amino functionalized β-CD or *tert*-butyl aniline via amidation. To prevent the system from forming a hydrogel, adamantyl end-functionalized PEG was added as capping agent, yet it was found that the addition of the stopper effected the nanoparticle formation in water only slightly. This fact was attributed to the poly anionic nature of the poly(isobutyl-*alt*-maleic acid) that prevents the system from aggregation due to electrostatic repulsion. Nevertheless, under acidic conditions or at high ionic strengths aggregation was observed. A polycationic system was utilized by Tseng *et al*. [107]. Adamantyl-grafted poly(amidoamine) dendrimers, β-CD-grafted branched PEI, adamantyl functionalized PEG, and adamantyl-grafted $Zn_{0.4}Fe_{2.6}O_4$ superparamagnetic nanoparticles were assembled into nanoparticles in aqueous solution. Furthermore, Doxorubicin molecules were added to perform drug delivery. The release of the drug molecules was triggered via an external magnetic field that interacts with the embedded superparamagnetic nanoparticles and the release could be measured via fluorescence of the Doxorubicin molecules. Finally, the effects of the drug release were studied *in vitro* as well *in vivo*. In a similar manner a small interfering ribonucleic acid (siRNA) delivery system was presented by Davis *et al*. [108], which is described in detail in the next section. A DNA-based hybrid material based on CD/guest chemistry has been described by Xu *et al*. [109]. A β-CD centered star polymer, namely PGMA reacted with ethanolamine and a linear PGMA reacted with adamantyl amine, were synthesized. Both polymers were used to form a supramolecular brush and pDNA was condensed into the brushes. Finally, low cell viability and enhanced gene transfection *in vitro* was found. A similar approach made use of a β-CD centered four-arm PDMAEMA with a disulfide moiety between polymer and core [110]. Furthermore, adamantyl end-functionalized poly(poly(ethylene glycol)ethyl ether methacrylate) was synthesized and a supramolecular miktoarm star polymer formed. Addition of pDNA led to the formation of DNA/polymer hydrid particles that were studied with regard to redox-triggered release due to disulfide breakage, toxicity, and gene transfection *in vitro* and *in vivo*. A β-CD centered star polymer was employed as vector for siRNA by ElSayed *et al*. [111]. Copolymerization of hexyl methacrylate, DMAEMA, and DMAEMA methyl ammonium salt via

ATRP led to the desired star polymer. Notably, the polymers were coupled to the core via acid-labile hydrazone linkage to enable hydrolytic degradation of the star polymer after siRNA delivery. The star polymers were condensed with siRNA and the uptake into HeLa cancer cells was investigated. Feiters and coworkers presented a β-CD-based polymer/enzyme conjugate [112]. Vesicles from β-CD functionalized PS were formed in aqueous solution and adamantyl-PEG-functionalized horseradish peroxidase was conjugated in a supramolecular fashion, while the catalytic activity of the enzyme was retained.

In the case of hybrid materials, incorporating CDs and inorganic materials several examples have been described in the literature, such as inorganic nanoparticle centered stars from SiO_2 nanoparticles [86], CdS quantum dots [87], and gold nanoparticles [88], Kaifer *et al*. presented β-CD functionalized gold nanoparticles that could be aggregated via ferrocene functionalized dilinkers. Furthermore, the aggregation process could be reversed via redox stimulus [113]. In a similar way, Ravoo *et al*. showed a light-responsive aggregation of β-CD decorated SiO_2 nanoparticles via the addition of small molecule diazobenzene linkers [114]. A polyhedral oligomeric silsesquioxane grafted with β-CD was utilized by Li *et al*. and azobenzene end-functionalized PEG-*b*-PDMAEMA was attached in a photoresponsive fashion [89]. Yang *et al*. grafted azobenzenes onto mesoporous silica nanoparticles and Rhodamine B was loaded [115]. To encapsulate the model compound entirely, the pores were capped with a β-CD functionalized linear PGMA. Furthermore, the release of the model compound was studied with regard to light and temperature stimuli as well as the addition of competing binding agents. Thus the β-CD functionalized polymers acted as "nanovalves." Another mesoporous silica hybrid was described by Zhao *et al*. [116]. β-CD was attached to the silica surface via disulfide bonds and Doxorubicin was added as cargo. Subsequently, adamantyl end-functionalized PEG and folic acid/adamantyl hetero bifunctional PEG were added, forming a supramolecular complex. The particles were utilized for drug delivery, where the folic acid acted as targeting unit toward cancer cells and the PEG units as antifouling barrier and stabilizer to extend the circulation period. After cell internalization, reductive glutathione inside the cell led to disulfide bond cleavage, enhancing the drug release due to removal of the CD capping on the mesoporous silica carrier.

1.4.5 Planar Surface Modification

Surface functionalization plays a significant role in contemporary polymer science and supramolecular interactions provide powerful abilities to advance surface chemistry. Mono layers of CDs on surfaces have been entitled "molecular printboards" by Reinhoudt and Huskens [117]. A variety of grafted structures was presented with that concept in mind, such as on gold [117], Si [118] or SiO_2 [119]. In addition, patterned surfaces have been utilized in order to obtain spatially controlled host grafting and subsequently spatially controlled supramolecular complexation, for example, via micro contact printing [119, 120]. A variety of guest functional moieties have been grafted on surfaces in a supramolecular fashion, such as proteins [121], fluorescent

dyes [120b], and Eu^{3+} luminescent complexes [120a]. Remarkably, azobenzene functionalized cell recognition peptides were grafted onto an α-CD functionalized gold surface that showed reversible and photocontrollable cell attachment [122].

1.5 APPLICATIONS

Taking the previous chapters into consideration, a broad variety of architectures and more complex assemblies are available. Especially when the stimuli responsive nature of CD/guest complexes is taken into account, there certainly are applications for CD-based materials. As described in the last section a very important application for CD-based materials is drug delivery, in particular because CD/host guest chemistry is usually occurring in aqueous solutions and plain CDs are utilized to great extent in drug delivery already [19, 123].

An example for drug delivery via CD-based macromolecular architectures was presented by Zhuo *et al*. [124]. A dilinker containing α-CD and β-CD was employed to connect a PNIPAM and a PCL block. Cell-targeting ligands were attached as well as PEG units in order to protect the core-shell assemblies of the supramolecular diblock copolymer in the body. After formation of noncovalently connected micelles [125], drug delivery experiments were performed that showed tumor-triggered release of loaded Doxorubicin molecules. Davis *et al*. presented a CD-based nano particle for siRNA delivery (refer to Figure 1.9) [108, 126]. A polymer with CD units in the backbone was synthesized via a condensation copolymerization approach. Thus a difunctionalized β-CD monomer and the difunctional dimethylsuberimidate monomer were utilized to obtain a polycationic polymer (CDP). Furthermore, imidazole endgroups were introduced. In order to stabilize the delivery vehicle, adamantyl end-functionalized PEG was added (AD-PEG), yet an adamantyl and targeting ligand (human transferrin, Tf) functionalized PEG was added as well in order to engage cell receptors and induce endocytosis (AD-PEG-Tf). Adding a mixture of the three components to a siRNA solution led to the formation of PEG stabilized polycationic nanoparticles with targeting ligands on the outside and

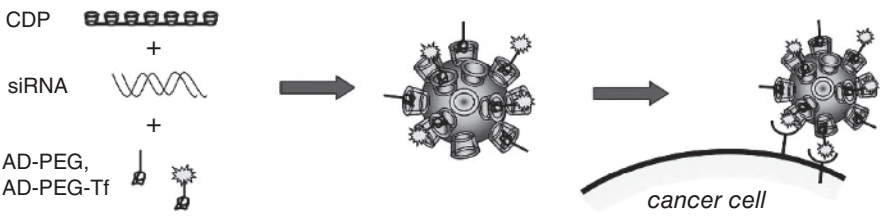

Figure 1.9 Formation of a CD-based supramolecular nano particle for siRNA delivery via mixing of a CD containing copolymer (CDP), siRNA, adamantyl end-functionalized PEG (AD-PEG) and adamantyl end-functionalized PEG with targeting ligand (AD-PEG-Tf) [108]. Reprinted with permission from [107]. Copyright 2009 American Chemical Society.

siRNA in the inside. Nanoparticles with diameters ranging from 60 to 80 nm were obtained. *In vivo* delivery was probed for DNAzymes, pDNA, and siRNA. The delivery system proved to be very efficient and eventually went to clinic trials. The examples above show that CD complexes are a very efficient tool for the formation of macromolecular assemblies with regard to drug delivery applications.

Apart from drug delivery other applications have emerged as well, such as in sensing. Reed *et al*. formed a self-assembled monolayer of β-CD on a silicon nanowire field-effect transistor [127]. The sensor was capable of detecting thyroxin molecules in solution and even to discriminate between the respective enantiomers. Furthermore, the streptavidin–biotin interactions could be probed via addition of orthogonal linker molecules, such as a double adamantyl functionalized biotin derivative. In addition, the sensing was reversible and the sensor could be regenerated for further use of the device.

Harada *et al*. introduced a new concept and type of materials in 2011—the so-called macroscopic self-assembly (refer to Figure 1.10a) [128]. Small centimeter-size blocks containing either CD functionalized gels or guest functionalized gels were brought together on a petri dish in water. Shaking led to recognition of the respective CD and guest functionalized blocks. For visualization different dyes were added to the respective gel blocks in order to show that the attachment of the blocks proceeds selectively. This concept was exploited for a variety of examples, for example, different guests and different CDs [128, 131] and stimuli-responsive complexation [48, 132]. Recently, Yan *et al*. utilized poly(ionic liquid) membrane strips functionalized with either β-CD or ferrocene moieties in the formation of a supramolecular velcro (refer to Figure 1.10b) [129]. The guest and CD functionalized strips were pressed together—zipped, so to speak—and showed strong adhesion under air und in water with lap shear adhesion strengths of around 90 kPa. Furthermore, oxidation of the ferrocenes via application of an external current or addition of oxidizer led to disassembly of the membrane connection—the unzipping. The zipping–unzipping could be performed several times with only small losses in adhesion performance. In another macroscopic example Xie *et al*. utilized three types of macroscopic gels to generate complex stimuli responsive assemblies: A β-CD and carboxylic acid containing gel (RH), a β-CD containing gel (NRH), and a ferrocene containing gel (NRG) (refer to Figure 1.10c) [130]. Due to the incorporation of carboxylic acids, the RH gel showed swelling/deswelling depending on ionic strength or pH. A combination of the RH and the NRG gel led to adhesion, and a change in pH led to bending of the assembly due to swelling of only one-half of the assembly, namely the RH gel. Addition of the NRH gel led to further possibilities, such as 3D assemblies that showed extraordinary bending structures. Due to their reversible nature, supramolecular interactions are well suited for the construction of self-healing materials. Harada *et al*. recently showed an example of a β-CD/ferrocene based self-healing hydrogel (Figure 1.10d) [22a]. A hydrogel was formed from a β-CD containing acrylamido polymer and a ferrocene containing acrylamido polymer. Cutting of the gel and rejoining led to reformation of the initial structure after 24 hours. Stress–strain measurements showed a recovery of 84% of the initial strength after self-healing. Furthermore, treating the cut surface with an

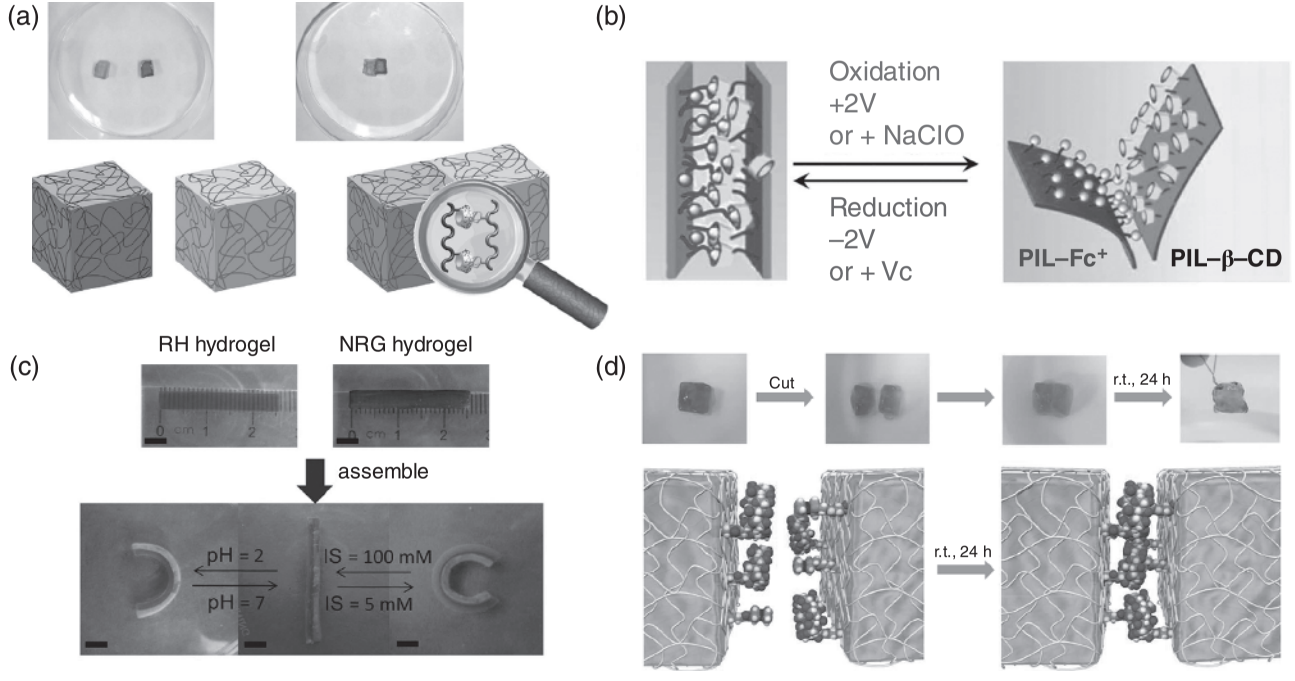

Figure 1.10 (a) Macroscopic self-assembly of an adamantyl containing hydrogel cube (green) and a β-CD containing hydrogel cube (red) [128] (Reprinted by permission from Macmillan Publishers Ltd: *Nat. Chem.* [126], copyright 2011), (b) β-CD/ferrocene based supramolecular velcro with reversible zipping/unzipping depending on the ferrocene oxidation state [129] (Reproduced from [127] with permission of The Royal Society of Chemistry), (c) combination of a β-CD and carboxylic acid containing gel (RH hydrogel) and a ferrocene containing gel (NRG hydrogel) with pH or ionic strength depending bending [130] (Adapted from [128] with permission of John Wiley and Sons), and (d) β-CD/ferrocene based self-healing hydrogel [22a] (Reprinted by permission from Macmillan Publishers Ltd: *Nat. Commun.* [21a], copyright 2011). (*See color insert for color representation of this figure*).

oxidant showed no self-healing, as oxidized ferrocenes do not complex with β-CDs, whereas subsequent treatment with a reductant led to self-healing of the cut.

1.6 CONCLUSION AND OUTLOOK

Supramolecular governed macromolecular architectures and CD-based complex macromolecular architectures, in particular, have a significant impact on polymer science. Relying on effective protocols for the synthesis of building blocks containing CD or guest moieties, CD complexation has found its way into macromolecular self-assemblies. The control over the functionalities of the utilized polymers, i.e. the primary structure, can be transferred into macromolecular assemblies. These assemblies can be considered as single polymers as well, assuming strong supramolecular association, resembling novel polymer compositions or topologies, namely the secondary structure. Thus complex macromolecular architectures such as block copolymers, star polymers, and brush polymers can be formed in a supramolecular fashion. A higher level of complexity can be achieved when these new supramolecular assembled macromolecules undergo further self-assembly into multi-polymer assemblies, namely the tertiary structure. Supramolecular governed macromolecular architectural polymers were utilized to form a variety of multi-polymer assemblies, such as micelles, vesicles, nanotubes, and hybrid materials. Combined with the large number of stimuli-responsive CD/guest complexes and stimuli-responsive polymers, a large variety of functional materials is accessible. Especially with regard to prospective applications, the utilized polymer systems can be tuned in a precise and convenient way via efficient chemistries and because of the modular character of supramolecular building blocks. Several potential applications have been investigated so far showing promising results, for example, drug-delivery, sensing, adhesives, and self-healing materials. In summary, we conclude that CD host/guest chemistry had significant impact on polymer and materials science and will play a key role in future developments. Certainly more complex structures and prospective applications will be investigated and presented in the near future.

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