Chem Soc Rev

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Cite this: *Chem. Soc. Rev.*, 2011, **40**, 2254–2266

www.rsc.org/csr

TUTORIAL REVIEW

Cyclodextrin-based inclusion complexation *bridging* supramolecular chemistry and macromolecular self-assembly

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Received 21st October 2010
DOI: 10.1039/c0cs00153h

Research into macromolecular self-assembly has been progressively developing since the 1970s but with a little affect from the achievements of supramolecular chemistry. In recent years, this situation has changed as more and more factors and concepts in supramolecular chemistry have been introduced into studies of the self-assembly of polymers. In this respect, inclusion complexation based on cyclodextrins plays a remarkable role. In this *tutorial review*, we address how inclusion complexation has been employed and used to promote the recent developments in macromolecular self-assembly. These include the amphiphilicity adjustment of macromolecules, non-covalent linkages for forming pseudo block copolymers and micelles, surface modification and functionalization of polymeric micelles and vesicles, and the combination of synthetic polymeric assemblies with biological moieties. Furthermore, the realization of the reversible stimuli-responsiveness of polymeric assemblies and materials, particularly hydrogels by means of controllable inclusion complexation is discussed as well.

1. Background

Generally, as a very broad and well-developed research area, macromolecular self-assembly is composed of two major fields, *i.e.* supramolecular polymers, which are formed from small molecules driven by non-covalent interactions, and self-assembly of multicomponent systems in which macromolecules serve as at least one of the components. For the former, the basic concepts and research methods are almost the same as those developed in supramolecular chemistry.[1] However, for the latter, self-assembly of block copolymers has been the main subject; the repulsion between unlike blocks and the cohesive interaction between the like blocks being the main driving force. So for a long time, such research has developed in parallel, with slight influences from supramolecular

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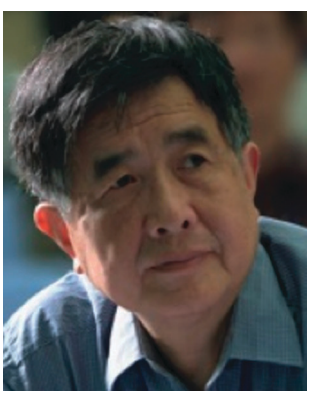

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chemistry.[2] It is only in recent years that the concepts and achievements in non-covalent interactions developed from supramolecular chemistry have progressively drawn the increasing attention of polymer scientists to be successively employed in macromolecular self-assembly, and thus greatly promoted its progress. Now, besides block copolymers, complementary homopolymers, random copolymers and oligomers, *etc*. can be used as building blocks to construct regular assembled bodies driven by a variety of non-covalent interactions.

The basic scope of non-covalent interactions in supramolecular chemistry covers ionic and dipolar interactions, hydrogen bonding, π interactions, van der Waals interactions, and the hydrophobic effect.[3] Inclusion complexation, on which we focus in this review, normally involves the interactions of two components, so called "host" and "guest" molecules. It is not generally recognized as one kind of the basic non-covalent interactions, because of its combination nature of several elemental supramolecular interactions. The binding ability of hosts and guests is mainly attributed to hydrophobic interactions and the complementary character of size and shape between their structures.[4]

Being the most widely used hosts, cyclodextrins (CDs) are a class of cyclic oligosaccharides that have molecular-compatible cavities. They are synthesized from starch *via* a simple enzymatic conversion and, with negligible toxicity, it makes them appropriate for a broad range of applications and industrial production on the thousands-of-tons scale. These semi-natural compounds commonly comprise several D-glucopyranoside units linked together by α-1,4-glycosidic bonds. α-, β- and γ-CDs, consisting of six, seven and eight glucopyranose units, respectively, are the most common ones. CDs are pictured as a shallow truncated cone, with the diameter of the primary hydroxyl rim of the cavity reduced compared with the secondary one. The exterior of the cavity is highly polar, because of the bristling hydroxy groups, while the interior is nonpolar.[5] Besides CDs, there are several important macrocyclic host families, such as crown ethers, calixarenes, and cucurbiturils. Until now, the contribution of these other families to macromolecular self-assembly is small compared to CDs, so we are going to focus on CDs as hosts in this review.

There are many different routes to establish macromolecular self-assembly *via* inclusion complexation. Linear or crosslinked supramolecular polymers are formed through intermolecular inclusion complexation between ditopic or multitopic building blocks of small molecules (Fig. 1a and b).[6] Whether they be linear or network structures, such supramolecular polymers feature non-covalent bonds between the repeating units. This tutorial review will not cover this field, but will concentrate on self-assembly driven by inclusion complexation for multi-component systems containing macromolecules as building blocks. In this area, one of the most well-known assemblies is pseudopolyrotaxane (PPR), formed by a linear polymer chain threading a series of CD cavities (Fig. 1c). This is a classic and successful model of supramolecular chemistry applied to macromolecular self-assembly. Strong hydrogen bonds between the adjacent threaded CDs further result in microcrystalline aggregation and then promote physical gel formation. Since the research in this field has been well developed and has been reviewed,[7] this tutorial review will only deal with a few specific cases of PPR hydrogel tightly related to our current main interest.

The inclusion complexation between CDs and various guests has been extensively investigated in supramolecular chemistry resulting in a broad scope of guest molecules available under different conditions. Quantitative results including binding constants, enthalpy and entropy changes have been well reviewed previously.[5] The host and guest molecules addressed in this review are listed in Fig. 2. One of the most investigated pairs, β-CD and adamantane (ADA) has been widely employed in macromolecular assembly as it has strong binding ability with an association constant around $1 \times 10^5\ M^{-1}$ in water. Many pairs with a binding ability that is adjustable to external environment, such as pH, light and voltage, have drawn great attention, as they could be used in constructing stimuli-responsive assemblies (Fig. 3a). Furthermore, as the interaction strength of different pairs covers a very broad range, it provides a good opportunity to realize reversibility of self-assembly just by competition between different pairs (Fig. 3b). However, such advantageous features of inclusion complexation were not sufficiently drawn attention and so were not employed in macromolecular self-assembly until about the beginning of this new century. In this *tutorial review*, we present the newest achievements of macromolecular self-assembly driven by or tightly related to inclusion complexation. This includes amphiphilicity adjustment and various superstructures built by inclusion complexation. We then focus on the stimuli responses and surface functionalization of the

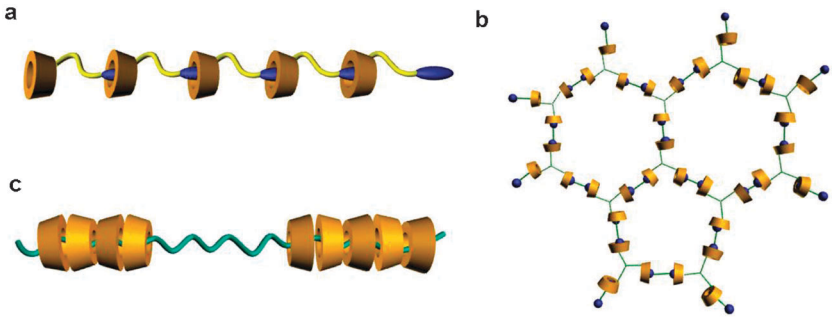

Fig. 1 Schematic features of some supramolecular structures based on inclusion complexation of CD: supramolecular polymer (a), supramolecular network (b), and PPR (c).

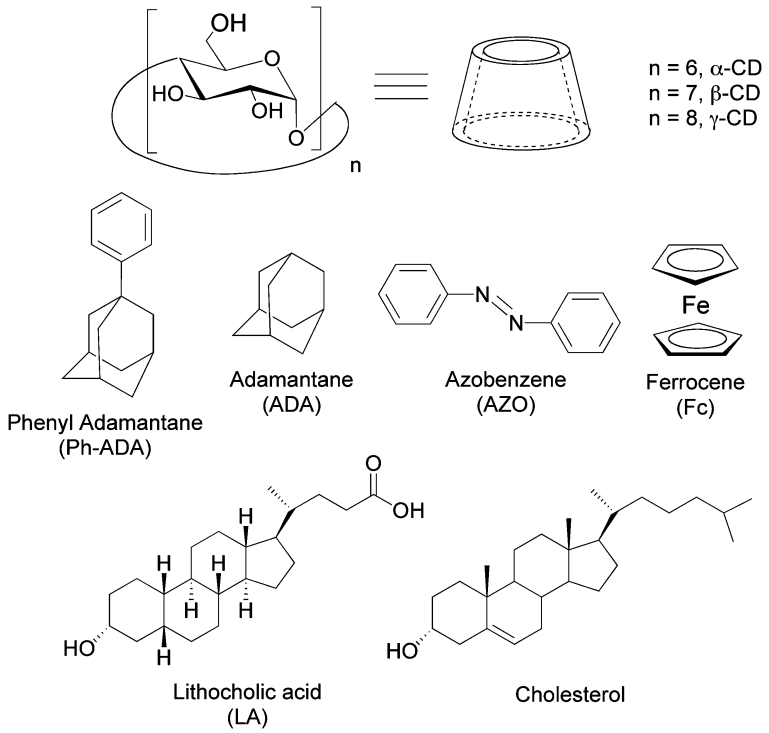

Fig. 2 Typical host and guest structures discussed in this paper.

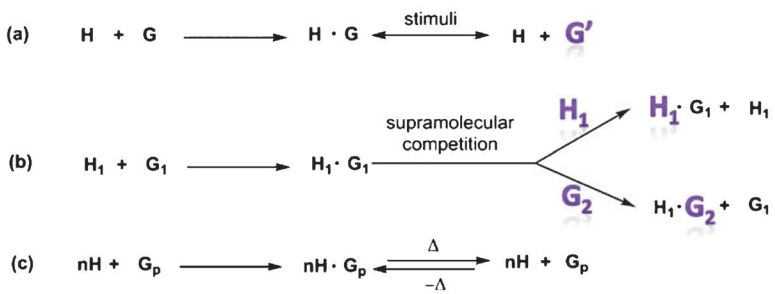

Fig. 3 Possible routes to tune the inclusion complexation in macromolecular self-assembly (H: host, G: guest, H·G: inclusion complex, G′: isomer of the guest, H_1 and H_2: competitive hosts, G_1 and G_2: competitive guests, G_p: polymeric guest).

obtained assemblies. Finally, polymeric hydrogels or networks obtained *via* inclusion complexation with particular focus on their reversibility will be demonstrated. It is worth mentioning that, although there are a number of host–guest pairs based on CDs, only a small amount of them have been introduced to macromolecular self-assembly, which means there is still a wide space for macromolecular scientists to explore.

2. Micellization driven by inclusion complexation

2.1 CD modification to polymers

The use of amphiphilic macromolecules as building blocks has drawn increasing interest because their controllable self-assembly, and the morphology transformation of the assemblies can be realized by tuning the amphiphilicity.[8] CDs are

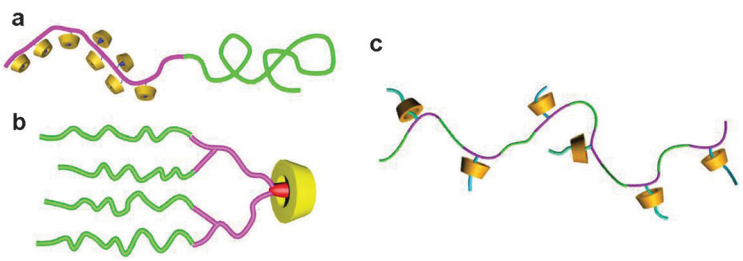

Fig. 4 Some examples of macromolecular amphiphiles formed *via* inclusion complexation.

particularly valuable and extensively employed in tuning the amphiphilicity of macromolecules. Generally, once part of a macromolecule containing a guest moiety is connected to CDs *via* inclusion complexation, the part will become more hydrophilic and thus the amphiphilicity of the macromolecule as a whole is turned. In terms of location and distribution of the non-covalent binding sites along the polymer chains, some typical examples are pictured in Fig. 4. As shown in Fig. 4a, the block copolymer composed of two hydrophobic blocks, *i.e.* polystyrene and adamantyl polyphosphazene, could be converted to an amphiphilic copolymer when the adamantyl units enter the cavities of the added β-CDs. Thus micelles with polystyrene as the core and β-CD-modified polyphosphazene as the shell were induced.[9] As shown in Fig. 4b, Kim *et al.* reported that a dendron amphiphile with a pyrene apex, formed vesicles in aqueous solution. By capping the dendron with β- or γ-CDs due to inclusion complexation between pyrene and CD, the amphiphilicity of the dendron was significantly altered which made the vesicles convert into nanotubes.[10] Modification of polymer chains with CDs could also make disassembly of micelles of amphiphilic copolymers. For example, alternating copolymers composed of sodium maleate and dodecyl vinyl ether units, initially formed micelles in water due to the hydrophobic interactions between the dodecyl chains. When free α-CD was introduced, the inclusion complexation of dodecyl with α-CD competed with and overcame the existing hydrophobic interactions and then induced the dissociation of the micelles[11] (Fig. 4c).

The performance of tuning the amphiphilicity of macromolecules by attaching CD onto binding sites along the polymers is obviously based on the knowledge of the host–guest interactions gained in supramolecular chemistry. It is understandable that the interactions between the free host and guest moieties may to some extent differ from those of the moieties bound to polymers. However, little has been explored in this respect so far. Such discussions were made for the specific case in Fig. 4c. It is known that dodecyl groups can form inclusion complexes with α-CD, β-CD and γ-CD with different stoichiometries.[12] When these associations had to compete with the existing hydrophobic interactions of the dodecyl groups on the polymer chain, α-CD reserved its strong binding tendency, while β-CD and γ-CD did not. The result was obtained from the chemical shifts of the methyl and methylene groups within dodecyl from ^{1}H NMR. This enhancement of binding selectivity indicates that molecular recognition can be greatly influenced by the microenvironment of the binding site, which is essential to the current investigation of biological events.

Harada *et al.*[13] went further to explore this microenvironment effect on host–guest binding behavior. As a pair of model compounds, Ph-ADA binds to β-CD more strongly than ADA (binding constant: 7.6×10^5 M^{-1} *vs.* 0.4×10^5 M^{-1}), because the phenyl group contributes to this binding and makes the binding site for β-CD deeper than ADA (Fig. 5a). However, when Ph-ADA and ADA were respectively attached to an alternating copolymer, the inclusion complexation selectivity of β-CD to ADA and Ph-ADA (Fig. 5b) was inverted (apparent binding constant: 6.6×10^2 M^{-1} *vs.* 2.4×10^2 M^{-1}). The hydrophobic associations of ADA or Ph-ADA in polymers contributed to this remarkable change. The strong hydrophobic interaction between neighboring Ph-ADA moieties destabilized the complex of β-CD/Ph-ADA substantially while that between ADA did not. To our opinion, this result is of significant importance for the research of macromolecular self-assembly driven by inclusion complexation: one should pay more attention to the possible effects on the complexation caused by connecting the host and guest moieties into macromolecules. Although the competitive binding ability of CDs to guest molecules has been well understood in supramolecular chemistry, little has been explored in polymer systems.

2.2 Various macromolecule-associated micellization driven by inclusion complexation

2.2.1 Non-covalently linked block copolymers. When the binding ability of a host–guest pair is rather strong, it can be employed to link two linear polymers with respective host and guest groups at the chain ends into a pseudo block copolymer. Although self-assembly of the pseudo block copolymers linked by ligand–metal interactions has been widely investigated for long time,[14] studies on pseudo block copolymers linked by inclusion complexation have just emerged. Shi *et al.* reported that ADA end-functioned poly(*N*-isopropylacrylamide) (PNIPAM) and β-CD end-functioned poly(4-vinylpyridine) (P4VP) formed a pseudo block copolymer *via* the ADA/β-CD interaction.[15] Micelles were further formed in pH 2.5 aqueous solution at 60 °C, with a hydrophobic PNIPAM core and a hydrophilic P4VP shell. When the condition was switched to pH 4.8 at 25 °C, PNIPAM became hydrophilic and P4VP slightly hydrophilic, then vesicles with a radius around 80 nm were formed, in which a P4VP layer is sandwiched between the two PNIPAM layers. Following their systematic study on double hydrophilic block copolymers (DHBC), Liu *et al.*[16] achieved non-covalently linked DHBC containing β-CD-terminated PNIPAM and ADA-terminated poly(2-(diethylamino)ethyl methacrylate) (PDEA). At room temperature, the polymer pair molecularly dissolved at pH < 6 but formed PDEA-core micelles at pH > 8 with PNIPAM as the hydrophilic outer layer of the micelles. In acidic media, above the LCST of PNIPAM, vesicular nanostructures formed with a PNIPAM layer sandwiched by the hydrophilic PDEA layers. Very recently, Yuan *et al.*[17] reported that β-CD ended PS (β-CD-PS) and Ferrocene (Fc) ended polyethylene oxide (PEO) (Fc-PEO) formed pseudo block copolymers of PS and PEO due to the inclusion complexation of β-CD and Fc. Its reversible assembly behaviour will be discussed later.

This non-covalently linked polymer method is not limited to linear polymers. Dendrons with a binding site at their apex were found to be able to form a non-covalently connected linear-dendron block copolymer,[18] which will be discussed in section 3. Since CD normally has 6–8 primary hydroxy groups on the upper rim of the cavity, it is convenient to initiate polymerization and form star-shape polymers with several arms. Li *et al.*[19] recently designed and synthesized a β-CD-core four-arm PNIPAM and functionalized PEGs with ADA groups at one or both of its ends. Thus they obtained non-covalently linked block copolymers with different architectures by inclusion complexation (Fig. 6). They found that

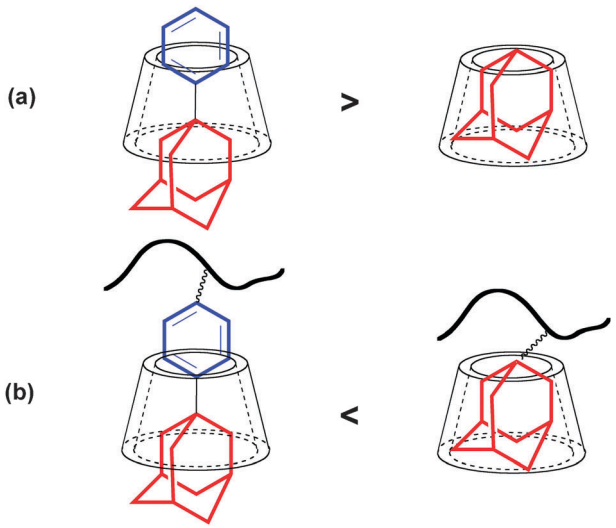

Fig. 5 Comparison of the inclusion complexation between β-CD/ADA and β-CD/Ph-ADA in free state (a) and on polymers (b).

the thermo sensitive behavior of the β-CD-core star PNIPAM in the block copolymers was changed significantly, *i.e.* the lower critical solution temperature (LCST) of these self-assembling systems was greatly increased depending on the ratio of ADA moiety to β-CD core and/or the length of the PEG blocks. For example, the LCST reached 39.2 °C when the PEG chain with ADA groups on both of its ends was used. This method of combining short PEG chains to PNIPAM by inclusion complexation provided an efficient way to control the LCST avoiding the conventional copolymerization of NIPAM with hydrophilic monomers. So this supramolecular approach might be promising for the production of intelligent systems for biomedical and pharmaceutical applications.

2.2.2 Non-covalently connected micelles. Our group established "block copolymer free" strategies for micellization of polymers.[20] Two complementary homopolymers, random copolymers, *etc.*, could self-assemble into micelles or vesicles, in which the component polymers are connected by interpolymeric interactions. So it was called a non-covalently connected micelle (NCCM). In our early stage of this work, hydrogen bonding was the only non-covalent interaction used. During the past five years, inclusion complexation has been successfully introduced to construct NCCMs.

As reported by Wang and Jiang, a hydrophobic linear polymer P*t*BA-ADA (P*t*BA, poly(*tert*-butyl acrylate)) containing ADA, and a hydrophilic linear[21] or lightly crosslinked[22] polymer PGMA-CD (PGMA, poly(glycidyl methylacrylate)) containing β-CD, were designed and prepared (Fig. 7). The two polymers were dissolved in DMF, where their interaction was weak. Water was then added as a selective solvent, in which inclusion complexation came to dominate. Thus, micelles with P*t*BA-ADA as core and PGMA-CD polymer as shell were formed. The core and shell was non-covalently linked by inclusion complexation between β-CD and ADA. Although the initial molar amount of β-CD and ADA was comparable, since most of ADA moieties were embedded in the hydrophobic core of the micelle, many empty β-CD cavities existed on the surface of the hollow sphere. Such micelles were featured by double-scale hydrophobic domains, *i.e.* the hydrophobic core has a size of about 100 nm and there are plenty of hydrophobic cavities of β-CDs with a size of 0.7 nm. Thus there is sufficient room for further surface modification, which will be discussed later. Moreover, when the shell was crosslinked and then the core was dissolved by switching the solvent from water to DMF, the micelles were converted into hollow spheres of PGMA-CD. Recently, Zhang *et al.*[23] reported inclusion complexation connected micelles from two block copolymers. The two copolymers based on PEG-*b*-PAA (PAA, poly(acrylic acid)) with respective β-CD and AZO modifications on the PAA blocks, self-assembled into micelles driven by inclusion complexation between β-CD and AZO. After crosslinking, the assembly structure was capable of loading/unloading pyrene, which is photo switchable by the inclusion complexation of CD/AZO.

2.2.3 Layer-by-layer hollow microcapsules. Layer-by-layer (L*b*L) assembly is a powerful method for fabricating multilayer thin films with controlled morphology and composition. This process has been widely investigated, although the driving forces are mainly restricted to electrostatic interactions. Few attempts have been made to build L*b*L multilayer films using inclusion complexation. Recently, polymers with binding sites for inclusion complexation were employed to build L*b*L microcapsules. To exclude other driving forces such as charge attraction, the host β-CD and guest Fc are respectively connected to the same polyelectrolyte, poly(allylamine hydrochloride) (PAH). A step-wise increase of layer thickness was observed when β-CD-grafted PAH and Fc-grafted PAH were alternatively self-assembled using a $CaCO_3$ sphere as a template. After the carbonate core has been dissolved, hollow microcapsules of PAH were obtained, which had reversible swelling and shrinking properties with changes in pH and/or ionic strength.[24]

2.2.4 Protein connection. Subsequently, studies using an inclusion complexation strategy went much further than one previously expected. It is generally considered that hydrogen bonding and metal ions are ubiquitous in living system, inclusion complexation is rather orthogonal compared to

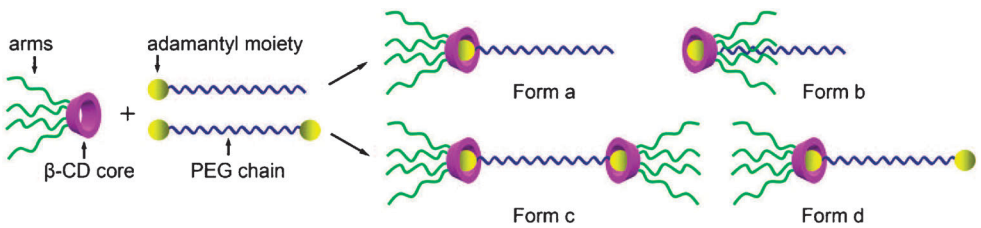

Fig. 6 Different chain architectures of pseudo block copolymers composed of β-CD-core star PNIPAM and PEG *via* inclusion complexation.[19]

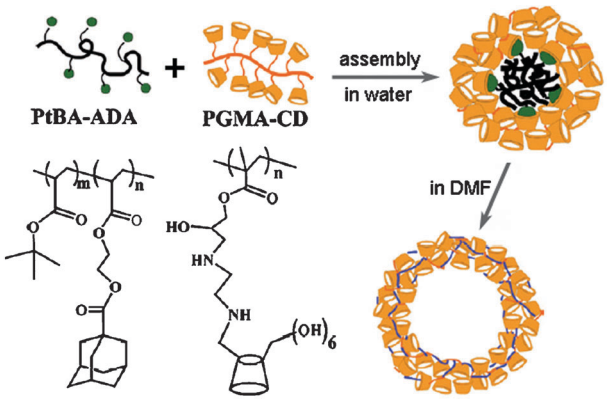

Fig. 7 NCCM and the corresponding hollow sphere built by inclusion complexation.[20a] (Reproduced with permission of Royal Society of Chemistry from ref. 20*a*).

other non-covalent interactions. On the other hand, CDs have been chosen as drug carriers since 1950s, because of their bioavailability and low toxicity,[25] which provide a solid background for further application in biological systems. Recently, the interaction between β-CD and lithocholic acid (LA) was introduced to protein association by Brunsveld and his coworkers.[26] Enhanced cyan fluorescent protein (eCFP) and enhanced yellow fluorescent protein (eYFP) were chosen as model proteins. LA and β-CD were linked to eCFP and eYFP, respectively. Then the protein complexation took place, which was promoted by inclusion complexation between β-CD and LA. The protein complex was characterized by SDS-PAGE for molecular weight and fluorescence for FRET (Förster resonance energy transfer) process (Fig. 8). The heterodimerization between the two proteins has been proved, with a constant of $(1.6 \pm 0.2) \times 10^6\ M^{-1}$, which is similar to that of free β-CD and LA. After the complex was further microinjected to Madin-Darby canine kidney cells, enhanced fluorescence was observed and was also easily switched off *via* supramolecular substitution with incubation of exogenous β-CDs, which were conjugated to a cell-penetrating peptide. These results demonstrated that the supramolecular interaction is not disrupted by either the cellular environment or by the endogenous cholesterol during the time scale of 1 h. That is understandable as the affinity of cholesterol for β-CD was more than two orders of magnitude lower than that of LA. The *in vitro* result clearly showed the orthogonality of inclusion complexation to other kinds of non-covalent interactions, which is quite promising for further biological applications. This work proved the concept to introduce synthetic supramolecular elements to biomacromolecules, in which the two factors worked cooperatively. Then the synthetic supramolecular chemistry can modulate the interactions of biomacromolecules easily, reversibly and non-biologically, which provides a useful platform for further exploration of biological events.[27]

We have presented a brief view showing that inclusion complexation is a powerful tool for macromolecular self-assembly. In fact many more results have emerged confirming this idea, which could not be included in this tutorial review because of the limited space.[28] Scientists are pursuing future materials, integrated with multiple functionalities, which should be liable to various external stimuli and have reliable quality. This requires a well-defined, hierarchical and orthogonal assembly of several kinds of non-covalent interactions; inclusion complexation of course cannot be excluded.

3. Reversible micelles and vesicles with inclusion complexation

Reversibility is a basic and crucial feature of supramolecular systems.[29] In designing and fabricating new supramolecular materials, the realization of reversibility is particularly important as it could enable these substances to be superior to conventional materials.[30] In principle, material reversibility can be realized by reversible non-covalent bonds. AZO and Fc are the most popular guests for reversible inclusion complexation with CDs (Fig. 9). *trans*-AZO binds strongly to α- or β-CD, while *cis*-AZO can not bind or binds very weakly. With a few exceptions, CD normally binds to neutral or anionic compounds only. So the oxidized state of Fc binds very weakly to CDs because of its cationic nature, while the reduced state of neutral iron binds properly.[17] Many stimuli-responsive self-assemblies were

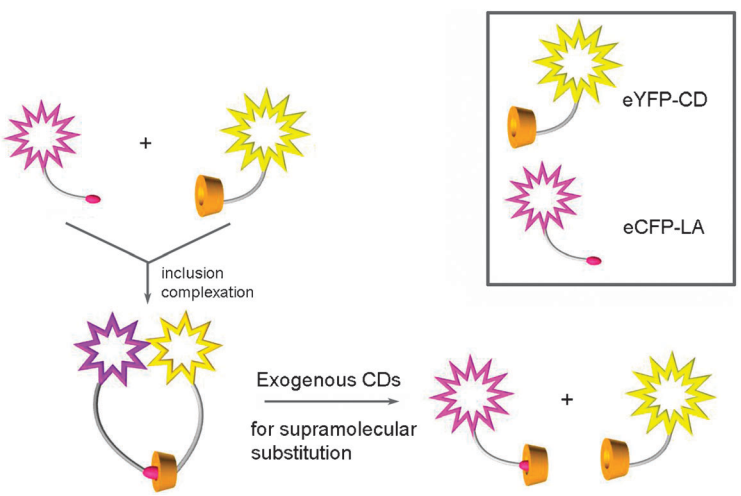

Fig. 8 Protein heterodimerization driven by inclusion complexation.

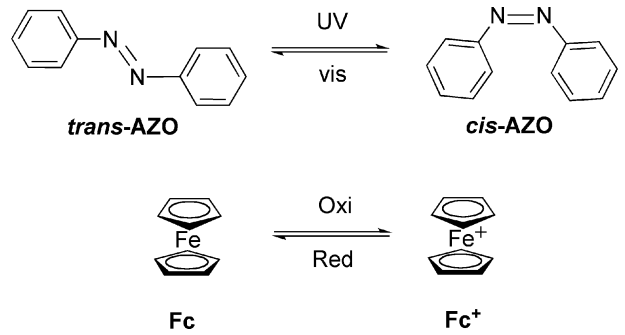

Fig. 9 Chemical structures of typical guests with reversible responsiveness.

initiated from this knowledge. In this part, we will focus on stimuli responsive self-assembly induced by inclusion complexation. To demonstrate this phenomenon clearly, we will discuss not only polymers but also small molecules as building blocks.

Zou and Jiang reported that inclusion complexation of CDs with AZO will convert a hydrophobic molecule containing the AZO into an amphiphile. As shown in Fig. 10, the hydrophobic compound (AZO-alkyl) possesses an AZO head and three alkyl tails (Fig. 10).[31] After β-CD was carefully introduced, inclusion complexation of β-CD with the AZO head changed the hydrophobic molecule into an amphiphile. The amphiphile further self-assembled into vesicles with diameter of 150–200 nm and membrane thickness of 10 nm in water. After UV light irradiation, although the alkyl chain was not affected, the photoisomerization of AZO from the *trans* to *cis* form induced dissociation of the inclusion complex, which made the amphiphile return to a hydrophobe. Thus the vesicles disappeared and irregular aggregates of the hydrophobic AZO-alkyl formed. A subsequent visible light irradiation made AZO switch back to the *trans* form leading to the regeneration of the amphiphile and then it self-assembled into vesicles. In addition, although α-CD and β-CD have different binding ability with AZO, this difference was not detectable in this assembly and disassembly process.

This concept of a photo-switchable assembly has been extended to macromolecules. Zou and Jiang constructed a polymeric amphiphile composed of β-CD ended PNIPAM (β-CD-PNIPAM) as the hydrophilic part, and AZO ended Frechét-type dendron (AZO-DEN) as the hydrophobic part[18] (Fig. 11a). When the amphiphile in THF was quickly injected into aqueous solution, vesicles with an average size ranging from 60 nm to 110 nm were formed, depending on the molar ratio of PNIPAM to dendron. As expected, the vesicles could be transformed into solid spheres under UV irradiation and switched back to vesicles under visible light. In this system, besides photo-reversibility, PNIPAM also brought the vesicle thermo-reversibility. As shown in the DLS results (Fig. 11b), with increasing temperature, the size of the vesicles changes little until the temperature reaches 29.5 °C, close to the LCST of PNIPAM. A decrease of R_h from 80 nm to 60 nm was observed within only 1 °C, which could be attributed to the coil–globule transition of PNIPAM chains on the vesicle surface. When the temperature increased further, PNIPAM became more hydrophobic leading to aggregation of the vesicles, as indicated by the dramatic size increase. It is important to know that disaggregation took place when temperature was decreased to below 28 °C, which was confirmed by SEM and AFM observations. In short, this self-assembled system based on CD-AZO interactions realized both optical and thermal responsiveness.

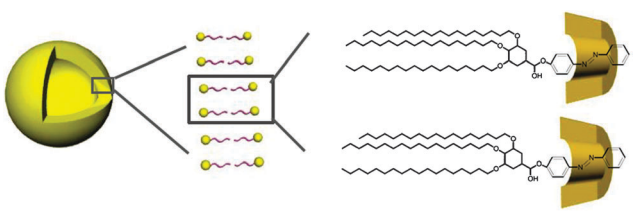

Fig. 10 Self-assembly of amphiphilic AZO-alkyl molecule capped with β-CD.

Inclusion complexation not only can induce the formation of vesicles, but also can dismantle existing vesicles. Zhang *et al.*[32] synthesized an amphiphile having a hydrocarbon chain with respective ends of AZO and pyridinium. The amphiphile formed vesicles in water. However, the disassembly of the vesicles was observed after α-CD was added because of the inclusion complexation of AZO with α-CD, which made the amphiphile become a hydrophile. However, after UV irradiation, *cis*-AZO led the complex to self-assemble into vesicles again, as a result of α-CD sliding to the alkyl chain. In this specially designed AZO compound, the AZO group was directly linked to the alkyl chain, which made the sliding of α-CD possible. All results mentioned in this section indicate that the concept of photo-reversible self-assembly driven by inclusion complexation is practical and reproducible in different amphiphilic systems.

Reversible vesicles were also demonstrated by using voltage as an external stimulus instead of light. A pseudo block copolymer of PS and PEO with a linkage of β-CD and Fc (section 2.2.1) formed stable vesicles in water.[17] The vesicles were dismantled by positive electro-stimulation (+1.5 V) for 5 h, which oxidized Fc into Fc^+. This voltage-dissociated inclusion complexation was proved by a half-wave potential ($E_{1/2}$) decrease of 0.11 V accompanying an increase in the peak currents. Further negative electro-stimulation (−1.5 V) reassembled the vesicles by reduction of Fc^+ to Fc after 5 h (Fig. 12). Therefore, this work proved that voltage is also a good choice of clean stimuli for reversible association and disassociation based on inclusion complexation.

Inclusion complexation could induce thermo-responsive assembly, because the binding ability of CD with different guests has its own entropy or enthalpy driven nature. An amphiphile containing a bipyridinium head and a bulky tail was taken to study the thermo-responsiveness of micelles (Fig. 13).[33] The amphiphile formed a water-soluble pseudo-rotaxane with α-CD below 60 °C. Since this structure is more entropy dependent, after heating, the amphiphile slid out of the α-CD cavities and formed micelles accommodating pyrene in the core. The whole process was fully thermo-reversible accompanying the release or load of the pyrene moiety, which was monitored by the absorption spectra of pyrene. It was very interesting that, in this system, if the *t*-Bu group at the

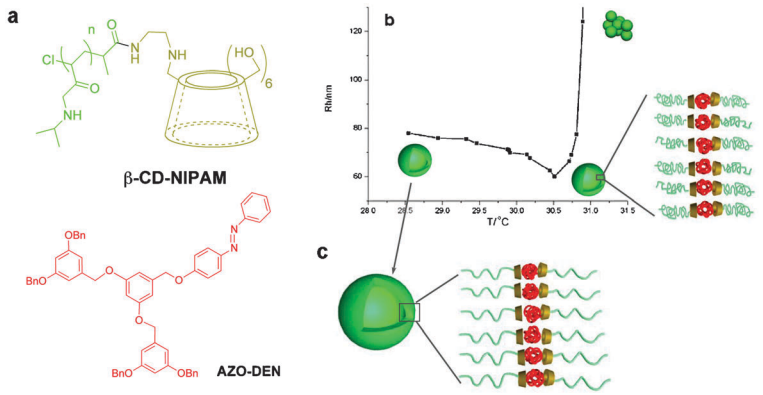

Fig. 11 (a) Chemical structure of the macromolecular/dendron building blocks. (b) Enlarged region showing the size change with temperature increase from 28.5 to 30.9 °C and the corresponding schemes of the vesicles below and above LCST. (Reproduced with permission of American Chemical Society from ref. 18)

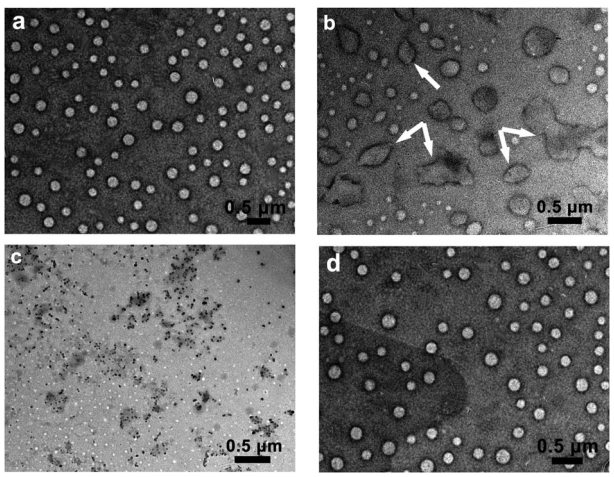

Fig. 12 TEM images of the reversible assembly and disassembly of the voltage-responsive β-CD-PS/Fc-PEO vesicles upon electric stimuli: (a) no external voltage, (b) +1.5 V (after 2 h), (c) +1.5 V (after 5 h), and (d) −1.5 V (after 5 h).[17] (Reproduced with permission of American Chemical Society from ref. 17).

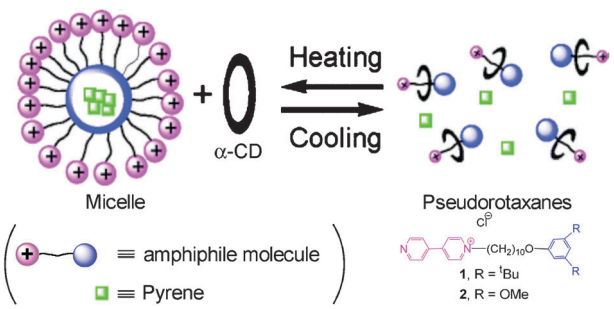

Fig. 13 Thermo-reversible amphiphile based on pseudorotaxanes.[33]

end was replaced by -OMe, α-CD was very stable on the chain of the amphiphile and could not be removed after heating. It is worth noting that this reversible thermo-responsiveness of the assembly is based on the thermal reversibility of inclusion complexation rather than the well-investigated thermal behavior of polymers such as PNIPAM chains.

4. Surface modification of self-assemblies by inclusion complexation

Polymeric vesicles (or polymersomes) produced by self-assembly have attracted increasing scientific interest in recent years,[34] because of their numerous potential applications, such as tunable delivery vehicles, nanoreactors and scaffolds for biological conjugation. Obviously, surface functionalization of the vesicles has been an effective route to make vesicles meet different requirements in a variety of applications. As we will see below, introducing host–guest interaction on the vesicular surface is a very simple and fruitful way for this purpose.

If CD is modified with long hydrophobic chains on one face, the structure itself becomes an amphiphile and can form vesicles in aqueous solution,[35] the resultant CD cavities are then ready for further modification through host–guest interactions. Guo and Jiang reported that a rigid, hydrophobic polymer chain, polyether imide (PI), with β-CD at both its ends easily self-assembled into vesicles, which typically contained about 1000 PI chains (Fig. 14a). The β-CD cavities on both the inner and outer surfaces are available for the vesicle modifications.[36] PEG with ADA at one of its ends was selected as the guest. The PEG modification to vesicles was monitored by DLS and ITC (isothermal titration calorimetry). The results showed that for shorter PEG chains (MW = 1.1k and 2k), the modification had two distinct steps: a fast one for the outer surface followed by a slow one for the inner surface. Thus it became possible to realize asymmetric modifications, *i.e.* small molecular guests such as ADA derivatives were added once the outer surface was modified by the PEG chains. Then the inner surface would be exclusively modified by ADA. In addition, for the short PEG chains, the β-CD cavities could

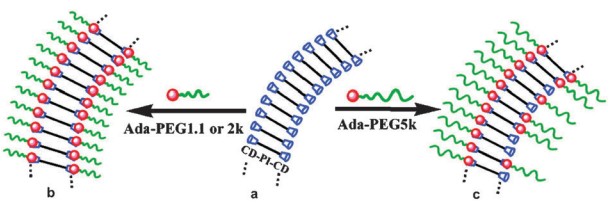

Fig. 14 Schematic representation of the surface modification process of the vesicles of β-CD-ended PI.[36]

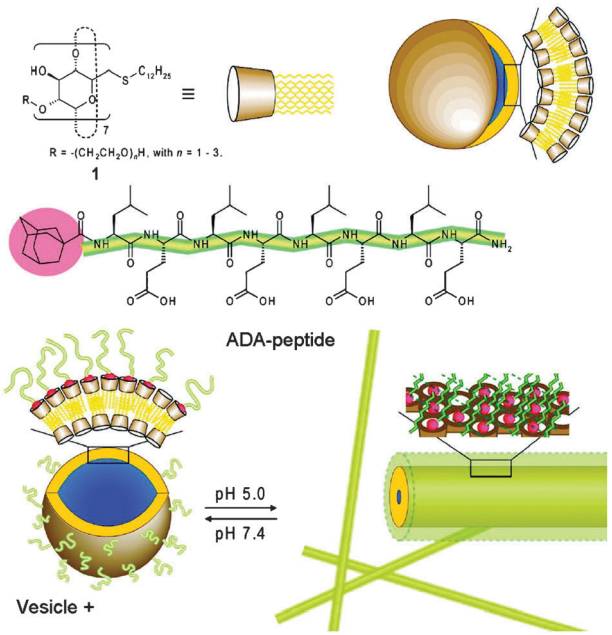

Fig. 15 Inclusion-complexation-assisted transition from vesicles to fibers.[37]

be almost quantitatively occupied; while for PEG with high MW (5k), the inner β-CD cavities could only be occupied partially as the PEG chain is too long to penetrate the PI membrane smoothly.

For the NCCMs mentioned in section 2.2.2, surface modification was performed by using a fluorescent chromophore 8-anilino-1-naphthalene sulfonate (ANS) as the guest.[21] The fluorescent intensity of ANS was found to apparently increase when it was added to the NCCM solutions, indicating that it moved from water to the hydrophobic cavities of β-CD. It was also observed that the fluorescent intensity of the solution decreased when non-fluorescent guests with a higher binding ability (for example, ADA) were added. This is attributed to ANS returning to water by being expelled from the β-CD cavities by ADA. Thus for such vesicles with the CD hosts on the surface, the modification is versatile leading to different functionalities.

Surface modification *via* inclusion complexation could assist morphological transition, as recently reported by Ravoo and Kros *et al.*[37] When a synthesized ADA-modified octapeptide was added to a CD-covered vesicle solution, which was prepared from dodecyl modified amphiphilic β-CDs, then the octapeptides attached to the vesicle surface at pH 7.4 through inclusion complexation. When the pH was switched to 5.0, the octapeptides had a strong tendency to form β-sheets, resulting in a transition of the vesicles into fibers (Fig. 15). Although this vesicle to fiber transition was not induced directly by inclusion complexation, it is the non-covalent linkage that enables the peptide to cover the surface of the assembly and makes this vesicle to fiber transition possible.

Inclusion complexation is also useful to reversibly conjugate proteins or carbohydrates onto vesicle surfaces without any disturbance of their biological activity. For this purpose, enzyme horseradish peroxidase (HRP) was covalently conjugated to ADA, and further anchored onto the surface of polymersomes with retained catalytic activity by inclusion complexation.[38] As the extracellular surfaces of most prokaryotic and eukaryotic cells display a dense layer of carbohydrates, which is commonly known as "glycocalix", carbohydrate modified vesicles could serve as an artificial "glycocalix" model to study carbohydrate–protein interactions during cell–cell and cell–matrix communications. Targeting such an artificial "glycocalix", vesicles of dodecyl-modified amphiphilic CDs were constructed and then their surface was attached by ADA-conjugated carbohydrates *via* β-CD–ADA interactions (Fig. 16).[39] Loading of the carbohydrate to the vesicles was proved successful *via* agglutination test with lectins, which had a specific binding ability to carbohydrates and thus led to the aggregation of the artificial "glycocalix". Furthermore, this binding between the carbohydrates on the vesicle surface and lectins was reversible as demonstrated by addition of competitive carbohydrate inhibitors such as mannose, which can occupy the binding sites on lectins; or by addition of β-CD, which competed with the vesicles to bind the ADA-conjugated sugars. Such work shows that self-assembly based on amphiphilic CDs may provide a alternative platform to mimic the microenvironment for the study of various signal transduction processes on cell surfaces, mediated by molecular recognition processes involving different types of carbohydrates and other kinds of small molecules.

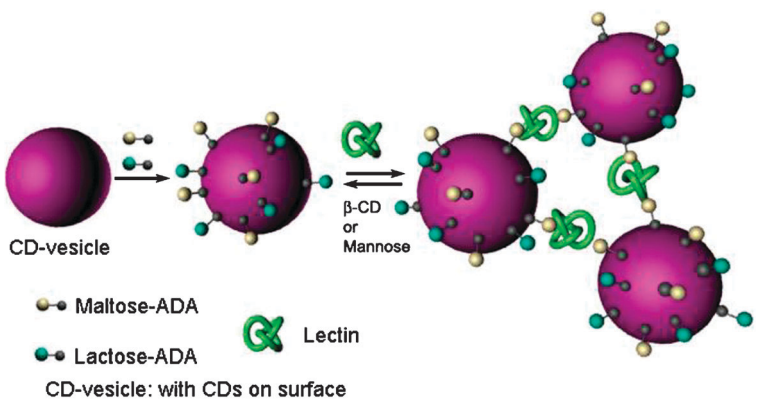

Fig. 16 Vesicles with carbohydrates on surface *via* inclusion complexation and their reversible aggregation.

5. Polymeric networks and hydrogels based on inclusion complexation

5.1 Supramolecular structures with inclusion complexation crosslinks

A polymeric hydrogel is a kind of basic soft material with a crosslinked network structure. Stimuli-responsive polymeric hydrogels are currently of great interest and have potential applications in many fields as "intelligent" materials because of their responsiveness to many external stimuli, such as pH, temperature, light, or magnetic fields. The tunable and efficient responsiveness of hydrogels depends on their network structure and crosslink strategies. As non-covalent bonds, inclusion complexation is a suitable method to serve as a reversible crosslinking factor due to its competitive nature. Furthermore, the density of the crosslink points based on inclusion complexation is relatively convenient to estimate, compared to other popular physical crosslinks such as the hydrophobic domains of polymers or microcrystals of threaded CDs. In this section, we will present recent progress in stimuli responsive, and even reversible hydrogels that use inclusion complexes as crosslinks.

Fig. 17 depicts some typical approaches to hydrogel or network structures, employing inclusion complexation as the crosslinking strategy. (a) Two linear polymers comprising respective host (*e.g.* β-CD) and guest (*e.g.* ADA) as side groups form networks in water.[40] (b) Two multi-arm star polymers with respective end groups of β-CD and cholesterol derivatives connect to each other forming a hydrogel due to the interaction between β-CD and cholesterol moieties.[41] (c) Bridged CDs (two CDs covalently linked *via* a very short chain) were proven to be able to crosslink linear random copolymers of NIPAM and ADA-containing units, leading to gel formation.[42] Such bridged CD caused a remarkable LCST decrease of the copolymer from 35 °C to around 15 °C as a result of the restriction to the mobility and solubility of the polymer. (d) γ-CD can include double strand linear poly-(ethylene imine) (LPEI) because of its wide cavity. When γ-CD was mixed with (PEO-*b*-LPEI)-*g*-dextran, a double strand complex of γ-CD and LPEI grafts formed at pH 10 leading to networks. When the pH value was adjusted to 4, LPEI was protonated, thus, γ-CD could not remain threaded on the LPEI chain, leading to an obvious viscosity decrease.[43] (e) Free CDs can form a CD tube after crosslinking reaction by epichlorohydrin.[44] Then the resultant CD tube can accommodate two long alkyl chains from both its ends serving as a cross-linker. Therefore, a polymeric network was formed by addition of the α-CD tubes to the solution of PEG monocetylether-*g*-dextran.[45] (f) It is well known that great contributions to supramolecular hydrogels came from CD based PPR, using the microcrystalline area of CDs as a physical crosslink. Based on the great discovery of the "molecular necklace", formed by PEG threading into a series of α-CD.[46] Li, Harada and Kamachi first reported the "sol–gel" transition of α-CD and PEG in aqueous solution in 1994 (Fig. 17f).[47] This discovery initiated broad interest and active research which has continuously progressed in the past fifteen years as recently reviewed.[7] The items (d) and (e) in fact represent examples of such progress with PPR hydrogels. The most significant character of the PPR hydrogel or network is its shear-thinning behavior. Moreover, the PPR hydrogel itself is thermo-reversible. Heating the PEG/α-CD hydrogels results in a homogeneous solution, and the sol returns to gel again after cooling. Such thermo and shearing responsiveness of PPR hydrogels, which are useful for clinical applications as injectable hydrogels have been extensively studied. So in this review, we will focus on the recent progress in reversible stimuli responsiveness and hybrization of the PPR hydrogels.

5.2 Hybrid hydrogels

Hybrid organic–inorganic hydrogels have drawn a great deal of interest recently, as they provide enhanced mechanical or rheological properties as well as new functionalities resulting from the various introduced inorganic species, which include silica particles, quantum dots, carbon nanotubes, exfoliated graphenes, *etc*. It is very interesting to note that for most of the hybrid hydrogels reported, the inorganic species were mainly introduced by supramolecular means, *i.e*. hydrophobic interactions and host–guest interactions between the organic matrix and the inorganic moiety. A pioneer work in this newly emerging area was reported by Harada *et al*.[48] (Fig. 18). β-CD-coated single walled carbon nanotubes (Py-β-CD/SWNT)

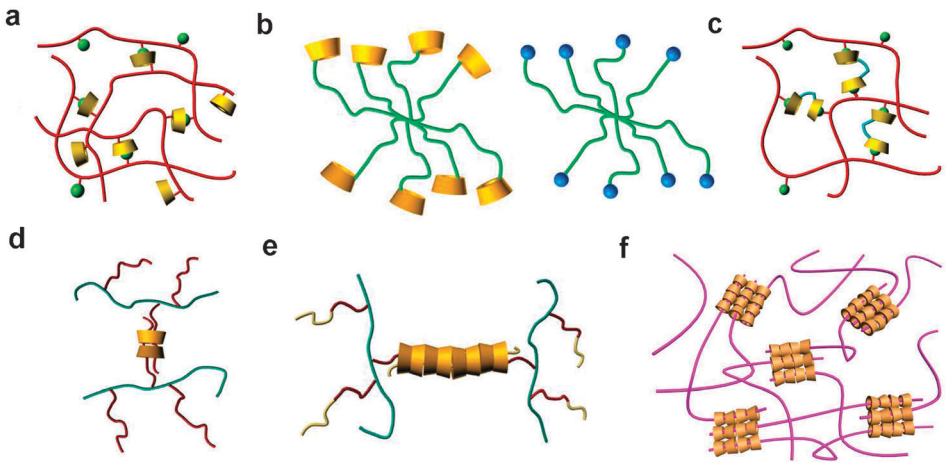

Fig. 17 Supramolecular structures formed by inclusion complex crosslinks.

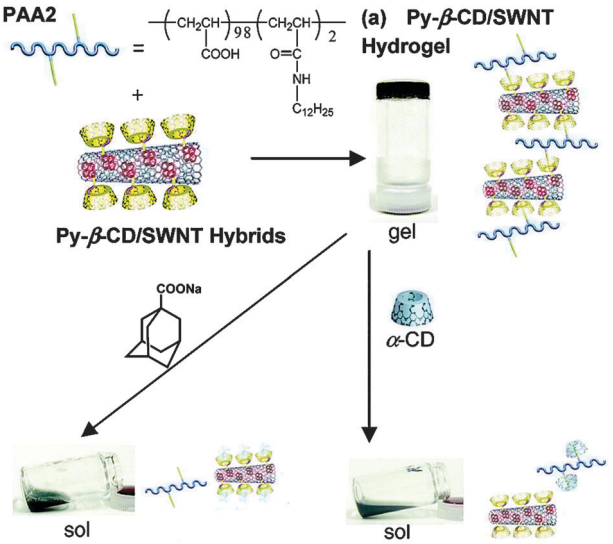

Fig. 18 Supramolecular hybrid hydrogel with SWNT and its "gel–sol" transition by supramolecular substitution.[48]

were found to be able to connect dodecyl-modified polyacrylate (PAA2) by inclusion complexation between the β-CD and dodecyl grafts. This resulted in the formation of a hydrogel. This hybrid hydrogel with homogeneously dispersed SWNTs showed a chemical-responsive property, *i.e.* a "gel–sol" transition took place when a competitive host α-CD or guest ADA carboxylate (ADA-COONa) was mixed with the hydrogel.

SWNTs were also introduced to α-CD/PEG based hydrogel by Chen *et al.*[49] Here SWNTs were coated with PPG blocks of Pluronic copolymers (PEG-*b*-PPO-*b*-PEG) and stabilized by the PEG blocks. Mixing these modified SWNTs with α-CD accelerated the formation of hydrogel based on α-CD/PEG. To some extent, it was unexpected that the viscosity and storage modulus of hybrid hydrogels would decline with an increase of SWNTs. Similarly, graphene sheets coated by the Pluronic copolymer were employed to construct a hybrid hydrogel when they were mixed with α-CD.[50] The hybrid hydrogel containing graphene sheets also possesses lower viscosity and strength compared with the native ones.

As generally stated in the literature, for all of the PPR hydrogels based on linear homopolymer PEG, relatively high-molecular-weight (MW $>$ 10k) PEG is necessary, because low-molecular-weight (LMW) PEG (MW $\leq$ 2k) only leads to precipitation with α-CD. However, a LMW PEG is more favorable than HMW PEG in medicinal use as the former can penetrate the human kidney membrane. In order to attain PPR-hydrogel from LMW PEG, Guo and Jiang introduced another crosslinking factor, β-CD functionalized silica nanoparticles (β-CD@SiO_2), into the system (Fig. 19A). ADA mono-ended LMW PEG (ADA-PEG, MW = 2k) chains were attached to the β-CD@SiO_2 particles forming water-soluble hybrid particles. When native α-CDs were then added to the particle solutions, as one end of the PEG has been blocked by β-CD@SiO_2, α-CD threaded onto the chain only from the other end. Here the physical aggregation of the threaded α-CDs and the hybrid particles cooperated with each other to promote the hydrogel formation based on LMW PEG

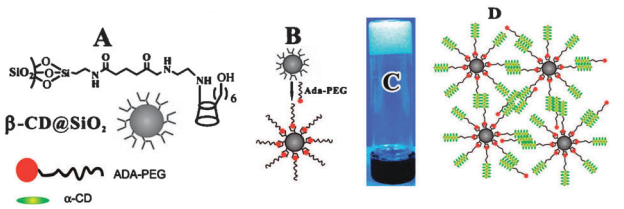

Fig. 19 (A) Chemical structure and (B) schematic representation of β-CD@SiO_2 and its inclusion complex with ADA-PEG. (C) Optical photo and (D) schematic representation of the supramolecular hydrogels made of ADA-PEG2K, α-CD, and β-CD@SiO_2.[51] Reproduced with permission of American Chemical Society from ref. 51.

(Fig. 19). In contrast to the hydrogels containing SWNTs and graphene, the present hybrid hydrogel exhibited a much higher modulus and viscosity than the native ones. In all these studies mentioned above, the functionalized inorganic moieties could be regarded as 'supercrosslinks' because each of the particles connects many polymer chains *via* supramolecular interactions.[51]

Very recently, we constructed a new type of hybrid hydrogel composed of CdS quantum dots and block copolymers based on the 'supracrosslink' concept.[52] As shown in Fig. 20, AZO end-functionalized block copolymer PDMA-*b*-PNIPAM (PDMA, poly(*N*,*N*-dimethylacrylamide)) and β-CD modified CdS quantum dots (β-CD@QD) formed hybrid complex due to inclusion complexation. This 'supracrosslink' contains a QD as the core, the block copolymers as the shell with the PNIPAM block as the outer layer. Hydrogels formed easily upon heating the aqueous solution of the complex at a concentration of or above 7% (weight), as a result of PNIPAM aggregation occurring above the LCST. The inclusion complex and the domains of the collapsed PNIPAM chains serve as two distinct crosslinks which give the hydrogel excellent dual sensitivities: first, "gel–sol" transition takes place when a stronger guest such as ADA or a stronger host such as α-CD are mixed with the hydrogel, and second, reversible "gel–sol" transitions can also be realized by temperature adjustment across the LCST of PNIPAM.

5.3 Photo-switchable "sol–gel" and "gel–sol" transitions

Photo-switchable reversibility of PPR hydrogels of α-CD and PEG was realized solely by a supramolecular method. For this purpose, we designed and synthesized a water soluble AZO pyridinium salt AZO-N^+ (Fig. 21).[30] When this AZO-N^+ compound was mixed with the PPR hydrogel, since the AZO unit possesses a much greater ability to form inclusion complexes with α-CD than the PEG unit did, the threaded CD molecules were gradually pulled off leaving the PEG molecules as free chains. This made the physical gel become a transparent solution in a few minutes. As we mentioned earlier, *cis*-AZO cannot bind to α-CD, so UV light irradiation to the solution made the AZO–CD complex dissociate and then α-CD molecules returned to the PEG chains, which reconstructed the hydrogel. However, this process took a few hours. The subsequent visible light irradiation, as expected, caused the gel dissociation again. Such "gel–sol–gel" transitions were achieved for several cycles without any disturbance due to

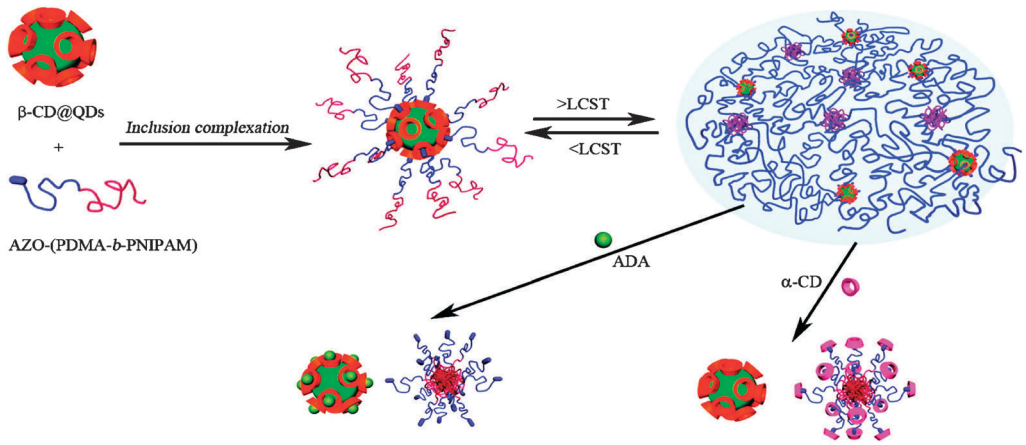

Fig. 20 Dual responsive hydrogel with a hybrid supracrosslink and its corresponding dual "gel–sol" transitions.[52]

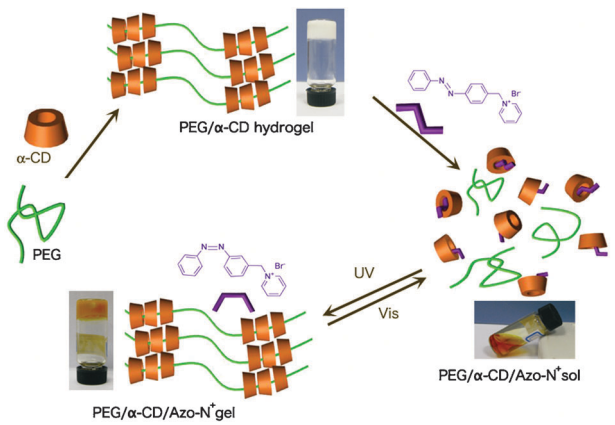

Fig. 21 "Gel–sol–gel" transitions driven by competitive inclusion complexation: (clockwise from left) free PEG; PEG/α-CD hydrogel; PEG/α-CD/Azo-N^+ sol after UV irradiation; gel after UV light irradiation.

the light initiated clean transformation of AZO. The photoreversible PPR hydrogels were simply achieved *via* competition between three pairs of host–guest interactions. This study proved that the strength of the interactions is in the sequence of *trans*-AZO-N^+/α-CD > PEG/α-CD > *cis*-AZO-N^+/α-CD. This success in achieving reversibility shows the great importance and potential of the materials controlled by inclusion complexation.

6. Outlook

We have demonstrated recent advances of the fruitful ten-year marriage between macromolecular self-assembly and supramolecular chemistry based on inclusion complexation. However, the influence and promotion of supramolecular chemistry to macromolecular self-assembly achieved so far is still far from sufficient. Among the large accumulation of knowledge and data in supramolecular chemistry, only a very small part has been noticed and employed in macromolecular self-assembly. Great challenges remain for polymer scientists to explicate the established supramolecular concepts in macromolecular matrixes and further develop multiple non-covalent interactions in complicated systems such as biological environments. With this goal, and given that inclusion complexation is mainly driven by hydrophobic interactions, the effectiveness of well-known principles, such as the size-shape fit concept and competitive binding ability in macromolecular systems, systematic work in future research is required. In addition, the effects of the macromolecular environment on the interactions need to be explored further. Based on the results achieved so far for constructing various polymeric assemblies caused by supramolecular chemistry, one should consider more sophisticated designs of supramolecular materials with, for example, dedicated and even logic multi-responsiveness, directed by supramolecular principles.

Illustration of graphical abstract

The graphic abstract is inspired by a Chinese fairy tale about *Altair* and *Vega*. In the story, they were a loving couple separated by the Milky Way. They were allowed to meet each other only once a year when magpies made a bridge across the Milky Way. To us, supramolecular chemistry and macromolecular self-assembly look like the couple. The two research fields are easy to see each other but hard to meet. Now, inclusion complexation based on cyclodextrins builds a broad bridge for their fruitful reunion.

Acknowledgements

We thank National Natural Science Foundation of China (NNSFC No. 20834004, 20904005 and 20774021) and Ministry of Science and Technology of China (2009-CB930400 and 2011CB932503) for financial support.

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