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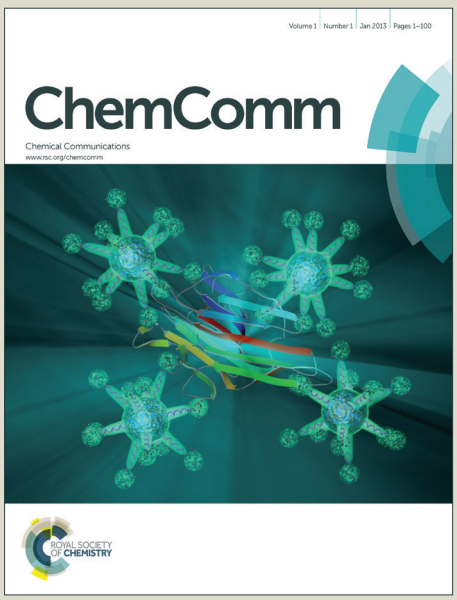

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Nanoassemblies driven by cyclodextrin-based inclusion complexation

Cite this: DOI: 10.1039/xoxxoooooox

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Received ooth January 2012,
Accepted ooth January 2012

DOI: 10.1039/xoxxoooooox

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Nanoscaled supramolecular systems have attracted significant attention because of their promising applications in many fields. This review focus on recent advances in the construction of nanoassemblies driven by cyclodextrin (CD)-based inclusion complexation and their application in biomedical and biomimetic filed. As a result of the reversibility of the CD-based host-guest interactions, CD-based driving forces provide the opportunity to generate complex and sophisticated nanoassemblies with tunable properties.

1 Introduction

Nanoparticles, such as micelles, vesicles, and nanogels are of great interest because of their wide application in fields of biosensing and bioimaging,[1, 2] drug and gene delivery,[3] electronics,[4] energy production[5, 6] and regenerative medicine.[7] Self-assembly is an enormously powerful technology for the preparation of nanostructures. The term self-assembly refers to quite a fascinating phenomenon where unassociated, disorderly objects come together in some fashion to form organized structures without any external stimuli.[8] Nanoassemblies exhibit unique chemical and physical properties, and can be used as nanomedicine, sensors, reactors and other novel devices. Among the various self-assembly process, one of the most extensively studied subject was the self-assembly of block or graft copolymers, in which incompatible polymer chains are connected covalently.[9-12] The driving force of such self-organization was the intramolecular repulsion between incompatible segments. But in recent year, using intermolecular non-covalent interactions as the major driving forces to prepare nanoassemblies have drawn much attention due to the simplicity of the preparing process, broadness of the available materials. Moreover, the reversibility of noncovalent interactions has allowed the incorporation of reversible and switchable functionality into nanassemblies. Non-covalent interactions include hydrogen bonding,[13] π-π interactions,[14] van der waals interactions,[15] ionic and dipolar interactions,[16] hydrophobic forces,[17] and host-guest interactions.[18] In this minireview, we review the current progress in studies on nanoassemblies driven by cyclodextrin (CD) based host-guest recongnitions and the application of these nanoassemblies. The topic about cyclodextrin-based materials has been reviewed several times from different points of view, for example, cyclodextrin-based inclusion complexation was the bridge to connect two different fields. [19] This article focuses on the nanoassemblies which formed driven by inclusion complexation between CD and the guests. Meanwhile the suparmolecular assemblies modified with CDs will not be covered.

In host-guest systems, the host molecules can spatially accommodate a variety guests through noncovalent interactions. There are numbers of synthetic receptors act as host molecules that inherent a cage-like supramolecular structure such as CD, cucurbit[n]uril (CB[n]),[20] cyclodextrins,[21] cyclophanes,[22] calixarenes,[23] and crown ethers[24, 25]. CDs are one of the most widely used hosts owing to their extremely low toxicity and wide availability. Cyclodextrins (CDs) are a series of natural cyclic oligosaccharides composed of 6, 7, or 8 D-glucose units linked by 1, 4-glycosidic bonds, and name α-CDn, β-CD, or γ-CD respectively. The physical structure of cyclodextrin is a torus shaped molecule that has a hydrophilic exterior and a relative hydrophobic core.[26-28] CDs are capable of including a variety of compounds ranging from small molecules, ions, proteins, to polymers with high selectivity. According to the type of guest molecules and driven forces, the formation of CD-based nanoassemblies can be classified as 1) driven by inclusion complexation between CD units and hydrophobic groups, and 2) driven by inclusion complexation CD molecules and polymer chains.

2 Nanoassemblies formation via interations between CD units and hydrophobic groups

The inclusion complexation between CDs and various small molecular guests has been extensively in supramolecular chemistry. Introducing CDs and guest moieties onto polymer chains, or inorganic particles can result in the formation of reversible, high-rider morphologies like micelles and vesicles.

2.1 Organic nanoassemblies

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The micellization of amphiphilic macromolecules is the most common way to produce nanoassemblies. Recently, novel "block copolymer free" strategies have been established for micellization of polymers. Homopolymers, dendrons etc. were connected by interpolymeric interactins, resulting in the formation of noncovalently connected micelles (NCCM) or vesicles. Inclusion complexation was introduced to construct NCCM since 2006.[29] Due to the inclusion complexation between CD and many guests are sensitive to external stimuli, the resultant nanoassemblies showed stimulus-response reversibility.

2.1.1 pH- responsive nanoassemblies

pH is an important environmental factor in typical physiological, biological and chemical systems, and can be manipulated easily in many applications. Consequently, pH-sensitive supramolecular materials, such as nanoassemblies have attracted a broad range of interest.

Generally, pH-responsive nanoassemblies are achieved by introducing pH-sensitive component, such as polyelectrolytes, and acid-labile groups into the system. For example, Alexander et al. constructed a pH-responsive hierarchical supramolecular assembly from a cyclodextrin vesicle and an adamantine (ADA)-modified octapeptide.[30] At pH 7.4, the octapeptides attached to the vesicle surface through inclusion complexation between β-CD and ADA. When the pH was switched to 5.0, the octapeptide changed from random coil to *β*-sheet domains, leading to a transition of the vesicles into fibers (Figure 2.1).

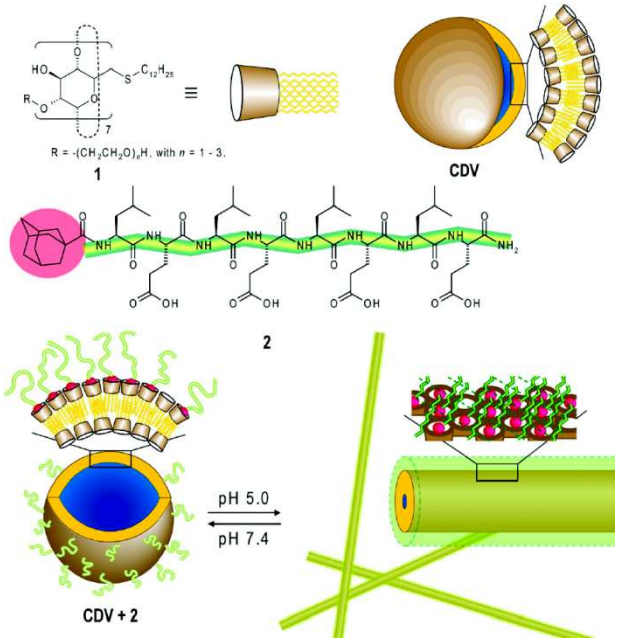

Figure 2.1 The Chemical Structures of the *β*-CD Derivative (**1**), Which Self-Assembles into Cyclodextrin Vesicles (CDVs), and the Adamantane Modified Octapeptide (**2**), Which Binds to the CDV.[30]

Hao et al. reported pH-responsive vesicle-like particles around 120 nm based on inclusion complexes between γ-hydroxybutyric-β-CD and methyl orange (MO).[31] These vesicles had orderly bilayered membranes with the hydrophobic parts (methyl subunit) inside the bilayers and hydrophilic parts (CD subunit) facing the inner and outer aqueous solution medium. After addition of acid, MO showed a visual transition (changing color from yellow to red, and tertiary amine was protonated into ammonium. As the results, the color of nanoassemblies changed, and vesicle-like structure was destroyed.

2.1.2 Photo-responsive nanoassemblies

Light is a very important remote stimulus. It has two advantages: 1) it can be remotely applied for a short period of time with high spatial and temporal precision; 2) it provides a wide range of adjustable parameter, such as wavelength, duration, and intensity. Using the photocontrolled inclusion and exclusion reaction of azobenzene (Azo) with CD, reversible photocontrol of the self-assembly of nanoparticles can be realized.

Zhang et al. fabricated supramolecular assemblies composed of AZO-containing surfactants and α-CDs. As shown in Figure 2.2, under alternating vis and UV irradiation, the α-CD binded with AZO or slid onto the alkyl chain. The amphiphilicy of the supramolecules was subsequently changed, resulting in the formation and dissociation of vesicle-like aggregates.[32]

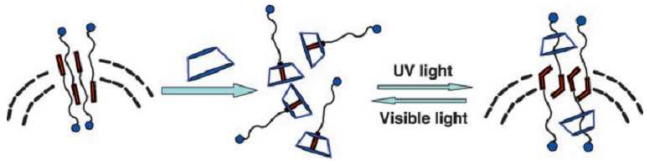

Figure 2.2 Photocontrolled reversible supramolecular assembly of AZO-containing surfactant with α-CD. Red bar: ZAO, blue spot: pyridinium group.[32]

Zhou and coworkers reported a kind of photoresponsive vesicles constructed by the noncovalent coupling between a hydrophobic hyperbranched poly(3-ethyl-3-oxetanemethanol) with an apex of an AZO group (AZO-HBPO)and a hydrophilic hyperbranched polyglycerol with an apex of a β-CD (CD-HPG).[33] Under the visible light irradiation, an amphiphilic supramolecular dendrimer (HBPO-*b*-HPG) was formed through the AZO/CD host-guest interaction and such amphiphilic supramolecules can further self-assemble into unilamellar bilayer vesicles with a narrow size distribution. Under the irradiation of UV light, the photoisomerization of AZO from the *trans* to *cis* form induced dissociation of the inclusion complex, which induced the scission of the supamolecular HBPO-*b*-HPG. Thus the vesicles disassembled (Figure 2.3). The assemlby and disassembly can be reversibly controlled under alternating vis and UV irradiation.

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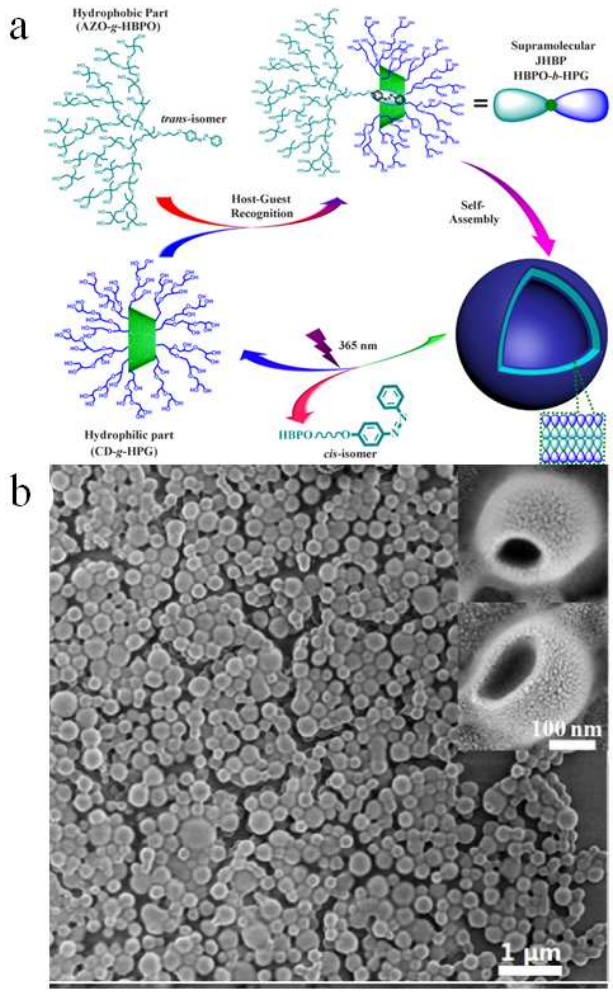

Figure 2.3 (a) Self-assembly and disassembly processes of the supramolecular vesicle and (b) SEM images of the particles.[33]

Our group developed a kind of photoreversible micelles by combination of sodium alginate (Alg), tetradecyltrimethylammonium bromide (TTAB), α-CD, and 4-(phenylazo)benzoic acid (PBA).[34] The micelles were formed under visible light but disrupted under UV light illumination as a result of the competition of host-gust interactions between α-CD, AZO and alkyl chains. It should be noted that all the components of these photoresponsive composites are commercially available components.

Using light-responsive CD-AZO interactions as driving forces, reversible and large-scale cytomimetic vesicle aggregation was also be realized by Yan et al.[35] Firstly, vesicles functionalized with β-CD or AZO was prepared respectively. The two kinds of vesicles then aggregated through multivalent intervesicular host-guest interactions between the CD and AZO groups (Figure 2.4a). By the means of real-time observation, content mixing assays, and component mixing assays, it was found that the membrane fusion is accompanied by the vesicle aggregation process (Figure 2.4b). The visicle aggregation process was not highly efficient, but also totally reversible under alterating irradiation with UV and Vis light.

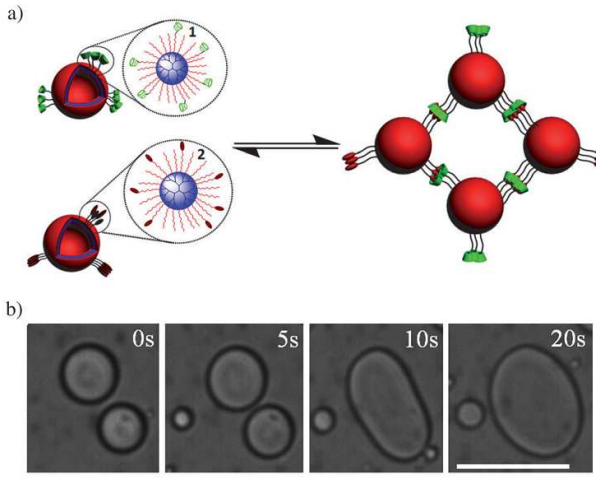

Figure 2.4 a) Reversible aggregation of. vesicles functionalized with β-CD and AZO b) Real-time fusion sequences of two giant vesicles.[35]

2.1.3 Redox-responsive/Voltage-Responsive nanoassemblies

As basic chemical reactions, a tremendous number of redox reactions take place in living systems and the outside environment. Using redox reactions to modulate material properties has received considerable attention.

It is well known that β-CD can interact with ferrocene (Fc) and its derivatives to form 1:1 inclusion complexes, but cannot include the oxidized Fc to form inclusion complexes because of the mismatch between the host and guest. Using the redox-responsive interactions between β-CD and Fc, many reversible nanoassemblies were developed in recent year.

For instance, Hao's group developed a serious of oxidizing-responsive vesicles, which made from supramolecular amphiphiles based on inclusion complexes between Fc derivatives and β-CD.[36] As shown in Figure 2.5, the Fc-containing molecule recognized β-CD by the Fc moiety, and this complex acted as a supramolecular amphiphile and formed vesicles. After the oxidization, the breakaway of β-CD disassembled the vesicles.

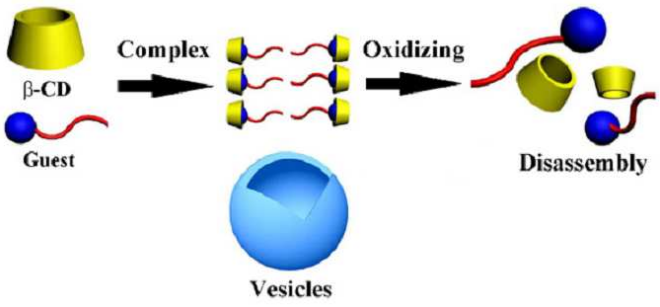

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Figure 2.5 Illustration of the oxidizing-responsive controlled assembly and disassembly of Fc derivatives and β-CD.[36]

When conducting electrical stimuli, a certain magnitude of voltage or current is applied to induce a redox reaction of Fc. Compared with the redox stimuli, the electrical stimuli can reduce the redox reaction of the system without bringing any redox pollution, making it favourable to be applied in industry and biological systems. Yuan and coworkers reported voltage-responsive vesicles and micelles based on the assembled of hydrophobic homopolymer with β-CD end-decoration and hydrophilic homopolymer with Fc end-decoration.[37, 38] Through the host-guest interactions between β-CD and Fc, the two homopolymers connected together, forming a supramolecular amphiphile. Such amphiphiles can further self-assemble into vesicles or micelles. The assembly and disassembly of the vesicles or micelles could be reversibly tuned through electrochemical control voltage. Figure 2.6 showed the schematic of the voltage-responsive controlled assembly and disassembly of vesicles. Voltage-controlled drug releasing based on these systems was also conducted successfully.

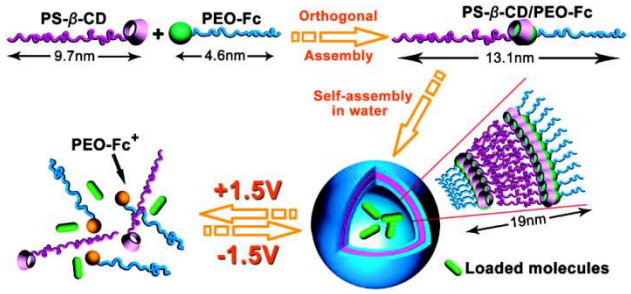

Figure 2.6 Structure of PS-*β*-CD and PEO-Fc and illustration of the voltage-responsive controlled assembly and disassembly of PS-*β*-CD/PEO-Fc supramolecular vesicles.[37]

Recently, Yuan et al. also developed another kind of brush-like supramolecular copolymer based on the side chain reversible host-guest interactions between β-CD and Fc. This kind of supramolecular polymer brushes can further self-assemble into micelles in aqueous that exhibit reversible assembly and disassembly behavior under an electrochemical redox trigger, which opens up a new route to building dynamic block copolymer topologies.[39]

2.1.4 Thermoresponsive nanoassemblies

Inclusion complexation could induce thermoresponsive formation of nanoassemblies because the ability of CD with many guests has enthalpy driven nature.

As shown in Figure 2.7, Osakada and coworkers demonstrated that amphilies with an alkyl group formed a water-soluble pseudorotaxane with α-CD below 60 °C.[40] Since this structure is highly entropy-dependent, the amphiphile slid out of the α-CD cavities and formed micelles at a high temperature.

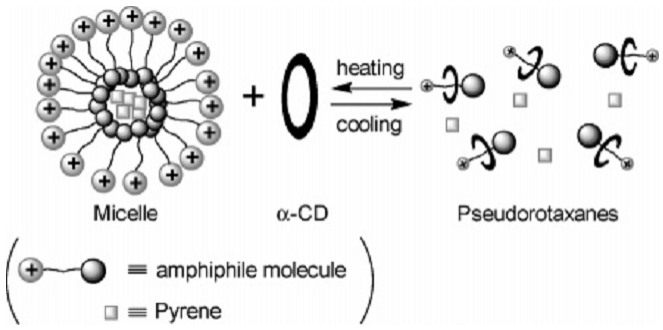

Figure 2.7 Illustration of the thermo-responsive formation and dissociation of amphilies/α-CD micelles.[40]

2.1.5 CO_2-responsive nanoassemblies

Carbon dioxide (CO_2), as an important endogenous cell metabolite with good biocompatibility and nontoxic nature, is a promising candidate as stimuli agent. So far, to develop a kind of CO_2-resonsive host-guest supramolecular system and exploration of how a gas can affect the self-assembly mechanism is still quite challenging.

Zhao's group developed a new kind of class of supramolecular block glycopolypeptides to simulate the component of natural viral capsids and their controllable self-assembly and disassembly process by CO_2 trigger.[41] As shown in Figure 2.8, the end-functionalized biopolymers dextran β-cyclodextrin distal (Dex-CD) was noncovalent orthogonally coupled to a benzimidazole terminal poly(L-valine) through the CD/BzI host-guest interactions. The CO_2-cleavable CD/BzI host-guest block junction modulates the biomimetic virus-like assemblies to display a reversible assembly and disassembly process tuned by CO_2. It is expected that these tunable nanoparticles will allow researchers to better mimic cytomembranes and understand cellular functions

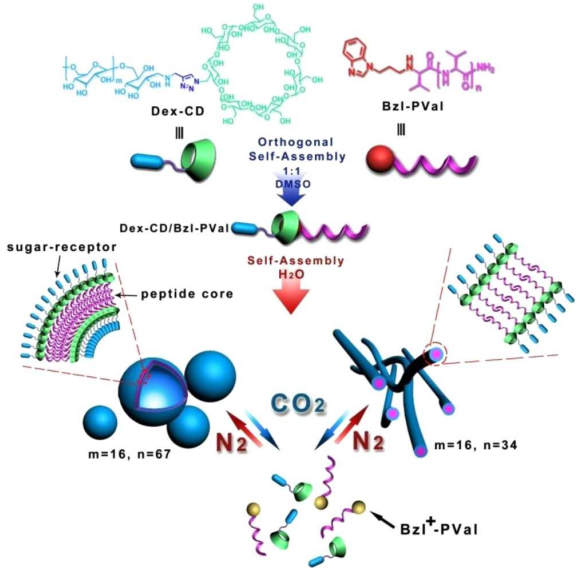

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Figure 2.8 Schematic illustration of the CO_2-switchable assembly and disassembly behavior mimicking the diversiform viral capsids.[41]

2.1.6 Multi-responsive nanoassemblies

In nature, the feed back behaviors generally occur due to a combination of multiple factors. Therefore, systems that can respond multi-stimuli would be of great interest and generate more flexibility for application.

Mutil-responsive nanoassemblies can be elegantly fabricated by linking polymers having inherent stimuli-sensitive properties using the stimuli-responsive inclusion complexation beween CD and guest moites. Jiang's group reported a dual reversible self-assembly of PNIPAM-based non-covalently connected amphiphiles formed by host-guest interactions between β-CD and AZO.[42] Dendrons with Azo-head groups was hydrophobic building blocks and β-CD ended linear poly(N-isopropylacrylamide) (β-CD-PNIPAm) was hydrophilic block. The formed non-covalently connected amphiphile was able to self-assembled into bilayer vesicles in water. As shown in Figure 2.9, optical switching of the assembly and disassembly was realized by alternating vis and UV irradiation because of the photoswitchable AZO-cyclodextrin interactions. Due to the thermal induced coil-globule transition of the PNIPAM chains, the vesicles also showed reversible formation and dissociation in respond to heat stimuli.

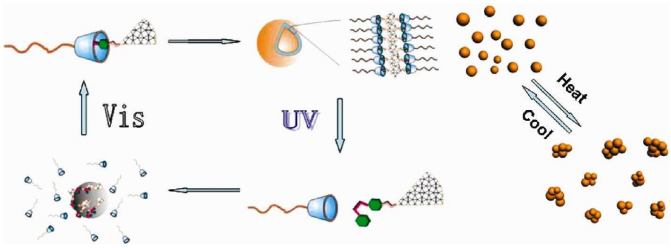

Figure 2.9 Schematic illustration of the photoswitchable self-assembly and disassembly and the temperature-responsive properties of the non-covalently connected amphiphiles.[42]

Liu et al. reported a pH- and thermo-responsive double hydrophilic diblock copolymer connected by inclusion complexation between β-CD and adamantly (Ad) moieties.[43] The β-CD-PNIPAM was used as a thermoresponsive building block and Ad-terminated poly(2-(diethylamino)ethy methacrylate) (Ad-PDEA) was used as a pH-responsive building block. At room temperature, the supramolecular PNIPAM-PDEA molecularly dissolved at pH<6 and formed PDEA core micelles at pH>8. In acidic media, vesicular nanostructures were formed at temperatures above the lower critical solution temperature (LCST) of PNIPAM (Figure 2.10).

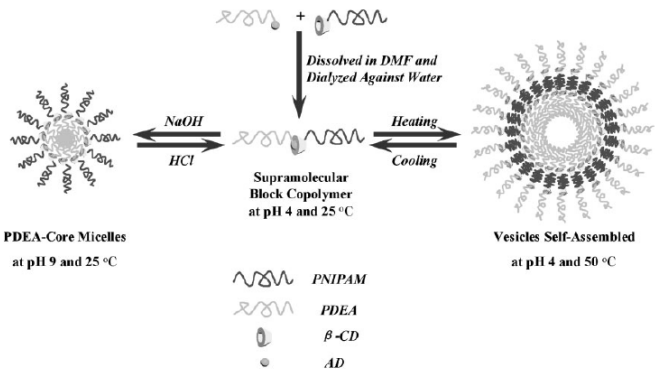

Figure 2.10 Schematic illustration of assembly and disassembly of pH- and thermo-responsive double phydrophilic dibolck copolymer.[43]

Recently, Yuan et al. developed a kind of stimuli-responsive ABC triblock copolymer poly(N-isopropylacrylamide)-blockpoly(ε-caprolactone)-block poly(N,N-dimethylaminoethyl methacrylate) (PNIPAM-*b*-PCL-*b*-PDMAEMA), in which PNIPAM was connected with PCL through thiol−ene Michael addition, while PDMAEMA was linked with PCL by the molecular recognition between β-CD-based host in PDMAEMA and Ada-modified guest in PCL.[44] The amphiphilic triblock copolymer could self-assemble into vesicular micelles in water. By tuning the level of CO_2 and temperature, reversible variation on the morphology and size of the assembly could be achieved (Figure 2.11).

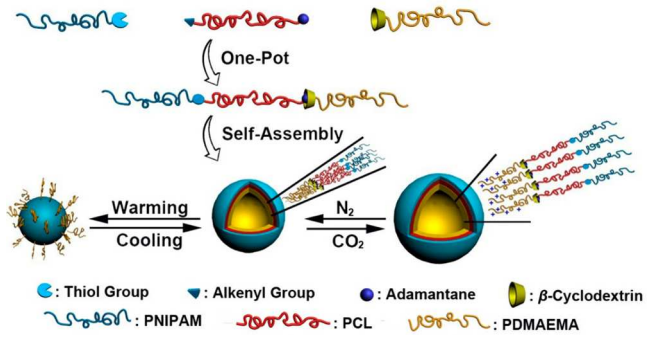

Figure 2.11 Schematic illustration of the CO_2 − Temperature dual stimuli-responsive process for the self-assembly and disassembly of the triblock copolymer.[44]

2.2 Hybrid nanoassemblies

Hybrid organic-inorganic nanoassemblies have drawn a great deal of interest as they may provide new functionalities resulting from the various introduced inorganic species.

Our group developed a kind of vesicular gold aggregates assembled through host-guest interaction between β-CD and Ad moieties.[45] Firstly, β-CD covered gold nanoparticles. Then Ad-modified PEG and PNIPAM were introduced on the surface of gold nanoparticles through inclusion complexation. Due to the thermal induced coil-globule transition of the PNIPAM chains, the hybrid particles became amphiphilicity above the LCST of

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PNIPAM, resulting in the formation of hybrid vesicles. also showed reversible formation and dissociation in respond to heat stimuli. The formation and dissociation of vesicles showed the temperature-dependent behavior (Figure 2.12). Because of the presence of gold such hybrid vesicles show great potential in the areas of therapeutic treatment such as radiofrequency ablation and photothermal therapy.

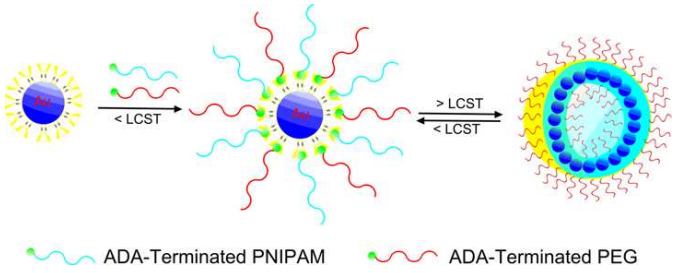

Figure 2.12 Schematic illustration of constructing amphiphilic AuNPs by CD inclusion and thermo-controlled self-assembly of amphiphilic AuNPs with mixed polymer brushes into vesicular structures.[45]

Peng's group developed a kind of PNIPAM-coated gold nanoparticlesby aself-assembly of the AZO-terminated PNIPAM on the surface of α-CD-capped gold particlesvia the host-guest inclusion between AZO and α-CD. The attachment–detachment of AZOe-terminated PNIPAm on α-CD capped Au particles can be reversible controlled using light irradiation, which endowed thermosensitive Au particles with tunable smart properties.[46]

Using the $CaCO_3$ particles as template and the layer-by-layer (LbL) assembly driven by host-guest interaction, hybrid particles with LbL shell were able to be achieved.[47, 48] After removing the carbonate core, LbL hollow microcapsules were obtained. Compared with traditional electrostatic LbL assembly, few high molecular weight polycations, which showed obvious toxicity to organism, were introduced to these kind microcapsules.

3 Nanoassemblies formation via interations between CD and Polymer chains

CDs are able to form inclusion complexes with not only small molecules, but also different kinds of polymers such as polyethers, polyamines, polyesters, conjugated polymers, and polyolefins.[49-51] The CD thread on the polymer chain and the adjacent CD molecules packed closely through hydrogen to form water insoluble channel-like crystallites. These CD-based polymeric systems are called polypseudorotaxanes and polyrotaxanes. Both polypseudorotaxanes and pseudopolyrotaxane structure have been utilized to constructassembly systems, such as nanoassemblies.

Our group developed a novel strategy to construct hollow assemblies via selectively inclusion complexation between CD and the chains of double hydrophilic copolymers.[52-57] Figure 3.1 showed the schematic illustration of the formation of alginate-*g*-poly(ethylene glycol) (Alg-*g*-PEG)/α-CD hollow sphere. Due to the steric fittings, the CDs selectively stacked along the PEG blocks to form rod-like insoluble segments, while the alginate acted as a coil segments. Consequently, water became a selective solvent for the Alg-*g*-PEG/α-CD complexes. So the micelles-like aggregates were formed. The requirement of efficient space-filling packing resulted in that the rod-like blocks packed parallel to form hollow structure.

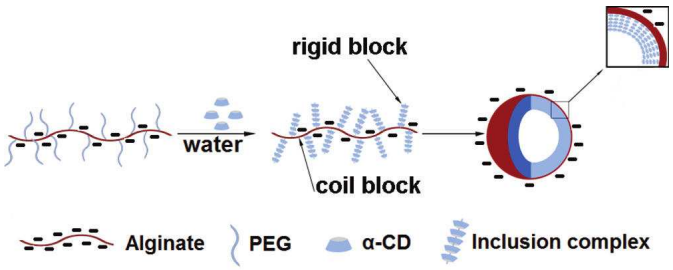

Figure 3.1 Schematic illustration of the formation of the Alg-g-PEG/α-CD hollow sphere.[53]

It was demonstrated that the hollow assemblies could be made from not only graft copolymers, but also block copolymers, such as poly(ethylene glycol)-poly(propylene glycol)-poly(ethylene glycol) (PEG-PPG-PEG) and polyethylenimine-poly(ethylene glycol) (PEI-PEG). Further studies showed that the morphology of PEI-PEG/α-CD assemblies could change from hollow spheres to tubular aggregates by varying the rod-like block fraction (Figure 3.2).

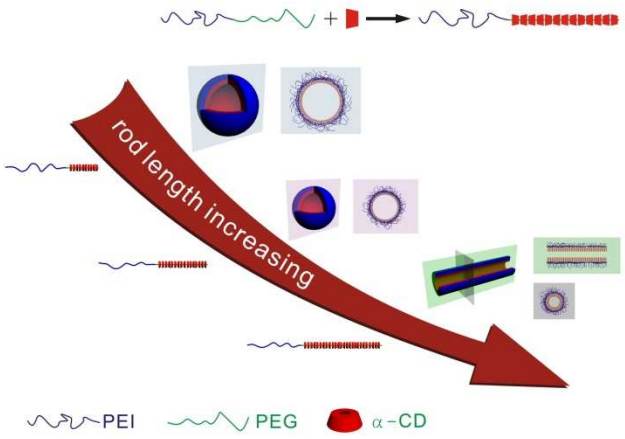

Figure 3.2 Schematic illustration of the formation of the PEI-PEG-α-CD aggregates.[56]

Kim et al. reported mesporous silica particles, which could be used for the controlled release of guest molecules by using a pH-sensitive CD/PEI polypseudorotaxane motif.[58] As shown in Figure 3.3, the pores of silica particles were filled with guest molecules and then blocked by threading of CDs onto the surface-grafted PEI chains at pH 11. At pH 5.5, CDs underwent reversible decomplexation with PEI, leading to the release of guest molecules.

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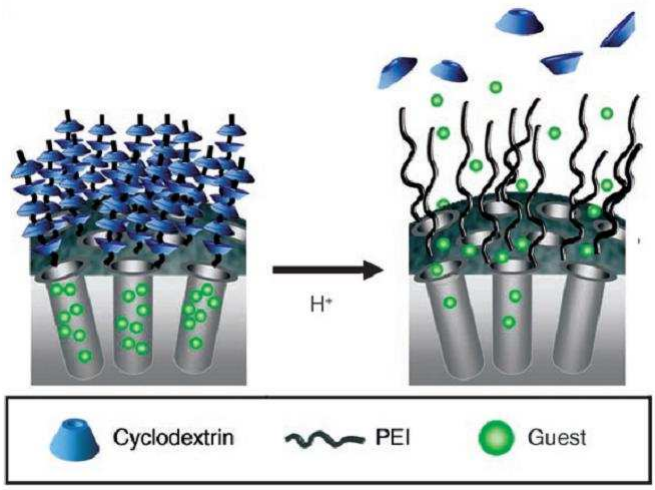

Figure 3.3 Schematic of pH-responsive release of guest molecules from the pores of mesoporous silica particles.[58]

Ren et al used used α-CD as "molecular chaperones" to facilitate the self-assembly of a series of ABA triblock copolymers, poly(2-(dimethylamino)ethyl methacrylate)-*b*-PEG[included by α-CDs]-*b*-poly(2-(dimethylamino)ethyl methacrylate) (DMA-*b*-PEGCD-*b*-DMA), which was synthesized via atom transfer radical polymerization (ATRP) of 2-(dimethylamino)ethyl methacrylate (DMA) initiated by a polypseudorotaxane initiator of bromoisobutyryl-modified PEG and α-CD, in the synthesis of polymeric vesicles.[59] They discovered that the α-CD inclusion complex of DMA-*b*-PEG-*b*-DMA induced micelle-like aggregation in aqueous solution with disordered core. At acidic pH values, the DMA groups were ionized. The rigid polyrotaxane segments tend to pack in parallel to form ordered crystalline columns mainly by hydrophobic and packing interactions. The ICs then induced self-assembly into micelles with a core of hexagonally packed polyrotaxanes, which further organize into disks induced by water evaporation (Figure 3.4). It is the first time to study a hierarchical self-assembly of a supramolecular block copolymer.

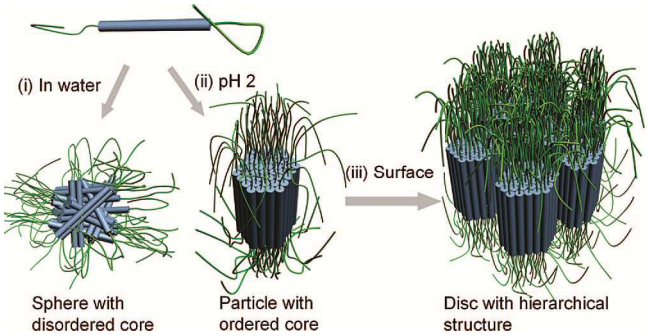

Figure 3.4 Schematic illustration of the formation of the pH-dependent self-assemblies.[59]

4 Applications

4.1 Controlled drug delivery

Recent studies have demonstrated that spatioternporally and anatornically controlled drug delivery and release can be achieved using nanosystems which can be activated or guided by physicochemical signals or pathophysiological features, such as pH, temperature, redox potential etc. Due to the dynamic structure and tunable performance, CD-based nanoassemblies with reversible properties have been used for controlled drug delivery. For example, the voltage-responsive micelles discussed in section 2.1.3 could be used as drug carriers to load anticancer drug (paclitaxel) and release the drug molecules under the voltage stimuli. Zhang and coworkers reported a kind of core-shell nanoassemblies with a tumor-triggered targeting property for cancer treatment.[60] These core-shell assemblies were formed by connecting the hydrophobic chain and hydrophilic chain via host-guest interaction. PEG chains were introduced to these nanoassemblies via benzoic-imine bonds and peptides containing the Arg-Gly-Asp sequence were also introduced as target ligands. Due to the protection of PEG, the targeting property of nanoassemblies was switched off before reaching the tumor sites. But in tumor sites, the targeting property was switched on because the PEG removed through the hydrolysis of benzoic-imine bonds (Figure 4.1).

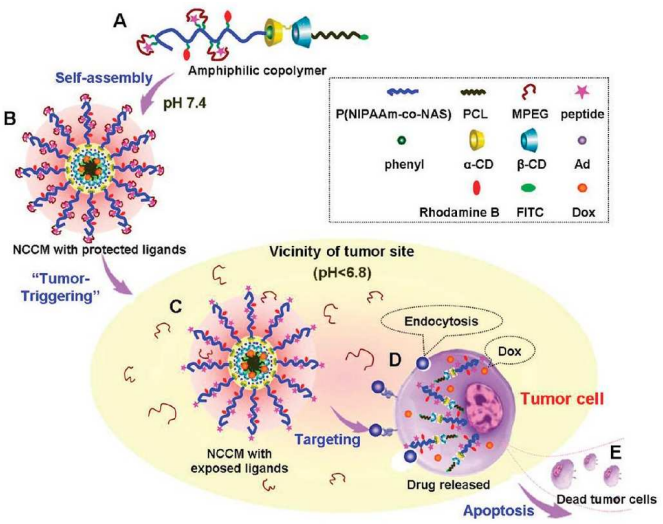

Figure 4.1 Schematic illustration of the formation of shell-core nano-assemblies with switchable tumor cell triggered targeting.[60]

4.2 Gene delivery

Nonviral gene delivery vectors, such as liposome, many cationic polymers and their derivative and dendrimers have received much attention because they are safer and simpler to handle than viral vectors. However, a great challenge of nonviral delivery vectors is their much less gene expression than the viral vectors. Recently CDs have been applied as building blocks for nonviral vectors, playing the role of transfection enhancers.

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For instance, Kissel groups reported cationic inclusion complexes formed by threading α-CD over poly(ethylene glycol)-poly(ε-caprolactone)-polyethylenimine copolymer. It was found that these inclusion complexes could interact with DNA efficiently. The resulting DNA polyplexes showed transfection efficiencies in the same order of magnitude as PEI and 100 × lower toxicity compared with PEI.[61] Li et al. designed cationic polyrotaxanes composed of multiple oligoethylenimine-grafted CDs that were threaded and blocked on a pluronic PEG-PPG-PEG block copolymer chains. These supramolecules showed good DNA binding ability, low cytotoxicity and high gene transfection efficacy that is similar to that of high molecular weight PEI (25 kDa).[62]

Our groups developed two kinds of CD-containing nanoassemblies for gene delivery. One kind of nanoassemblies was hollow nanospheres based on inclusion complexation between β-CD and PEG-PPG-PEG (F127), which could encapsulate PEI/DNA in the hollow core.[63, 64] The resulting complexes displayed similar or more efficient gene trasfection in comparison with PEI/DNA, but much less cytotoxicity. Another kind of nanoassemblies was rod-like nanoparticle prepared by self-assembly of α-CD and PEG-PEI.[65] The rod-like particles can bind DNA effectively and showed over 4 times higher gene delivery capavility than its spherical counterpart and PEI (25kDa). (Figure 4.2) Furthermore, the cytotoxicity of rod-like particles was found to be about 5 times lower than that of nanospheres, and 50 times lower than that of PEI (25kDa). These results indicated that shape was an important parameter for the design of gene delivery vectors.

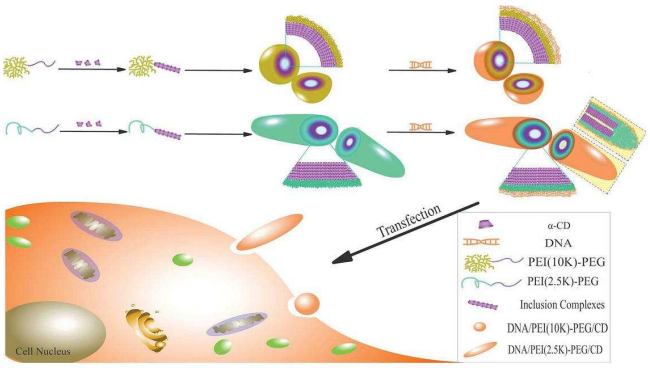

Figure 4.2 Schematic illustration of the formation of DNA/PEI-PEG/α-CD nanospheres and nanorods for gene delivery.[65]

Zhu and Liu developed a novel redox-responsive cationic supramolecular polymers via host-guest recognition between a β-CD dimmer (β-CD_2) and a ferrocene dimmer (Fc_2) for gene delivery. This small molecule-based supramolecular polymer exhibited effective DNA condensation ability and H_2O_2-triggered DNA release behavior. (Figure 4.3).[66] It has been demonstrated that cancer cells produce high amounts of H_2O_2. So this redox-responsive vector can be considered as an interesting candidate for gene delivery.

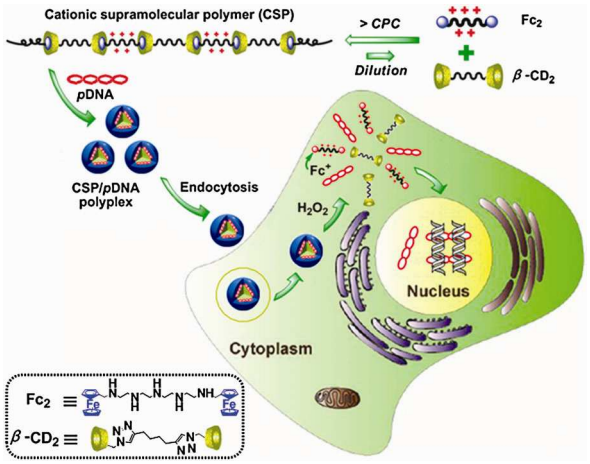

Figure 4.3 Illustration of the cationic supramolecular polymer constructed via orthogonal host-guest interactions between β-CD_2 and Fc_2 as well as its H_2O_2-induced DNA release behavior.[66]

4.3 Enzyme Immobilization and biomimetic systems

Enzyme immobilization is confinement of enzyme to a phase (matrix/support) different from the one for substrates and products. Immobilized enzymes can be used in organic syntheses to fully exploit the technical and economical advantages of biocatalysts or in the biomedical field aiming to detect bioactive substances or to treat a disease condition.

It was found that the CD-based hollow spheres developed by our group were good candidates for enzyme immobilization. The enzyme molecules could be encapsulated in hollow spheres directly in aqueous solution through the self-assembly of rod-coil copolymers and CDs complexes. The CD-based hollow spheres showed semi-permeability which could prevent big enzyme molecules from leaving while allowing small substrates and products to pass through to maintain the enzyme activity. The encapsulated enzymes exhibited improved stability.[55, 67, 68]

The CD-based hollow spheres can also be used to build a biomimetic energy converter for ATP biosynthesis.[69] As shown in Figure 4.4, these bioreactors comprised a CD-based hollow sphere (encapsulating glucose oxidases (GODs)) as inner support and ATPase liposome as the out layer. The CD-based hollow spheres served to make the system more mechanically robust, and prevent liposomal fusion and aggregations. When glucose was added into the suspension of these biomimetic capsules, proton gradients could be formed between the exterior and interior of the capsules and subsequently drove the rotation of ATPase to synthesize ATP. ATP will be an important fuel source for powering future nanodevices based on biomimetic technology. Therefore, this ATP generation system has great potential to play a crucial role in the operation of biologically inspired nanodevices.

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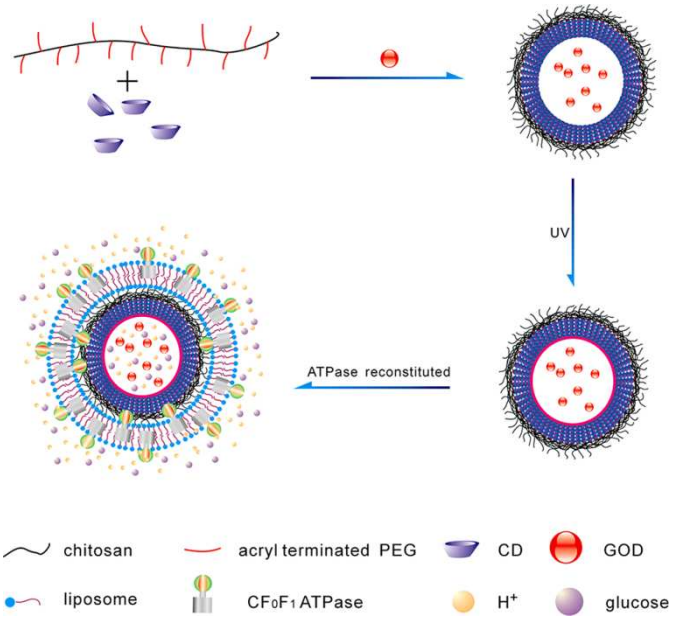

Figure 4.4 Schematic illustration of the formation of CD-based microcapsule containing ATPase and the ATP synthesis process in this microcapsule.[69]

5 Conclusions and perspectives

CD-based interactions offer some new routes towards the synthesis of highly complex and sophisticated nanoassemblies for a wide range of applications. As a result of the reversibility of the CD-based host-guest interactions, stimuli-responsive nanoassemblies can be elegantly designed and fabricated. CDs are excellent biocompatible and parent CDs already used in drug-delivery or food, therefore, CD-based nanoassemblies have great potential in biomedical and biomimic field. Although many studies have focused on the design and preparation of advanced CD-based nanoassemblies, most of these studies are in the proof-of-concept stage. The successful translation of these laboratory innovations to tackling specific real world remains great challenging. Smarter materials designs are expected for a better balance of higher functions, and practicality and safety. It is anticipated that the utilization of CD-based inclusion complexation is a promising pathway to design and generate new nanoassemblies with unique properties and will certainly play a significant role in the future of polymer science

Acknowledgements

This work was funded by the National Natural Science Foundation of China (Grant Nos. 51373174), the CAS Knowledge Innovation Program (Grant No. KSCX2-EW-J-22), and West Light Foundation of CAS.

Notes and references

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1. R. Hu, X. B. Zhang, Z. L. Zhao, G. Z. Zhu, T. Chen, T. Fu and W. H. Tan, *Angewandte Chemie-International Edition*, 2014, **53**, 5821-5826.
2. J. M. Hu, C. H. Li, Y. Cui and S. Y. Liu, *Macromol Rapid Comm*, 2011, **32**, 610-615.
3. Z. S. Ge and S. Y. Liu, *Chem Soc Rev*, 2013, **42**, 7289-7325.
4. Z. L. Wang, *Acs Nano*, 2008, **2**, 1987-1992.
5. C. J. Liu, U. Burghaus, F. Besenbacher and Z. L. Wang, *Acs Nano*, 2010, **4**, 5517-5526.
6. E. Serrano, G. Rus and J. Garcia-Martinez, *Renew Sust Energ Rev*, 2009, **13**, 2373-2384.
7. L. Mu and R. L. Sprando, *Pharmaceut Res*, 2010, **27**, 1746-1749.
8. E. R. Wright and V. P. Conticello, *Adv Drug Deliver Rev*, 2002, **54**, 1057-1073.
9. W. Tian, X. Y. Wei, Y. Y. Liu and X. D. Fan, *Polym Chem*, 2013, **4**, 2850-2863.
10. C. G. Mu, X. D. Fan, W. Tian, Y. Bai and X. Zhou, *Polym Chem*, 2012, **3**, 1137-1149.
11. C. G. Mu, X. D. Fan, W. Tian, Y. Bai, Z. Yang, H. Yao and H. Chen, *J Polym Sci Pol Chem*, 2013, **51**, 1405-1416.
12. Y. Bai, X. D. Fan, W. Tian, H. Yao, L. H. Zhuo, H. T. Zhang, W. W. Fan, Z. Yang and W. B. Zhang, *Polymer*, 2013, **54**, 3566-3573.
13. Y. Q. Zhu, L. Liu and J. Z. Du, *Macromolecules*, 2013, **46**, 194-203.
14. Y. Q. Zhu, L. Fan, B. Yang and J. Z. Du, *Acs Nano*, 2014, **8**, 5022-5031.
15. K. Tahara, S. B. Lei, J. Adisoejoso, S. De Feyter and Y. Tobe, *Chem Commun*, 2010, **46**, 8507-8525.
16. D. J. Hoffart, J. Tiburcio, A. de la Torre, L. K. Knight and S. J. Loeb, *Angewandte Chemie-International Edition*, 2008, **47**, 97-101.
17. T. T. Liu, W. Tian, Y. Q. Zhu, Y. Bai, H. X. Yan and J. Z. Du, *Polym Chem*, 2014, **5**, DOI: 10.1039/C4PY00501E.
18. L. Tan, Y. Liu, W. Ha, L. S. Ding, S. L. Peng, S. Zhang and B. J. Li, *Soft Matter*, 2012, **8**, 5746-5749.
19. G. S. Chen and M. Jiang, *Chem Soc Rev*, 2011, **40**, 2254-2266.
20. U. Rauwald and O. A. Scherman, *Angewandte Chemie-International Edition*, 2008, **47**, 3950-3953.
21. A. Harada, *Accounts Chem Res*, 2001, **34**, 456-464.
22. P. J. Cragg and K. Sharma, *Chem Soc Rev*, 2012, **41**, 597-607.
23. H. J. Kim, M. H. Lee, L. Mutihac, J. Vicens and J. S. Kim, *Chem Soc Rev*, 2012, **41**, 1173-1190.
24. J. Yin, C. H. Li, D. Wang and S. Y. Liu, *J Phys Chem B*, 2010, **114**, 12213-12220.
25. Z. S. Ge, J. M. Hu, F. H. Huang and S. Y. Liu, *Angew Chem Int Edit*, 2009, **48**, 1798-1802.
26. E. M. M. Del Valle, *Process Biochem*, 2004, **39**, 1033-1046.
27. T. Loftsson and D. Duchene, *Int J Pharm*, 2007, **329**, 1-11.
28. A. Vyas, S. Saraf and S. Saraf, *J Incl Phenom Macro*, 2008, **62**, 23-42.
29. J. Wang, M. Jiang, *J Am Chem Soc*, 2006, **128**, 3703-3708.

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30. F. Versluis, I. Tomatsu, S. Kehr, C. Fregonese, A. W. J. W. Tepper, M. C. A. Stuart, B. J. Ravoo, R. I. Koning and A. Kros, *J Am Chem Soc*, 2009, **131**, 13186-+.
31. H. C. Zhang, L. Z. Sun, Z. N. Liu, W. An, A. Y. Hao, F. F. Xin and J. Shen, *Colloid Surface A*, 2010, **358**, 115-121.
32. Y. P. Wang, N. Ma, Z. Q. Wang and X. Zhang, *Angewandte Chemie-International Edition*, 2007, **46**, 2823-2826.
33. Y. Liu, C. Y. Yu, H. B. Jin, B. B. Jiang, X. Y. Zhu, Y. F. Zhou, Z. Y. Lu and D. Y. Yan, *J Am Chem Soc*, 2013, **135**, 4765-4770.
34. Z. Q. Dong, Y. Cao, X. J. Han, M. M. Fan, Q. J. Yuan, Y. F. Wang, B. J. Li and S. Zhang, *Langmuir*, 2013, **29**, 3188-3194.
35. H. B. Jin, Y. L. Zheng, Y. Liu, H. X. Cheng, Y. F. Zhou and D. Y. Yan, *Angewandte Chemie-International Edition*, 2011, **50**, 10352-10356.
36. H. C. Zhang, F. F. Xin, W. An, A. Y. Hao, X. Wang, X. H. Zhao, Z. N. Liu and L. Z. Sun, *Colloid Surface A*, 2010, **363**, 78-85.
37. Q. Yan, J. Y. Yuan, Z. N. Cai, Y. Xin, Y. Kang and Y. W. Yin, *J Am Chem Soc*, 2010, **132**, 9268-9270.
38. L. Peng, A. C. Feng, H. J. Zhang, H. Wang, C. M. Jian, B. W. Liu, W. P. Gao and J. Y. Yuan, *Polym Chem*, 2014, **5**, 1751-1759.
39. A. C. Feng, Q. Yan, H. J. Zhang, L. Peng and J. Y. Yuan, *Chem Commun*, 2014, **50**, 4740-4742.
40. Y. Suzaki, T. Taira, D. Takeuchi and K. Osakada, *Organic Letter*, 2007, **9**, 887-890.
41. Q. Yan, H. J. Zhang and Y. Zhao, *Acs Macro Lett*, 2014, **3**, 472-476.
42. J. Zou, B. Guan, X. J. Liao, M. Jiang and F. G. Tao, *Macromolecules*, 2009, **42**, 7465-7473.
43. H. Liu, Y. F. Zhang, J. M. Hu, C. H. Li and S. Y. Liu, *Macromol Chem Physic*, 2009, **210**, 2125-2137.
44. B. W. Liu, H. Zhou, S. T. Zhou, H. J. Zhang, A. C. Feng, C. M. Jian, J. Hu, W. P. Gao and J. Y. Yuan, *Macromolecules*, 2014, **47**, 2938-2946.
45. W. Ha, Y. Kang, S. L. Peng, L. S. Ding, S. Zhang and B. J. Li, *Nanotechnology*, 2013, **24**.
46. C. H. Luo, F. Zuo, Z. H. Zheng, X. Cheng, X. B. Ding and Y. X. Peng, *Macromol Rapid Comm*, 2008, **29**, 149-154.
47. C. Li, G. F. Luo, H. Y. Wang, J. Zhang, Y. H. Gong, S. X. Cheng, R. X. Zhuo and X. Z. Zhang, *J Phys Chem C*, 2011, **115**, 17651-17659.
48. Z. P. Wang, Z. Q. Feng and C. Y. Gao, *Chem Mater*, 2008, **20**, 4194-4199.
49. G. Wenz, B. H. Han and A. Muller, *Chem Rev*, 2006, **106**, 782-817.
50. A. Harada, Y. Takashima and H. Yamaguchi, *Chem Soc Rev*, 2009, **38**, 875-882.
51. J. Araki and K. Ito, *Soft Matter*, 2007, **3**, 1456-1473.
52. X. W. Meng, J. Qin, Y. Liu, M. M. Fan, B. J. Li, S. Zhang and X. Q. Yu, *Chemical Communications*, 2010, **46**, 643-645.
53. X. W. Meng, W. Ha, C. Cheng, Z. Q. Dong, L. S. Ding, B. J. Li and S. Zhang, *Langmuir*, 2011, **27**, 14401-14407.
54. W. Ha, H. Wu, Y. Ma, M. M. Fan, S. L. Peng, L. S. Ding, S. Zhang and B. J. Li, *Carbohydrate Polymers*, 2013, **92**, 523-528.
55. Q. Li, B. Xia, M. Branham, W. Ha, H. Wu, S. L. Peng, L. S. Ding, B. J. Li and S. Zhang, *Carbohydrate Polymers*, 2011, **1**, 120-126.
56. C. Cheng, X. J. Han, Z. Q. Dong, Y. Liu, B. J. Li and S. Zhang, *Macromol Rapid Comm*, 2011, **32**, 1965-1971.
57. J. Qin, X. W. Meng, B. J. Li, W. Ha, X. Q. Yu and S. Zhang, *Journal of Colloid and Interface Science*, 2010, **350**, 447-452.
58. C. Park, K. Oh, S. C. Lee and C. Kim, *Angewandte Chemie-International Edition*, 2007, **46**, 1455-1457.
59. L. X. Ren, F. Y. Ke, Y. M. Chen, D. H. Liang and J. Huang, *Macromolecules*, 2008, **41**, 5295-5300.
60. C. Y. Quan, J. X. Chen, H. Y. Wang, C. Li, C. Chang, X. Z. Zhang and R. X. Zhuo, *Acs Nano*, 2010, **4**, 4211-4219.
61. X. Shuai, T. Merdan, F. Unger and T. Kissel, *Bioconjugate Chem*, 2005, **16**, 322-329.
62. J. Li, C. Yang, H. Z. Li,X. Wang, S. H. Goh, J. L. Ding, D. Y Wang and K. W. Leong, *Advanced Materials*, 2006, **18**, 2969-2974.
63. M. M. Fan, Xi-Zhang, B. J. Li, X. Sun and S. Zhang, *J Control Release*, 2011, **152**, E141-E142.
64. M. M. Fan, X. Zhang, J. Qin, B. J. Li, X. Sun and S. Zhang, *Macromol Rapid Comm*, 2011, **32**, 1533-1538.
65. M. M. Fan, W. Z. C. Zhang, C. Cheng, Y. Liu, B. J. Li, X. Sun and S. Zhang, *Particle & Particle Systems Characterization*, DOI: 10.1002/ppsc.201300383.
66. R. J. Dong, Y. Su, S. R. Yu, Y. F. Zhou, Y. F. Liu and X. Y. Zhu, *Chem Commun*, 2013, **49**, 9845-9847.
67. W. Ha, X. W. Meng, Q. Li, M. M. Fan, S. L. Peng, L. S. Ding, X. Tian, S. Zhang and B. J. Li, *Soft Matter*, 2010, **6**, 1405-1408.
68. W. Ha, X. W. Meng, Q. A. Li, M. M. Fan, S. L. Peng, L. S. Ding, X. A. Tian, S. Zhang and B. J. Li, *Soft Matter*, 2011, **7**, 1018-1024.
69. J. H. Li, Y. F. Wang, W. Ha, Y. Liu, L. S. Ding, B. J. Li and S. Zhang, *Biomacromolecules*, 2013, **14**, 2984-2988.

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