REVIEW

Cucurbituril-based supramolecular engineered nanostructured materials

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Cucurbituril (CB) is a unique macrocycle with a rigid symmetrical structure, which is composed of two identical hydrophilic portals decorated with partially negatively charged carbonyl groups and a hydrophobic cavity. A number of different nanostructured materials, including nanoparticles, nanocomposites, vesicles and rods, have been prepared by taking advantage of the varying cavity size of the CB homologues, their ability to accommodate more than one guest in their cavities, their rigid symmetrical structures, as well as the water solubility of CB7. These nanostructures could find a wide range of potential applications in the areas of self-healing materials, nanomedicine, plasmonics, and nanocatalysis. Here, we review the recent progresses in the synthesis, properties and application of CB-based supramolecular engineered nanostructures, which are either constructed through CB-assisted self-assembly or from post-functionalized-CB homologues.

1. Introduction

The products of the acid-catalyzed condensation of glycoluril with formaldehyde were first reported as a white amorphous material by Behrend *et al.* in 1905.[1] In 1981, Mock and co-workers revisited the work of Behrend and determined the structure of this material as a macrocycle containing six units of glycoluril.[2] Nowadays, it is known as cucurbit[6]uril (CB6), in which 6 represents the number of glycoluril units in the macrocycle. In 1990s, Kim and co-workers reported a series of very elegant works on CB6 substantially contributing to the field of CB.[3–5] In 2000, three new CB homologues, CB5, CB7 and CB8 having 5, 7 and 8 glycoluril units, respectively, were discovered.[6,7] In particular, the discovery of CB7 has excited the supramolecular chemistry community because of its both large cavity and water solubility, which are very important features for biological applications.[8–11] In 2002, Day and co-workers reported CB10 interlocked with CB5.[12] The very fast development of the cucurbituril field has led to the preparation of a number of different CB homologues and derivatives in recent years. For example, the inverted CB6 and inverted CB7,[13] the chiral nor-seco-cucurbituril (±)-bis-ns-CB6 and the nor-seco-CB10,[14] have all been reported. Recently, the synthesis of large CB derivatives as hemi-CB12 [15] and twisted CB14 [16] has also been described.

CBs have two hydrophilic portals decorated with partially negatively charged carbonyl groups and a hydrophobic cavity. Owing to these features, they serve as an excellent host for hydrophobic molecules. The host–guest interaction of CBs is based on two main intermolecular forces: a hydrophobic effect and ion dipole interactions at the carbonyl portals. The higher binding affinity compared to the same class of macrocycles (cyclodextrins, calixarenes) is attributable to their shape (narrow portals and wider hydrophobic cavity) and the carbonyl groups, which provide selective binding through positively charged guest molecules. Mock and co-workers extensively studied the selectivity, recognition and self-sorting properties of CB6.[17,18] However, CB-related studies were exponentially increased by the isolation and characterization of CB7 and CB8 with larger cavities compared to CB6 and also due to the water-solubility of CB7. Thus, selectivity, high binding affinity, recognition properties and the water-solubility of some CB homologues allow the use of CB family in biological, photo-chemical, electrochemical, catalytic and optoelectronic applications. In addition, CBs are very useful building blocks in the preparation of nanomaterials. There are numerous studies on the host–guest chemistry of CB homologues and their recognition properties, as well as a number of excellent review papers outline the synthesis, properties and applications of CB homologues.[19–24]

In this review, we mainly focus on the synthesis, properties and application of CB-based nanostructures, which are either constructed through CB-assisted self-assembly or from post-functionalized-CB homologues. We also briefly discuss the synthetic routes used in the CB-functionalization.

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2. Synthesis of nanostructures assembled through CB-assisted self-assembly

Numerous different nanostructures have been constructed by taking advantage of the interesting features of CBs. The characteristic of two identical portals decorated with partially negatively charged carbonyl groups and their rigid symmetrical structures were advantageous for the preparation of metal nanoparticles; CBs acted as a capping agent to stabilize the gold or silver nanoparticles in the aqueous solutions. Moreover, CB-capped gold nanoparticles have been utilized in surface enhanced Raman scattering spectroscopy and plasmonics, as well as in catalysis.

By varying the cavity size of the CB homologues and their ability to accommodate more than one guest in their cavity, the rigid symmetrical structure and the water solubility of some of the homologues allowed the preparation of nanoparticles, nanocomposites, vesicles and rods.

In the following section, we review the recent work related to CB-containing metal nanoparticles and CB-assisted self-assembled nanostructures through host–guest chemistry.

2.1 Supramolecular assemblies of cucurbituril with metal nanoparticles

Here, we mainly discuss the following points: CB's role as a capping agent to stabilize metal nanoparticles, such as gold and silver, CB-containing hybrid nanostructures made out of appropriately functionalized polymeric nanoparticles and metal nanoparticles, as well as the function of CB in the formation of plasmonic nanostructures. These nanostructures could find applications in the area of sensing, optoelectronic device fabrication, surface-functionalized assemblies and catalysis.

2.1.1 Synthesis of CB-containing gold and silver nanoparticles.
Water-dispersible gold and silver nanoparticles have many potential applications, including catalysis, chemo- and bio-sensors, biomedical applications, as well as plasmonics.

To utilize these nanoparticles for catalytic applications, preferably as capping agents, which stabilize the nanoparticles, should not strongly bind to the surface of the metal nanoparticles. To this end, CBs have been determined to be suitable for this purpose.

One of the first works regarding CB-containing gold nanoparticles was conducted by Corma and co-workers. They claimed the formation of gold clusters inside the cavity of CB, but this was not studied further.[25] Geckeler et al. reported the synthesis of water dispersible gold nanoparticles in the presence of CB7 without using any reducing agent.[26] They concluded that CB act as a capping agent to stabilize the gold nanoparticles, as well as it act as a reducing agent.

They also demonstrated the use of these nanoparticles as a catalyst for the reduction of nitrophenol in the presence of sodium borohydride. They explained the catalytic ability of these nanoparticles via the loose attachment of CBs through carbonyl portals to the gold surfaces, and hence making room for substrates, which can interact with the surface in order to progress the catalysis.

Sherman et al. substantially contributed towards the development of this field by conducting detailed works. In one of the early works, they prepared CB5-capped gold nanoparticles by reducing $HAuCl_4$ with $NaBH_4$ in the presence of various amounts of CB5 (Fig. 1).[27] They observed the formation of dynamic aggregates consisting of a controllable ratio of singly- and doubly-capped CB5.

The same group further conducted a detailed systematic work on the supramolecular capping of CB homologues (CB5–CB8).[28] First, metastable gold nanoparticles were prepared by reducing $HAuCl_4$ with $NaBH_4$, and then CB solutions were added to these metastable gold nanoparticle aqueous dispersions to further stabilize the gold nanoparticles by capping them with CB homologues. These CB-capped nanoparticles were stable in solution, and were found to form reversible aggregates based on singly- and doubly-capped CBs. The system was further stabilized by the complexation of sodium cations with the vacant carbonyl portals of the singly capped CBn molecules.

Although ligandless, CB-capped silver nanoparticles could potentially find many interesting applications, but they have not been as widely studied as gold nanoparticles. Masson et al. studied the formation and stabilization of silver nanoparticles with CB5, CB6, CB7 and CB8, as well as cucurbituril-based pseudorotaxanes in aqueous medium.[29] In this work, nanoparticles of silver-CB were prepared by reducing $AgNO_3$ with $NaBH_4$ in the presence of CB homologues. CB homologues caused different effects on the silver nanoparticles. CB7 and CB8 allow the formation of stable solutions of narrowly dispersed nanoparticles with the sizes of 5.3 nm and 3.7 nm, respectively, whereas CB5 and CB6 induced rapid aggregation and sedimentation. The authors attributed the instability of Ag nanoparticles and the aggregate formation in the presence of CB5 and CB6 to the rigidity of CB5 and CB6, which results in the possible lack of suitable arrangement at the silver surface. However, the stable CB-capped Ag nanoparticle aqueous dispersion, in the case of CB7 and CB8, could be due to the more
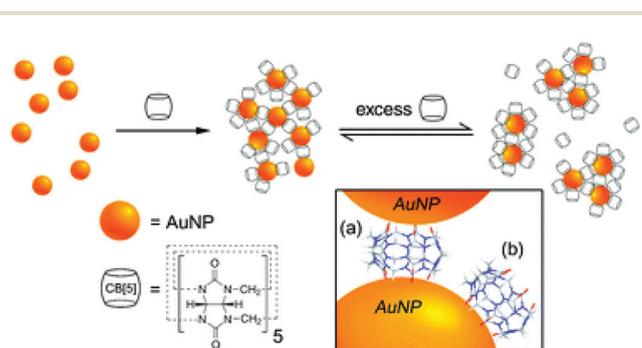
Fig. 1 The preparation of CB5-capped gold nanoparticles and the formation of dynamic aggregates consisting of a controllable ratio of singly- and doubly-capped CB5. (Reprinted with permission from ref. 27. Copyright 2010 Royal Society of Chemistry.)

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Org. Biomol. Chem., 2015, 13, 330–347 | 331

flexible nature of CB7 and CB8. Thus, they could be distorted to interact with Ag nanoparticle surfaces for the requirement of the stabilization. They also supported this assumption for interactions between the silver nanoparticles and carbonyl portals of CBs by computer modelling.

They determined that large excesses of silver or CB7 could trigger aggregate formation, and the optimal AgNO₃/CB7 ratio for the formation of stable nanoparticles should be maintained at 1 : 1–2 : 1. Moreover, it was shown that even filling the cavity of CBs with a bulky and positively charged guest hardly affects the stability of Ag/CB7 nanoparticles. This is a very important feature, because the availability of the cavity of CB7 could be beneficial in many applications, such as sensing.

The synthesis of Janus nanoparticles composed of Ag and AgBr has also been reported.[30] Basically, Janus nanoparticles are nanoparticles with two or more different regions on which materials with different chemical and physical properties coexist.[31] These nanoparticles could find many interesting applications, ranging from photonics to biomedical applications. In particular, metal Janus nanoparticles could be utilized as photocatalysts. In this work, AgBr nanoparticles were prepared from an aqueous solution of AgNO₃ and NaBr via a nanoprecipitation method, and the resulting nanoparticles were capped with CB5 or CB7 to further stabilize the nanoparticles. When these nanoparticles were irradiated with an electron beam, Ag⁺¹ could be reduced to Ag⁰; in this way they managed to obtain patchy nanoparticles containing AgBr and Ag surfaces. It was shown that CBs could stabilize both AgBr and Ag⁰ containing surfaces of the Janus nanoparticles. Most importantly, the degree of transformation could be directly followed through a transmission electron microscope.

Very recently, the preparation of CB7-capped gold nanoparticles in the absence of metallic cations and organic ligands has been reported.[32] The nanoparticles were prepared by reducing HAuCl₄ with H₂O₂ and applying a 532 nm laser light (18–20 mJ per pulse) to ablate the AuNPs generated in situ. CB-capped nanoparticles were determined to be stable for a prolonged period of time without forming any aggregates. Moreover, these CB-capped nanoparticles showed enhanced catalytic activity toward the reduction of dissolved O₂, due to a cooperative effect between their components by fixing oxygen to the nanoparticle surface and increasing the local concentration of oxygen.

2.1.2 The use of CB-capped gold nanoparticles in surface enhanced Raman scattering. Surface enhanced Raman scattering (SERS) is an optical phenomenon arising from the conjugation of molecules with metal nanoparticles, such as gold or silver, which show surface plasmon resonance due to the oscillations of free electrons.[33] The Raman signals are significantly increased in the regions between closely spaced nanoparticles, which are called 'hot spots', and as a result even the signal of a single molecule can be detected. Owing to the high sensitivity, this technique is very attractive for chemical and biological sensing.[33]

However, creating proper hot spots is not a trivial task and considerable efforts have been devoted to obtain efficient and reproducible results. In order to create hot spots, metal nanoparticles should be induced to form defined aggregates. Scherman and co-workers demonstrated that an aqueous dispersion of CB-capped gold nanoparticles could be used as a substrate for SERS.[34,35] To this end, the aggregation of gold nanoparticles with CB5 produced a rigid, fixed and reproducible interparticle separation of 0.9 nm. They observed a strong and reproducible SERS from the AuNP:CB5 aggregates. Here, CB acted as a SERS reporter, in which the exploited resonant plasmon modes could be tuned in a spectral position and time through the concentration of CB5 and the NP diameter. They also demonstrated a SERS-based assay using the host–guest complexation ability of CB, in which the analyte molecule was subjected to intense field enhancement on the plasmonic hot spot created by the CB-junctions.

When gold nanoparticles were capped with CB8, which is a member of the CB family with a large cavity, it was possible to create precise subnanometer junctions between gold nanoparticles, while its cavity simultaneously trapped small molecules, allowing their reproducible SERS detection.[36] The inclusion of a complex formation of CB8 with guests could produce characteristic SERS signals and this, in turn, could be very useful for the absolute quantification of a range of molecules down to 10⁻¹¹ M levels (Fig. 2).

One-dimensional metal nanoparticle chains are very important in the area of plasmonics, owing to their high symmetry and ability to propagate the plasmonic effect and energy transfer along the chain.[37] However, finding a precise junction between the nanoparticles to fabricate these nanostructures presents some challenges. Scherman and co-workers demonstrated the use of CB7 as nanojunctions of 0.9 nm in the electrokinetic assembly of one-dimensional nanoparticle chains (Fig. 3).[38] A nanoporous polycarbonate membrane was used and the process was controlled by the applied voltage, the nanoparticle/CB7 concentration ratio, time and temperature. Extinction spectroscopy was used for the real-time analysis of the growth mechanism based on the chain plasmonics. TEM images also confirmed that the chain length and linearity of the structures could be controlled by tuning the parameters.

2.1.3 Supramolecular hybrid nanostructures. The formation of morphologically controlled, highly ordered arrays of
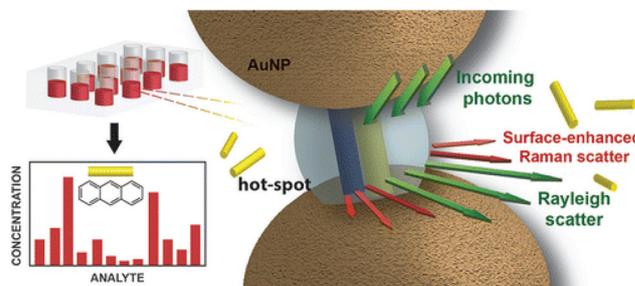
Fig. 2 Schematic of host–guest SERS analysis using ternary complexation: the CB8 aggregates AuNPs and localizes the analyte in the hot-spot for SERS analysis. (Reprinted with permission from ref. 36. Copyright 2012 American Chemical Society.)
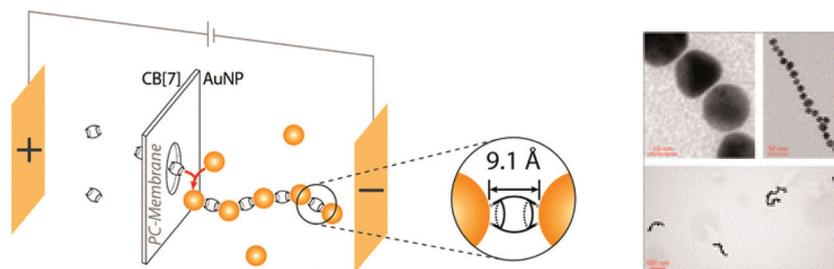
Fig. 3 The use of CB7 as nanojunctions of 0.9 nm in the electrokinetic assembly of one-dimensional nanoparticle chains. (Reprinted with permission from ref. 38. Copyright 2013 American Chemical Society.)

nanoparticles is required in order to exploit the ability of metal nanoparticles in device fabrication. For this endeavour, many approaches have been adopted to form organic–inorganic composite materials. Among these, the use of a supramolecular approach can offer additional advantages, such as controlled structures can be obtained, and the system can be made reversible using a host–guest approach in particular.

Shermann and co-workers prepared a gold nanoparticle-polymer nanocomposite using the host guest chemistry of CB8.[39] It is well known that CB8 can accommodate more than one guest in its cavity and has high affinity toward some guests, also it can form ternary complexes by simultaneously binding with electron rich and electron deficient guests, such as a naphthol (Np) derivative and a methyl viologen dication

(MV^{2+}), respectively. In order to prepare nanoparticle-polymer composites, first, MV^{2+} (guest 1) attached gold nanoparticles and poly(2-hydroxyethyl acrylamide)-co-(naphtholtriazole acrylamide), which contains the second guest of the Np units (guest 2), were prepared (Fig. 4). A nanocomposite was obtained through a ternary complex formation between CB8 and guest one and two in water. In the absence of the second guest and upon a one electron reduction of viologen, a 2:1 inclusion complexation between MV^+ and CB8 took place, which caused interparticle aggregation in water and led to precipitation.

The same approach, which was used in the preparation of the supramolecular gold-polymer composite material, was extended for the fabrication of mono-disperse supramolecular
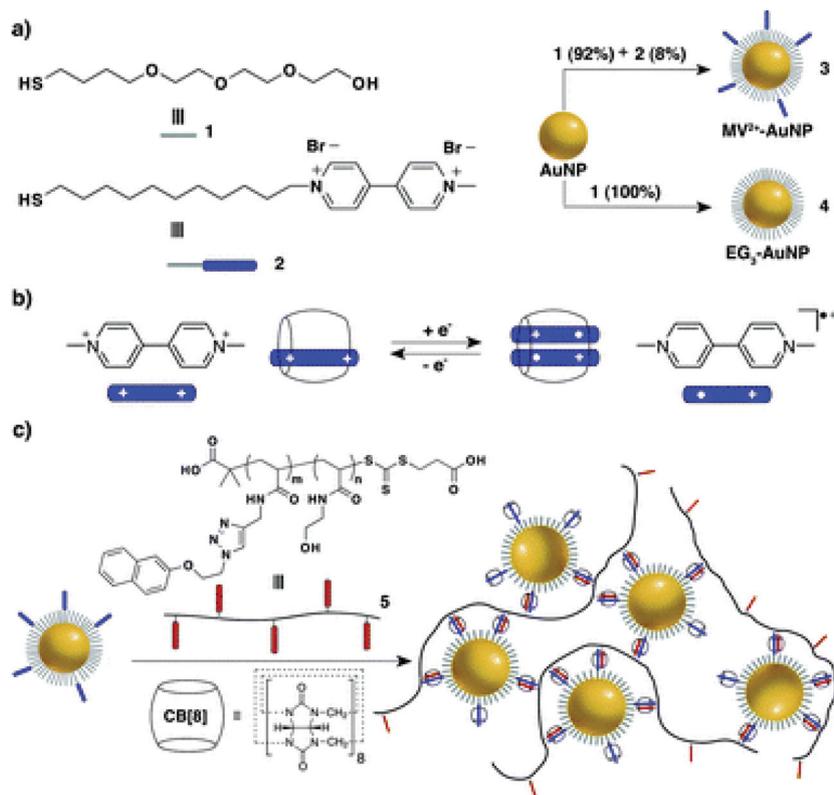
Fig. 4 The preparation of a gold nanoparticle-polymer nanocomposite using host–guest chemistry of CB8. (Reprinted with permission from ref. 39. Copyright 2011 Royal Society of Chemistry.)

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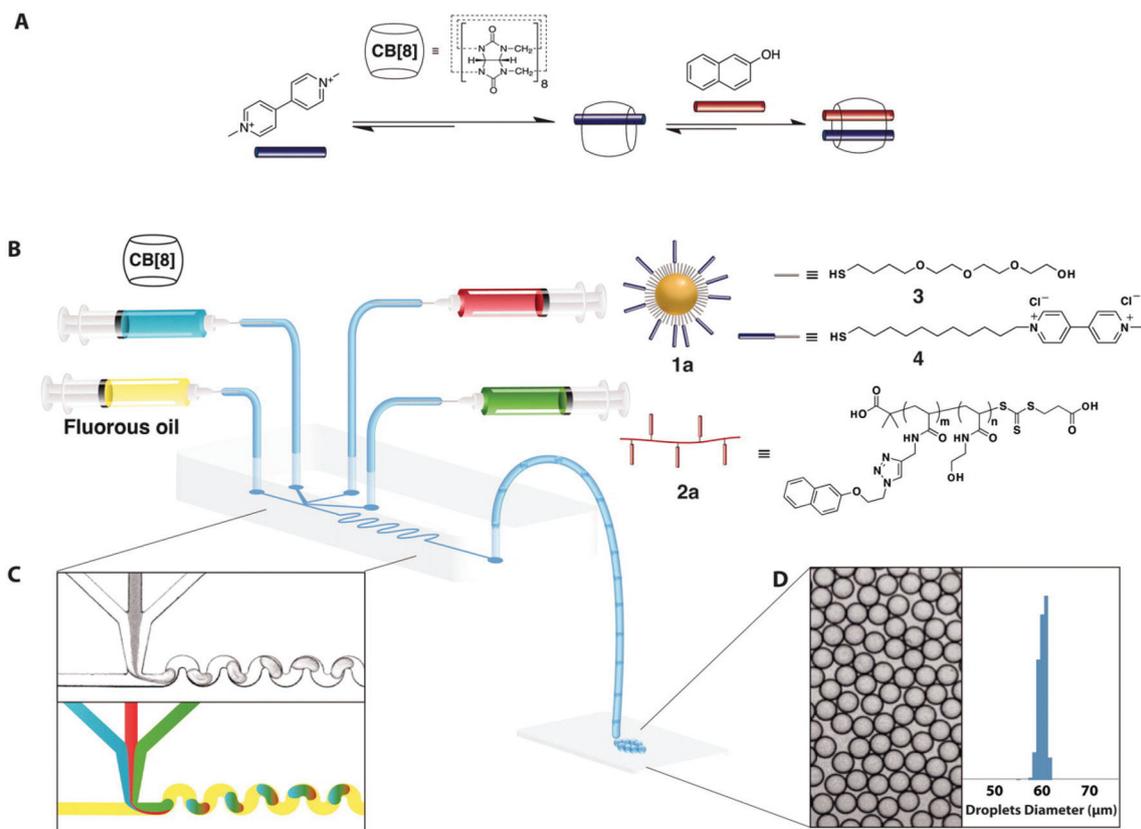
Fig. 5 The fabrication of mono-disperse supramolecular microcapsules using a microfluidic approach. (A) Schematic representation of the ternary complex formation between methyl viologen dication (MV^{2+}), 2-naphthol and CB8. (B, C, D) Microfluidic set-up for the preparation of hybrid-capsules. (Reprinted with permission from ref. 40. Copyright 2012 Science.)

microcapsules using a microfluidic approach (Fig. 5).[40] Micro-droplets with a narrow size distribution and with a mean diameter of 59.6 mm were first generated in a microfluidic device, using a T-junction geometry. These microcapsules comprise gold nanoparticles decorated with binding motifs MV^{2+} for CB8 and a polymer bearing naphthol functionalities. Stable hollow microcapsules obtained upon dehydration can be loaded with a wide range of materials during capsule formation, and then the controlled release of the guest can be triggered through an external stimulus as a result of the supramolecular host–guest chemistry incorporated in the capsule shell. Moreover, these microcapsules can be used as SERS substrates because of their plasmonic properties from the presence of gold nanoparticles in their structures.

Photoresponsive hybrid raspberry-like colloids (HRCs) were prepared by employing the host–guest chemistry of CB8 (Fig. 6).[41] The core of the colloids consists of 4-hydroxyazo-benzene-(Azo-)-functionalized silica microspheres, and the corona is based on methyl viologen (MV) decorated polymeric nanoparticles. HRCs were obtained by the formation of ternary complex between MV/*trans*-Azo and CB8 in water. The disassembly of the system could be realized through the conformational changes of *trans*-azo to *cis*-azo moieties upon light irradiation.

The host–guest chemistry of CBs was also utilized in the preparation of therapeutic gold nanoparticles.[42] Gold nanoparticles decorated with diaminohexane groups initially exhibited high toxicity toward cells, but the cytotoxicity of the nanoparticles were reduced upon the complexation of CB7 with diaminohexane groups by sequestering in endosomes. The toxicity of the nanoparticles was reversed by the administration of 1-adamantylamine (ADA), which has a higher affinity toward CB7 compared to 1,6-diaminohexane moieties, and by complexing with CB7 to leave behind toxic AuNP–NH$_2$, which shows their therapeutic effect toward cells (Fig. 7).[42]

An similar approach was also used to regulate the toxicity of conjugated polymer nanoparticles,[43] as well as to control the degree of protein–nanoparticle interactions by modulating the surface properties of NPs.[44]

Gold nanoparticles with different shapes can differ in their physical and chemical properties. Rod-shaped gold particles exhibit anisotropic optical and electronic responses, which are very important features in plasmonics.[45] These nanostructures could also find applications in optical devices, biochemical sensors, and in nanomedicine. For biomedical applications, they should be water dispersible and their surfaces should be modified with biocompatible functionalities.

One of the examples of gold nanorods (GNRs) protected by a hydrophilic CB7-based pseudorotaxane anchored monolayer was reported by Li and co-workers.[46] First, a 4,4′-bipyridinyl unit linked to an alkyl chain terminated with disulphide was
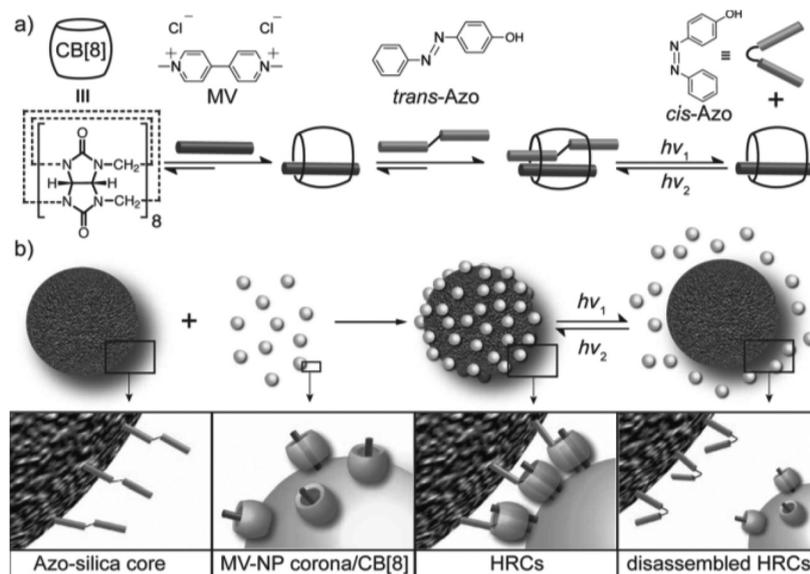
Fig. 6 (a) Ternary complex formation between MV, *trans*-azo and CB8 and the disassembly of a ternary complex by a light stimulus; (b) Photo-responsive hybrid raspberry-like colloids (HRCs) prepared by the host–guest chemistry of CB8. (Reprinted with permission from ref. 41. Copyright 2014 Wiley-VCH Verlag GmbH & Co. KGaA.)
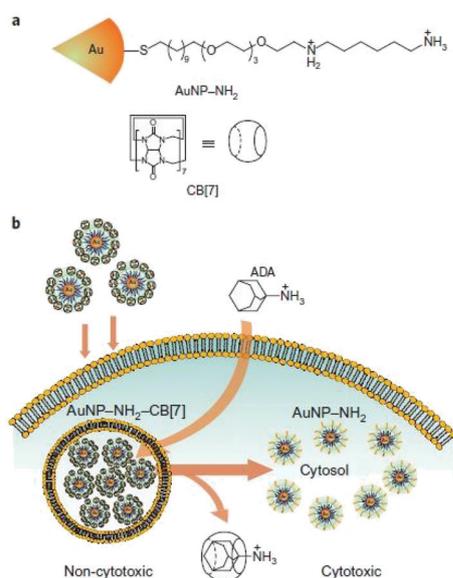
Fig. 7 Controlled release of gold nanoparticles triggered by 1-amino-adamantane. (Reprinted with permission from ref. 42. Copyright 2010 Nature Publishing Group.)

attached to gold nanorods, and the threading of this axle by CB7 in water resulted in the formation of a pseudorotaxane. These structures were characterized by TEM, Raman spectroscopy, UV/Vis/NIR spectroscopy, and cyclic voltammetry (CV).

The end-to-end assembly of Au nanorods can also be realized by the host–guest chemistry of CBs with suitable functionalities attached at the end surfaces of the nanorods (Fig. 8). Viologen end-functionalised AuNRs were prepared with the use of cetyltrimethylammonium bromide (CTAB) as a stabilising ligand.[47] When the bifunctional linker containing the second guest naphthyl moieties was introduced through ternary complex formation between the end groups of AuNRs, linker and CB8, the nanorods were assembled together to form oligomeric gold nanorod chains. Moreover, the length of the linker was determined to be quite important; while a long and flexible linker results in aggregate formation, a short linker provides end-to-end connection. When CB7 was used instead of CB8 as a host, no chain formation was observed. Furthermore, the use of the competitive guest instead of the linker produced no chain.

In another study, the contribution of CB in designing a theranostic platform was demonstrated in such a manner that CB7-functionalized iron oxide nanoparticles were prepared for drug delivery and magnetic resonance imaging (MRI) by microwave heating.[48] The degree of CB7 attachment was monitored by several techniques, including FTIR spectroscopy, Zeta potential, dynamic light scattering measurements, high resolution transmission electron microscopy (HRTEM) and powder X-ray diffraction (PXRD). Density functional theory (DFT) calculations suggested the interaction of the carbonyl oxygen of CB7 with surface Fe^{3+} ions. CB7-attached nanoparticles were found to be stable under a wide pH range (2–12) and have a transverse relaxivity, R2, of 113 s1 mM1. Nile red (NR) dye was loaded into the cavities of the surface-adsorbed CB7s, and intracellular delivery of the dye to HCT116 cells was observed by confocal laser scanning microscopy. The dye-loaded particles had a R2 of 172 s1 mM1.

2.2 CB-assisted formation of supramolecular nanostructures

By taking advantage of the rich host–guest chemistry of CB homologues, a number of different nanostructures have been prepared. In particular, the ability of CB8 to form ternary com-

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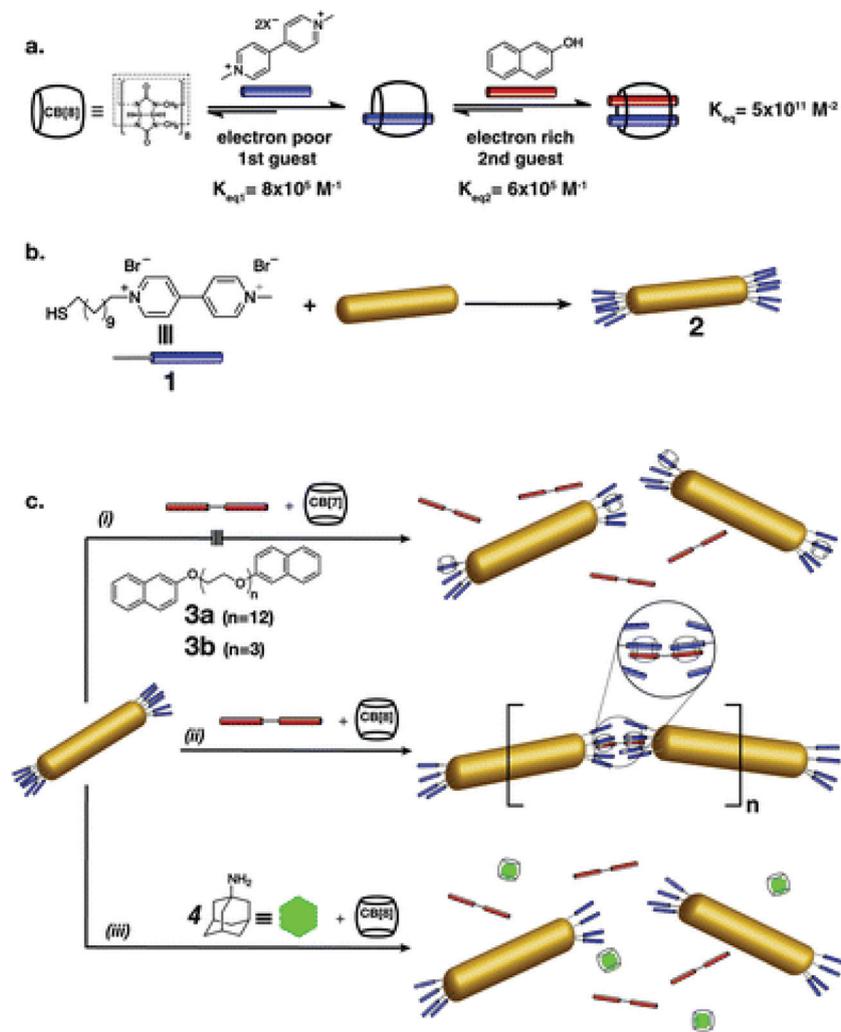
Fig. 8 (a) Formation of a ternary complex between methyl viologen, 2-napthol and CB8; (b) preparation of methyl viologen functionalized gold nanorods; (c) addition of either bi-naphthol linker with propyl or dodecyl spacers (i) with CB7, (ii) with CB8, or (iii) with CB8 in the presence of ada-mantylamine. (Reprinted with permission from ref. 47. Copyright 2013 Royal Society of Chemistry.)

plexes with electron rich (*e.g.* naphthol moiety) and electron deficient (*e.g.* viologen cation) species has been extensively used for the construction of supramolecular nanostructures, such as supramolecular hydrogel, nanoparticles, vesicles and supramolecular arrays. These nanostructures could find many interesting applications, especially in the area of self-healing materials, the delivery of drug or other therapeutic materials and the area of theranostics, as well as for controlling the viscosity of materials.

2.2.1 Supramolecular hydrogel. Basically, hydrogels are three-dimensional hydrophilic polymeric networks, which have a high capacity to hold water.[49] Depending on the structure of the polymer and the cross-linking density, their swelling degree may vary. These materials resemble biological tissues and as a result they are quite important for biomedical applications.[50]

Hydrogels can be prepared using a number of different methods, including the cross-linking of appropriate polymers through covalent bonds and non-covalent bonds (supramole-

cular approach). The supramolecular approach can offer reversibility to the structure and the resulting materials can be used for self-healing and tuning the mechanical properties of the materials for desired applications. Scherman and co-workers prepared a supramolecular hydrogel through a ternary complex formation between the host CB8 and multivalent hydrophilic copolymers bearing either pendant methyl viologen or naphthoxy derivatives, which are favourable guests for CB8.[51] When CB8 was added to colourless aqueous solutions of the polymers bearing the guests, a highly viscous, coloured supramolecular hydrogel was obtained. The degree of crosslinking could be controlled by varying the concentration of CB8 added. The resulting supramolecular hydrogel was found to be stimuli responsive and its properties could be tuned by external stimuli such as heat. It also exhibited thermal reversibility and a subsequent facile modulation of its microstructure upon further additions of CB8 and thermal treatment. The mechanical property of this hydrogel is comparable to existing supramolecular hydrogels.

336 | *Org. Biomol. Chem.*, 2015, **13**, 330–347

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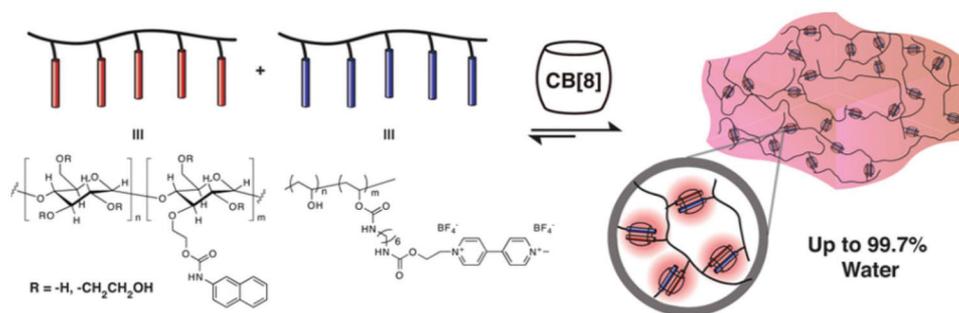
Fig. 9 Preparation of the cellulosic hydrogel with a water content of up to 99.7% in the presence of CB8. (Reprinted with permission from ref. 52. Copyright 2012 American Chemical Society.)

Using the same idea of a ternary complex formation ability of CB8 with MV^{2+} and naphthoxy derivatives, ultrahigh-water-content (up to 99.7% water by weight) supramolecular hydrogels exhibiting multistimuli responsiveness were reported (Fig. 9).[52] For this purpose, first cellulosic derivatives and poly(vinyl alcohol) were decorated with MV^{2+} and naphthoxy binding motifs. When these polymers, which contain 90% cellulosic solid content, were mixed with CB8, an immediate formation of a coloured, transparent hydrogel was observed. The mechanical properties of these hydrogels can be controlled, owing to the cross-links of non-covalent bonding, and this important feature allows for the rapid self-healing of the materials after the damage caused by deformation. Most importantly, these hydrogels are responsive to a number of external stimuli, including temperature, chemical potential and competing guests.

A similar approach was applied for the preparation of a nanocomposite hydrogel, which consisted of hard and soft polymeric domains.[53] The hard segment was made up of cellulosic nanocrystals (CNCs), which are mechanically strong colloidal rods with nanometer-scale lateral dimensions, and was functionalized with methacrylate polymer brushes bearing naphthyl units by surface-initiated atom transfer radical polymerization bearing naphthyl units. The soft segment was composed of poly(vinylalcohol) functionalized with viologen units. These domains can be bound together through supramolecular cross-links in the presence of CB8 in an aqueous medium to form supramolecular nanocomposite hydrogels, which have important features, such as high storage modulus, rapid sol–gel transition, and rapid self-healing, even upon aging for several months.

Dynamically cross-linked networks were also prepared *via* the recognition of amino acids by CB8.[54] In this work, water soluble styrenic monomers were copolymerised with synthetically derived aromatic amino acid monomers of phenylalanine and tryptophan, which are good guests for CB8. The resulting polymers have shown to form dynamic and self-healing physically cross-linked hydrogels *via* the recognition and binding of the amino acids to CB8. These materials have the potential to be used in areas, such as tissue engineering, to construct scaffolds.

Tan and co-workers reported the preparation of pH- and thermo-responsive supramolecular hydrogels based on the host–guest complexation of CB8 with the viologen units of poly(N-(4-vinylbenzyl)-4,4′-bipyridinium dichloride-co-acrylamide) (P4VBAM)s in water.[55] The hydrogel formed in a basic aqueous medium, in which CB8 could encapsulate two bipyridyl units to link the polymer chains. Reversibility could be achieved by adjusting the pH, as well as by heating and cooling the system.

2.2.2 Supramolecular nanoparticles, micelles, vesicles. Single chain nanoparticles, owing to their well-defined shape, size and composition, are highly appealing for many applications, including biomedicine and photonics. The host–guest chemistry of CB8 was successfully utilized in their preparation (Fig. 10).[56] For this purpose, a range of poly(N-hydroxyethyl-acrylamide) polymers were prepared by ATRP and were functionalized using an isocyanate conjugation with guest moieties (MV^{2+} and Np) for complexation with CB8. The size and dispersity of the nanoparticles could be controlled by carefully tuning the concentration of polymers and CB8. The addition of CB8 to a very dilute solution of the polymers yielded a single chain polymer nanoparticle, but at higher concentrations several chains collapsed together to form large nano-
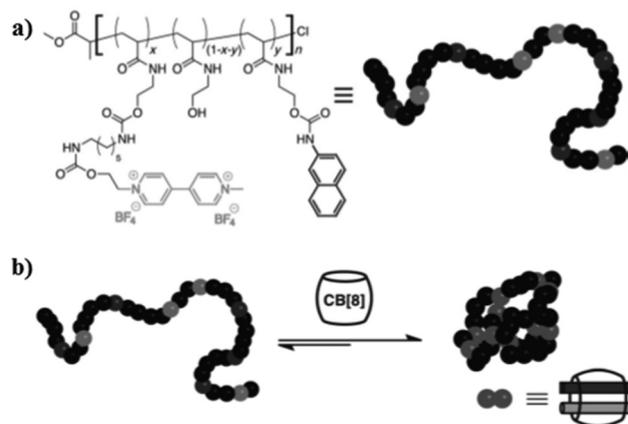
Fig. 10 (a) The structure of poly(N-hydroxyethyl acrylamide) polymer conjugated with guest moieties (MV^{2+} and Np) for complexation with CB8; (b) Single chain polymer nanoparticle formation through a ternary complex of CB8. (Reprinted with permission from ref. 56. Copyright 2012 Wiley-VCH Verlag GmbH & Co. KGaA.)

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Org. Biomol. Chem., 2015, **13**, 330–347 | **337**

particles with a broad polydispersity index. When CB7 was used, which has a smaller cavity than CB8 and cannot accommodate two guests at the same time, nanoparticle formation was not observed, further proving the formation of a ternary complex between the guests located at the termini of the polymers and the host CB8.

Using the supramolecular approach, core–shell polymeric microspheres with a cleavable shell were prepared in water.[57] In this study, the core component was based on a MV-functionalised polymeric microsphere and the shell was composed of Np-functionalised linear acrylate polymers containing hydrophilic oligoethylene glycol units and/or rhodamine-B units. The core and shell components were linked together through a ternary complex formation between CB8 and the residues of Np and MV^{2+}. The shell could be easily cleaved by introducing a competitive guest with a higher affinity toward CB8 compared to the existing guests on the system. These cleavable core–shell nanoparticles could have potential applications in the area of cancer therapy because the toxicity of the nano/microparticles could be switched on demand.

Supramolecular stimuli-responsive, reversible micelles[58] that can be used for the encapsulation of anticancer drug and controlled drug release have also been reported.[59] For the preparation of this system, double hydrophilic copolymers were used; one block was naphthalene-terminated poly(dimethylaminoethylmethacrylate) (PDMAEMA) as a pH-responsive segment and the second one was methyl viologen terminated poly(N-isopropylacrylamide) (PNIPAAm) as a temperature-responsive block. In mixing aqueous solutions of these two polymers in the presence of CB8, they were bound together to form micelles. The cargo of the pH-responsive nanocontainers could be unloaded through a pH-triggered release within endosomal and lysosomal vesicles at around pH 4, whereas the temperature-responsive nanocontainers were suitable for triggering *via* remote heating methods, such as infrared irradiation. The molecular weights of the polymers were maintained below 10 000 g mol^{-1} in order to facilitate the excretion *via* renal filtration after releasing the cargo.

When drugs are loaded into micelles through non-covalent interactions, there may be some drawbacks as the drugs could be prematurely released. Thus, conjugating the drugs to the micelle forming polymeric chains through a covalent bond, which can be cleaved under an appropriate stimulus could improve the performance of the micelles. In this context, Wang *et al.* prepared pH-responsive supramolecular prodrug micelles based on CB8 for intracellular drug delivery (Fig. 11).[60]

To form micelles, they synthesized naphthalene-terminated poly(ethylene glycol) (PEO-Np) and methyl viologen conjugated doxorubicin (MV-DOX). Aqueous solutions of PEO-Np, MV-DOX and CB8 were mixed in an equimolar ratio to form a ternary complex. Consequently, these amphiphilic ternary structures were self-assembled in water to form micellar structures. In the absence of doxorubicin, no micelle formation was observed; meaning that doxorubicin is essential to provide the hydrophobicity required for the micelle formation. DOX units
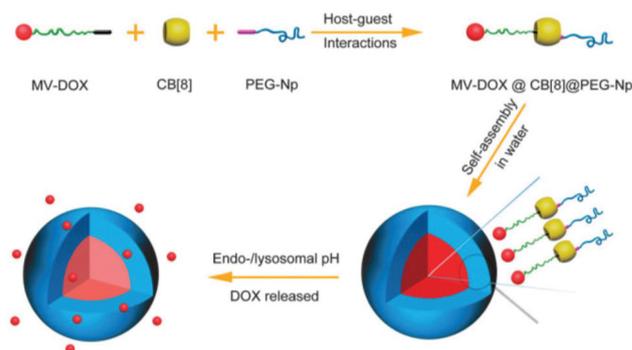
Fig. 11 Schematic of the formation of supramolecular prodrug micelles through ternary complexation and a controlled release of DOX by *endo*-/lysosomal pH stimulus. (Reprinted with permission from ref. 60. Copyright 2014 Royal Society of Chemistry.)

were linked to the polymer chains through hydrazone bonds, which could be cleaved under an acidic medium. A faster drug release was observed at pH 5 than at the physiological pH 7.4 when the micelles were exposed to aqueous solutions of buffers at pH 5 and pH 7.4.

Supramolecular peptide amphiphile vesicles were prepared in water through the host–guest complexation of CB8.[61] First, amphiphiles were prepared; for this purpose, a simple peptide sequence was decorated with pyrene, which acted as one of the guests for CB8, as well as a fluorescent sensor, and the viologen unit as a second guest was linked to a long hydrophobic tail. Vesicles were formed by the self-assembly of the prepared amphiphiles in water. The vesicles were reversible and their disassembly process could be triggered by competitive guests, such as 2,6-dihydroxynaphthalene and 1-adamantylamine. Upon the disassembly of the vesicles, pyrene-attached peptides were released into the surrounding environment and this, in turn, caused the simultaneous "switch on" of the fluorescence of the pyrene units. The vesicles were characterized by TEM and DLS, and their diameters were determined to be around 200 ± 60 nm. *In vitro* cell assays showed that these vesicles were readily taken up by HeLa cells and responded to multiple external triggers, indicating that their toxicity could be regulated using an appropriate stimulus.

These peptide amphiphile vesicles were also utilized for the encapsulation of basic fibroblast growth factor.[62] However, the vesicles used in this work contained PNIPAAm terminated with methyl viologen instead of a long hydrophobic alkyl chain. The ternary complex was formed between the short peptide terminated with the first guest pyrene and methyl-viologen-terminated PNIPAAm, and this led to the formation of an amphiphile, which self-assembles into the vesicles at physiological temperatures.

2.2.3 Supramolecular colloidosomes. Very recently, Sherman *et al.* reported the preparation of supramolecular colloidosomes.[63] Colloidosomes are microcapsules whose shells are composed of self-assembled colloidal nanoparticles. These colloidal nanoparticles are either fused together by thermal treatment or cross-link to achieve a stable but per-

338 | *Org. Biomol. Chem.*, 2015, **13**, 330–347

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meable surface. In this work, the authors first formed mono-disperse oil droplets using a microfluidic technique, and then the polystyrene-based nanoparticles, which are decorated with the binding motifs of MV for CB8, were self-assembled at the water-oil droplet interface. The PS-MV particles were reversibly cross-linked with a copolymer of poly(*N,N*-dimethylacryl-amide), comprising 10 mol% of naphthol-modified hydro-xyethylacrylamide (*p*-Np, 10.1 kDa) *via* a supramolecular complex of CB8. They also demonstrated the ability of these capsules to encapsulate, retain and subsequently trigger the release of cargo through disassembly of the ternary supramole-cular complex, which was achieved by introducing 1-adamanty-lamine (ADA) as a competitive guest for CB8. ADA forms a strong 1 : 1 complex with CB8, which displaces the methyl vio-logen and naphthol moieties (Fig. 12).

2.2.4 Ordered supramolecular arrays. The supramolecular approach was also employed for the functionalization and pat-terning of gold surfaces.[64] This was realized by self-assembled monolayers of the viologen-unit-linked decanethiol, which is one of the guests for CB8, formed on the gold substrate, and then the polymeric nanoparticles composed of the copolymer of styrene, vinyl styrene and 2-naphthyl methacrylate, were introduced to immobilize these mono-dispersed polymeric particles onto the surface through a ternary complex formation of CB8 with guest one and guest two as shown in Fig. 13. Using this approach, it was also possible to prepare patterned colloidal arrays.

In another work, a multistimuli responsive, reversible supramolecular system was constructed employing both redox and light-responsive guests, such as viologen and azobenzene derivatives.[65] This system might find practical applications in the fabrication of memory devices. Heteroternary complexes were formed between these guests and CB8 through host–guest chemistry. To show the practicality of this approach and to visualize the process, patterned surfaces were prepared by the micro-contact printing of a thiol-containing azobenzene derivative on a Au substrate. When the complexes of CB8 with the fluorescein-attached viologen were introduced in water, heteroternary complex formation takes place and the process can be clearly monitored due to the pres-ence of the fluorophore in the system. The system can be made reversible by irradiating with light, due to the confor-mational changes of the azobenzene derivatives from *trans*- to *cis*-isomer.
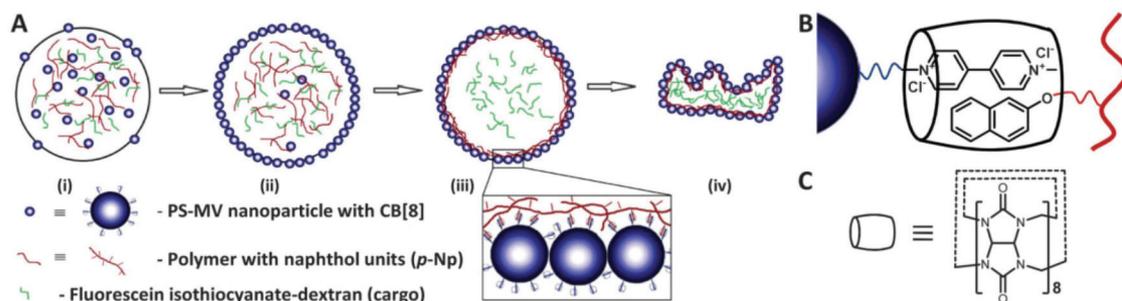
Fig. 12 (A) Schematic of colloidosome formation; (B) ternary supramolecular complex formation between PS-MV, *p*-Np and CB8. (C) The molecular structure of CB8. (Reprinted with permission from ref. 63. Copyright 2014 Royal Society of Chemistry.)
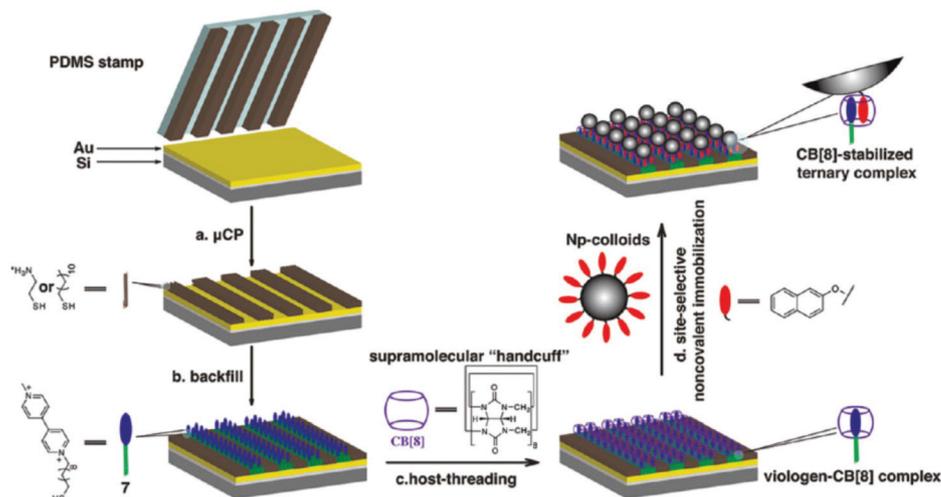
Fig. 13 Schematic representation of the site-selective non-covalent immobilization of Np-colloids on a micropatterned viologen-terminated Au substrate in the presence of CB8. (Reprinted with permission from ref. 64. Copyright 2010 American Chemical Society.)
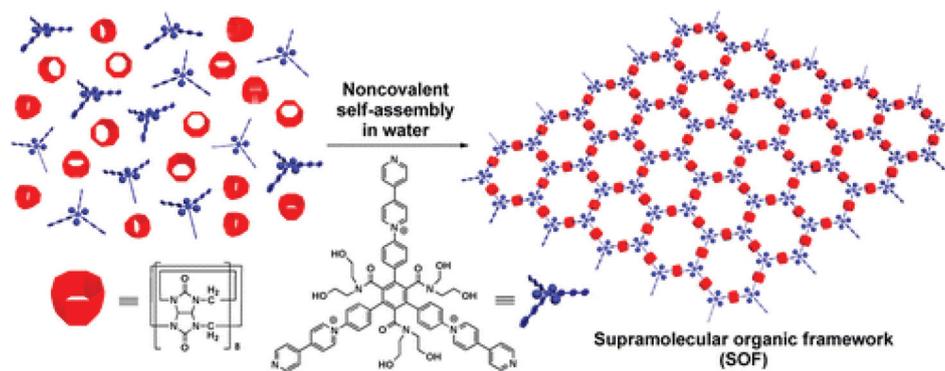
Fig. 14 Schematic representation of the CB8-mediated single-layer two-dimensional honeycomb supramolecular organic framework (SOF) formation in water. (Reprinted with permission from ref. 66. Copyright 2013 American Chemical Society.)

Li *et al.* designed and synthesized a CB8-mediated single-layer two-dimensional honeycomb supramolecular organic framework (SOF) in water.[66] 4,4′-bipyridin-1-ium (BP) units and hydrophilic bis(2-hydroxyethyl)carbamoyl groups were linked to a 1,3,5-triphenylbenzene core to suppress 1D stacking of the triangular backbone and to ensure solubility in water. When CB8 was added to this triangular core molecule, a 2D-network was obtained, due to homoternary complex formation between the two BP units and CB8 (Fig. 14). This 2D framework was characterized by various techniques, including ^{1}H NMR spectroscopy, dynamic light scattering, X-ray diffraction and scattering, scanning probe and electron microscope and by comparison with the self-assembled structures of the control systems.

In a slightly different design, SOF was prepared in such a manner that a viologen-units-attached triangular building block was utilized and SOF was formed by the dimerization of the viologen radical cation units in the presence of CB8.[67] The resultant supramolecular networks were characterized by various techniques, including UV-vis absorption spectroscopy, electron paramagnetic resonance, dynamic light scattering, solution and solid phase small angle X-ray diffraction, and AFM experiments.

It was also shown that CB8-based organic crystals with well-defined micro- and nanostructures could be prepared through the host–guest chemistry of CB8 with small organic molecules.[68] Using this approach, it is possible to control the shape, morphology and composition of the crystals. In particular, when optically active guests are used in their preparation, the resultant crystals might find interesting applications in the area of photonics and in solid state laser applications.

3.   CB-based nanostructures constructed from surface-functionalized CB homologues

Although functionalized CBs could find many potential applications in the area of nanostructured materials, their functionalization is challenging, and thus limits their use for

further applications.[69] In recent years, there considerable effort have been made to attach functional groups, especially on the periphery of cucurbiturils. Mainly, three different routes have been adopted for this purpose.[70–72]

Route 1 involves the use of glycoluril containing functional groups on the equatorial positions, before condensing with aldehyde to form CBs (Scheme 1: Route 1).[70] However, this method results in various mixtures of substituted and unsubstituted CBs, which are almost impossible to separate. Another method is to functionalize the aldehyde, and then condense to form the CBs (Scheme 1: Route 2). At first, this method was reported to be unsuccessful; however, Sindelar and co-workers, recently, reported functionalized CB6 on the methylene bridge starting from a functionalized aldehyde.[71] Many attempts to directly functionalize CBs failed because of their high chemical stability. Kim and co-workers developed a method to post-functionalize CBs directly with hydroxyl groups (Scheme 1: Route 3).[72]

This method involves the reaction of CB (n = 5–8) with potassium persulfate ($K_2S_2O_8$) in water to yield perhydroxy-CB [n], $(HO)_{2n}CB[n]$ (n = 5–8) as potassium ion complexes
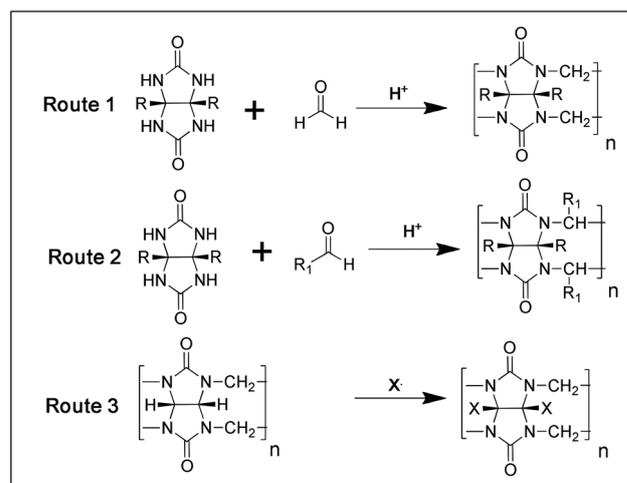
Scheme 1   Different routes for CB functionalization.
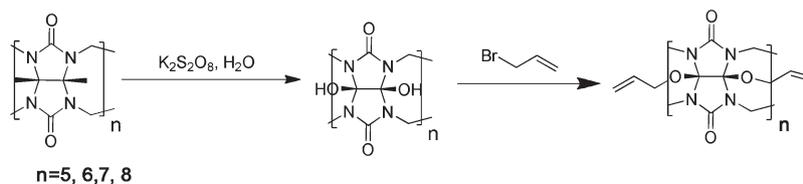
Scheme 2 Synthesis of perhydroxy CBs and allyoxy–CBs.

(Scheme 2).[72] A typical yield for the lower homologues CB5 and CB6 is in the range 40%–45% and 5% or less for the higher homologues CB7 and CB8, respectively. This decrease in yield could be explained by the instability of the perhydroxylated products. The mechanism of CB hydroxylation is not fully understood, although an OH radical generated by $K_2S_2O_8$ is expected to be involved. X-ray data revealed the presence of hydroxyl groups at the periphery of the CB $(HO)_{12}CB[6]$ and $(HO)_{10}CB[5]$. These hydroxy derivatives of CB[n]s are reported to be soluble in both DMF and DMSO. The perhydroxy CB[n]s can further be functionalized with other functional groups *via* a simple organic synthesis to obtain the desired functional groups on CB[n]s, as shown in Scheme 2.

Although fully substituted CB[n]s have great potential applications, attaching a single functional group on the parent CB[n] would guarantee a high level of control over molecular structures and topologies on the nanoscale. Several routes have been reported to synthesize mono-functionalized CBs starting with functionalized glycoluril or functionalized aldehyde. However, these methods involve very tedious separation techniques. Sherman and co-workers reported the first method to directly mono-functionalize CB[6].[73] Although the MonOH is more soluble in water compared to the parent CB[6], the solubility of MonOH in water is still not so high. This can be explained by the isostructure of MonOH with the parent CB[6] structure, as suggested by the crystal structure of MonOH as $MonOH \cdot 2Na_2SO_4 \cdot 23H_2O$. The mono-functionalized CB[6] can further be functionalized with reactive functional groups. Very recently, Kim and co-workers reported the isolation of mono-hydroxyl-functionalized CB7 by slightly modifying the synthetic reaction conditions used for the synthesis of perhydroxyCB[n].[74]

Although post-surface-functionalized CBs with reactive functional groups are very useful building blocks in the assembly of supramolecular structures, there are only a handful of examples. The following section will accordingly discuss examples, in which post-functionalized CBs were involved in the construction of nanoparticles, nanocapsules and nanosheets.

3.1 Nanocapsules

Polymeric nanocapsules were prepared through a facile, template-free synthetic method using well-designed, rigid and disk-shaped CB-based building blocks.[75] CB6 fully functionalized with allyoxy groups were polymerized through thiol–ene click chemistry by irradiating with light to form nanocapsules. The mechanism of their formation was suggested as formation of a 2D-network, which turns into a cap, and then a hollow sphere. This was also supported by theoretical calculations.

The cavity of CBs are available for sequestering suitable sized-hydrophobic molecules; this feature makes the polymer nanocapsules potentially useful in many applications, including targeted delivery and imaging. Moreover, the surfaces of the nanocapsules could be decorated with many useful reactive groups through host–guest chemistry. To demonstrate this, fluorescent probes linked to spermidine were attached to the nanocapsule surfaces *via* non-covalent interactions, and the nanocapsules were imaged using confocal laser scanning microscopy (Fig. 15).

Second-generation CB-based nanocapsules were synthesized using a slightly different design than the previous one, and have potential to be used in controlled cargo delivery. They were programmed to release loaded cargos in a reducing environment due to the presence of reducible disulfide bridges in their structures.[76] For their synthesis, first, hydroxyl groups of allyoxy-CB6 were treated with mercaptoethylamine to obtain disk shaped-rigid CB-based building blocks, and then upon the addition of a disulfide containing bifunctional active ester, 2D-polymeric networks were formed *via* amide bond formation, which gradually curved into spherical nanocapsules. Nanocapsule formation was supported by high resolution TEM (HRTEM) images, showing that they had an average diameter of 50–90 nm with hollow interiors (Fig. 16).

In order to demonstrate the applicability of polymer nanocapsules in controlled-drug release, carboxyfluorescein (CF)-encapsulated nanocapsules were prepared and the surface of the nanocapsules were decorated with galactose-spermidine to target overexpressed galactose receptors in HepG2 hepatocellular carcinoma cells. The internalization and reduction-triggered release of the fluorescent dyes from the capsules were monitored by confocal microscopy and the results were compared with the capsules loaded with fluorescent dyes but they did not have a reducible disulfide linkage in their structures. When reducible nanocapsules were internalized by the cells, an increase in the fluorescent emission was observed, due to the cleavage of the disulfide linkage and the release of the fluorescent dyes into the cytoplasm. However, in the case of non-reducible nanoparticles loaded with dyes, there was no increase in the fluorescent emission, indicating that the dyes were tightly placed inside the nanocapsules.

It was also shown that these nanocapsules could be decorated with metal nanoparticles (M = Pd, Au and Pt). The sulphur residues, as well as the carbonyl groups of the CBs on

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Org. Biomol. Chem., 2015, **13**, 330–347 | 341
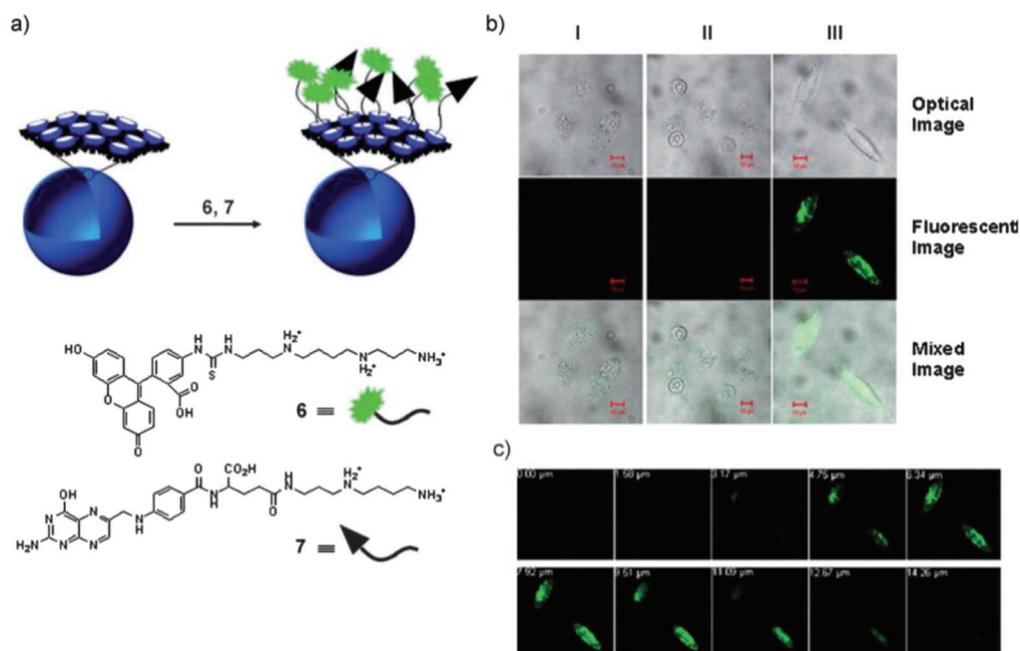
Fig. 15 Preparation of surface-decorated polymer nanocapsules and confocal microscopy images of the polymer nanocapsules incorporated into KB cells. (Reprinted with permission from ref. 75. Copyright 2007 Wiley-VCH Verlag GmbH & Co. KGaA.)
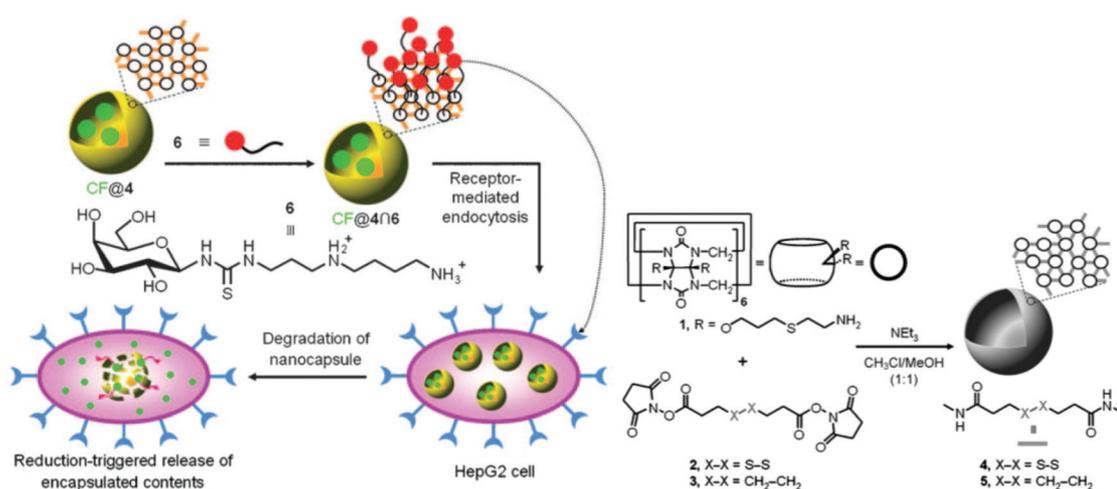
Fig. 16 Schematic representation of the surface modification of CF-loaded nanocapsules with galactose-spermidine through host–guest interactions, the receptor-mediated endocytosis, and the reduction-triggered release of the encapsulated CF to cytosol. (Reprinted with permission from ref. 76. Copyright 2010 Wiley-VCH Verlag GmbH & Co. KGaA.)

the surface of the nanocapsules, could act as ligands to stabilize these metal nanoparticles. The catalytic ability of the Pd-nanoparticle decorated nanocapsules were successfully demonstrated in the Suzuki coupling and in the Buchwald–Hartwig amination reaction (Fig. 17).[77]

3.2 Nanosheets

As mentioned above, during the formation of the nanocapsules, first, 2D-polymeric network types structures formed, and then these structures become cap-like, and finally spherical hollow nanocapsules. Kim and co-workers carefully investi-

gated the formation of 2D-networks by tuning the reaction conditions.[78] In particular, they observed that the bending rigidity of the building blocks and the solvent play an important role in determining that the 2D-networks formation will lead to nanocapsules or instead these networks will simply fold or curve not forming hollow nanocapsules. From the theoretical and experimental studies, they concluded that while poor solvent and building blocks with low bending rigidity allow nanocapsule formation, good solvent and high bending rigidity cause the formation of rolled 2D-polymeric structures. (Allyloxy)$_{12}$CB6 was cross-linked with 1,2-ethane-

342 | *Org. Biomol. Chem.*, 2015, **13**, 330–347

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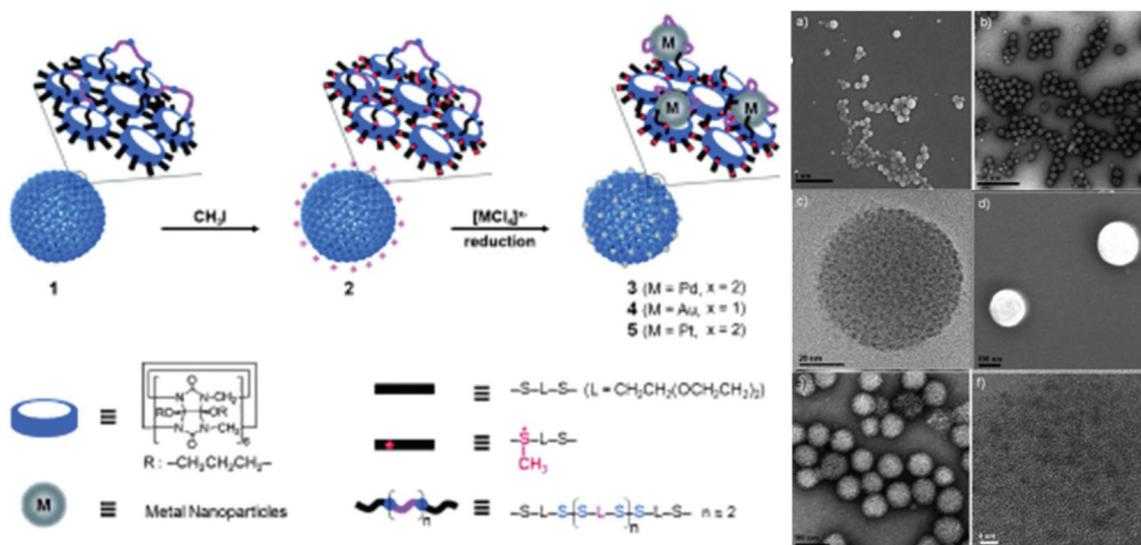
Fig. 17 Schematic presentation of the preparation of CB6-based nanocapsules decorated with metal nanoparticles (M = Pd, Au, and Pt), and TEM images of these hybrid nanocapsules. (Reprinted with permission from ref. 77. Copyright 2014 Wiley-VCH Verlag GmbH & Co. KGaA.)

dithiol through thiol–ene click chemistry by irradiating with light to form 2D-networks in DMF, which is a good solvent for the building blocks. In order to obtain free-standing, mono-layered films, the layers should not stack together. To achieve this, they added protonated spermine, which binds to CBs and provides positively charged surfaces, which can cause repulsion between the polymer film layers, and thus keeping them apart. These free-standing, one-molecular-thick polymeric films are very appealing and might find many important applications, spanning selective separation, transport and sensing.

The formation of vesicles and nanocapsules were also reported by a post-functionalization of the surfaces of CB6 with polymers using a radical initiator. Polyacrylamide grafted onto the equatorial position of the CB6 was prepared using potassium persulfate as the initiator and oxidant. These poly-acrylamide-grafted CBs were self-assembled into vesicles, and the formation of the vesicles were confirmed by microscopic techniques, including AFM, SEM and TEM.[79]

3.3 Nanoparticles

Functionalized CB6 was utilized in the preparation of nanoparticles to make use of its cavity for carrying hydrophobic drugs or for modifying its surface in targeting drug delivery.[80]

First, perhydroxy-CB6 was converted into (allyloxy)$_{12}$CB6, and subsequently 6-mercaptohexanol was attached through thiol–ene click chemistry. The functionalized CB6 was dissolved in water and, under sonication, a minimum volume of ethanol was added to induce the nanoparticle formation. The resulting nanoparticles were characterized with DLS and TEM techniques. Folate receptor, fluorescein isothiocyanate (FITC) and Nile Red (NR) as fluorescent tags for optical imaging were first attached to the spermidine derivatives in order to incorporate them onto the surfaces of the nanoparticles through the host–guest chemistry of CBs. The molecular structures of

Nile Red, folate receptor, spermidine, and functionalized CB6 are shown in Scheme 3. With and without folate receptor attached functionalized CB6 nanoparticles loaded with anti-cancer drugs, such as paclitaxel (PTX), were also prepared, and HeLa cells were incubated with these drug-loaded nanoparticles. IC$_{50}$ (50% of cell growth inhibition concentration) values were calculated to be 1.24 ± 0.20, 0.33 ± 0.10 and 0.08 ± 0.02 μg mL^{-1}; for free PTX, PTX-CB6NPs and PTX-CB6NP-folate receptor, respectively. It can be concluded that the CB6-NPs are remarkably effective even with a non-specific internalization of the drugs into the cytoplasm. Folate receptor also indicated the enhanced cytotoxicity due to the receptor mediated endocytosis. These results represent a promising usage of functionalized CB6 nanoparticles for the pharmacokinetics effect of the drugs.

3.4 Supramolecular scaffolds

Surface-functionalized CB6-based supramolecular hyaluronic acid (HA) hydrogels for tissue engineering applications were described by Kim *et al.*[81] In order to mimic an extracellular matrix, functionalized CB6s were attached to HA and mixed with diaminohexane-conjugated HA (DAH-HA) (Fig. 18). Due to the high affinity of diaminohexane units towards CB6, the supramolecular hydrogel was formed and served as an extracellular matrix, which allowed cell proliferation, and furthermore exhibited no cytotoxicity. The cell growth process and the stability of the matrix could also be monitored by confocal laser microscopy by incorporating fluorescent tags to the system through the host–guest chemistry of CB6. The *in situ* formation of supramolecular hydrogels under the skin of nude mice by sequential subcutaneous injections of CBs-linked HA and diaminohexane-conjugated HA solutions were also demonstrated. It was also shown that the hydrogel was bio-
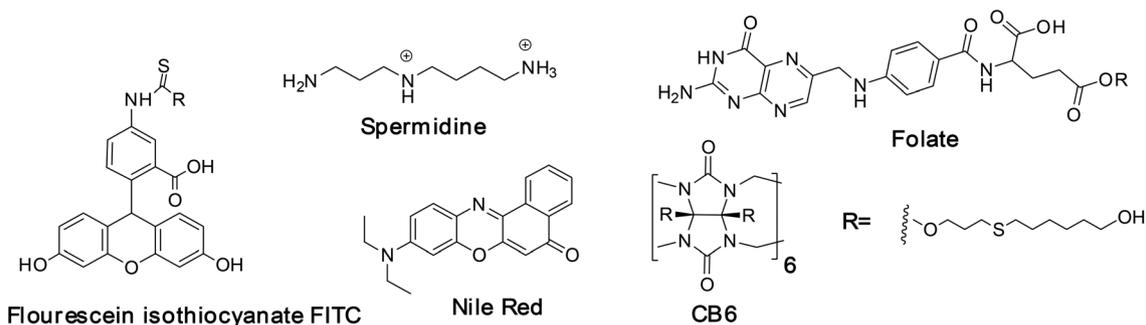
Scheme 3 Structure of Nile Red, folate receptor, spermidine and functionalized CB6 for nanoparticles synthesis.
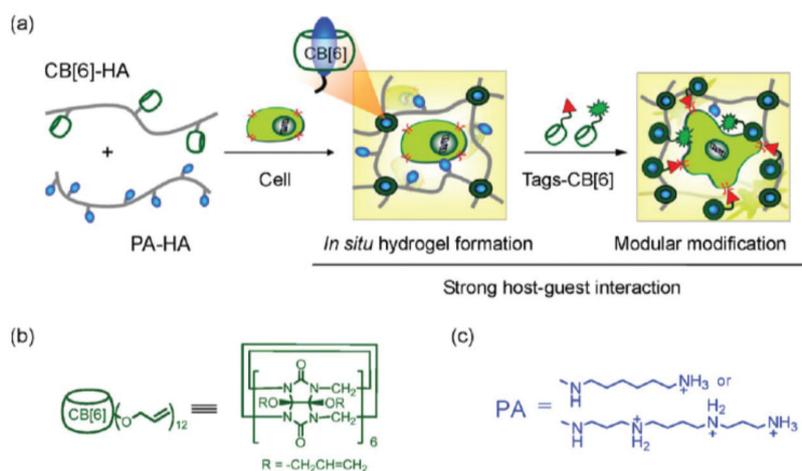
Fig. 18 (a) Schematics of the formation of a supramolecular biocompatible hydrogel through the host–guest chemistry of CB6 attached to HA and diaminohexane- or spermine-conjugated HA. The chemical structures of (b) allyloxy-CB and (c) diaminohexane and spermine. (Reprinted with permission from ref. 81. Copyright 2012 American Chemical Society.)
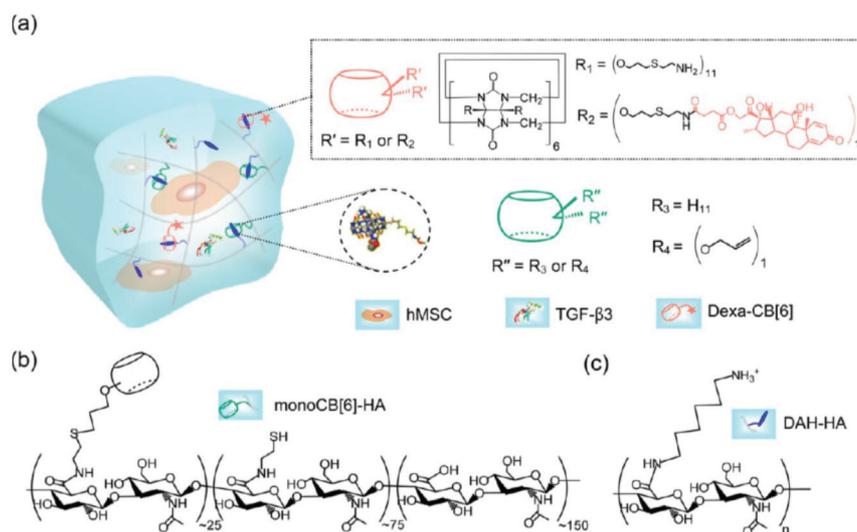
Fig. 19 Schematics of (a) supramolecular monoCB6/DAH-HA hydrogels encapsulating hMSCs and TGF-β3 with modularly modified Dexa-CB6 by the strong host–guest interaction between CB6 and DAH. The chemical structures of (b) monoCB6-HA and (c) DAH-HA. (Reprinted with permission from ref. 82. Copyright 2014 American Chemical Society.)

344 | *Org. Biomol. Chem.*, 2015, **13**, 330–347

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degradable, as enzymatic degradation occurred within 24 h after treating the hydrogel with the hyaluronidase enzyme.

Modifying the previously described approach,[81] supramolecular hydrogels were prepared as a scaffold, with the ability to deliver drugs in a controlled fashion for cartilage regeneration and other tissue engineering applications (Fig. 19).[82] For the preparation of hydrogels through the host–guest chemistry of CB6, first, two different hyalunaric acid (HA) derivatives were synthesized; one of them was prepared by attaching monoallyoxy-functionalized CB6 to HA via thiol-en chemistry, and the second one contained diaminohexane units grafted onto HA. Mixing these two HA derivatives in the presence of human mesenchymal stem cells (hMSCs) resulted in the formation of supramolecular cytocompatible hydrogels, which had a highly porous microstructure. It was observed that more than 95% of the hMSCs in these HA hydrogels survived and proliferated, even after incubation for 10 days. The differentiation of hMSCs was temporally controlled by changing the release profiles of the transforming growth factor-β3 (TGF-β3) and/or dexamethasone (Dexa) from the hydrolyzable Dexa-CB6. The effective chondrogenic differentiation of hMSCs was confirmed by biochemical glycosaminoglycan content analysis, as well as real-time quantitative PCR, histological, and immunohistochemical analyses.

4. Conclusions

In this review, we presented a number of CB-containing nanostructures, which were either constructed by the host–guest chemistry of CB homologues or formed through the self-assembly of post-functionalized CB6 or CB7.

By taking advantage of the rich host–guest chemistry of the CB homologues, a number of different nanostructures were prepared. In particular, the ability of CB8 to form ternary complexes with electron rich and electron deficient species has been well-exploited in the construction of supramolecular nanostructures, such as supramolecular hydrogels, nanoparticles, vesicles and supramolecular arrays. These nanostructures could find many interesting applications, especially in the area of self-healing materials, the delivery of drugs or other therapeutic materials, and in the area of theranostics, as well as for controlling the viscosity of materials.

Although post-surface-functionalized CBs with reactive functional groups are very useful building blocks for the assembly of supramolecular structures, until recently, the mono-functionalization of CB homologues has proven to be particularly challenging, which has thus limited their use for further applications. The yields are still quite low in the synthesis of perhydroxy or monohydroxy CBs, which is another limiting factor for their wide applicability. As a result of the aforementioned reasons, examples of post-functionalized CB-based nanostructures are relatively scarce in the literature compared to non-functionalized CB-based nanostructures. Therefore, it is quite important to find new methods, which could

provide high yields for the synthesis of functionalized-CB homologues, especially for CB7 and CB8 with large cavities.

In the future, we expect to see more work on multi-functional nanostructures based on post-functionalized-CB homologues.

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Org. Biomol. Chem., 2015, **13**, 330–347 | **347**