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Cucurbit[*n*]uril-based nanostructure construction and modification

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ABSTRACT

New fabrication method of nanostructures is of great importance for the applications of nanoscience and nanotechnology. This review summarizes cucurbit[*n*]uril (CB[*n*])-based nanostructure fabrication and modification approaches. These strategies include the use of CB[*n*]s as building blocks and supramolecular crosslinkers to fabricate nanostructures, to surface modify nanostructures, and as gatekeepers to control the release of encapsulated cargo. These nanostructures are used for drug delivery, bioimaging, chemical sensing, catalysis and other applications. CB[*n*]s often play a vital role in the fabrication of these nanostructures, and the realization of the applications.

1. Introduction

Nanoscience and nanotechnology have experienced great advances in the past half a century [1–3]. The early nanoscience and nanotechnology research focused on the design, construction and characterization of nanoarchitectures. Later, the focal point of nanoscience and nanotechnology has been shifting to the practical use of fabricated nanostructures. Some of the applications of nanotechnology include photoluminescence and imaging [4], drug delivery [5], chemical sensing [6], antimicrobial treatment [7], and electronics [8].

The construction and modification of nanoparticles, nanorods, nanofibers and other nanostructures are the cornerstone to develop applications in nanoscience and nanotechnology [9,10]. The approach to fabricate nanostructures is crucial for the chemical composition and stability, as well as the physical characteristics, including size, shape and uniformity. Surface property is another important factor for nanostructures, which has a major impact towards the aggregation, transmembrane efficiency, cargo loading and release.

Covalent crosslinking and noncovalent interactions are applied to construct nanostructures. Supramolecular interaction may be used to conveniently assemble nanostructures under a mild condition [11–15]. The dynamic supramolecular interaction is also favorable to achieve the desired size and shape [16,17]. Supramolecular interaction acts as a simple and efficient way to introduce functional groups to the nanostructure surface [18]. The supramolecular regulation of nanostructure surface will significantly impact the chemical and biological performance of the nanostructures [19].

Cucurbit[*n*]urils (CB[*n*]s) are a family of macrocyclic host molecules [20]. CB[*n*]s are generally considered to be water soluble in water. To further improve their aqueous solubility or recognition characteristics, CB[*n*] derivatives and analogues are designed and synthesized. CB[*n*]-type hosts have excellent binding affinity and selectivity towards suitable guests [21]. CB[*n*]s possess rigid, pumpkin-shaped architectures, and are composed of two electron-rich carbonyl portals, which are capable of binding with nanoparticle surface. These two important properties render CB[*n*]s promising candidates in the construction and modification of nanoarchitectures.

Since the beginning of the new millennium, CB[*n*] research has enjoyed more than two decades of prosperity. The unique structure and excellent property of CB[*n*]s have rendered them key ingredients to construct nanoarchitectures. For some applications in nanoscience and nanotechnology, these hosts are irreplaceable to achieve the desired functions [22–26].

This review article will summarize the advances on how CB[*n*]s are used to construct and modify nanostructures, and what applications have been achieved. As shown in Fig. 1, the approaches of CB[*n*]s used to construct or modify nanoarchitectures are classified into four categories: (1) as the building block of nanostructures; (2) as a supramolecular crosslinker inside nanostructures; (3) to mod-

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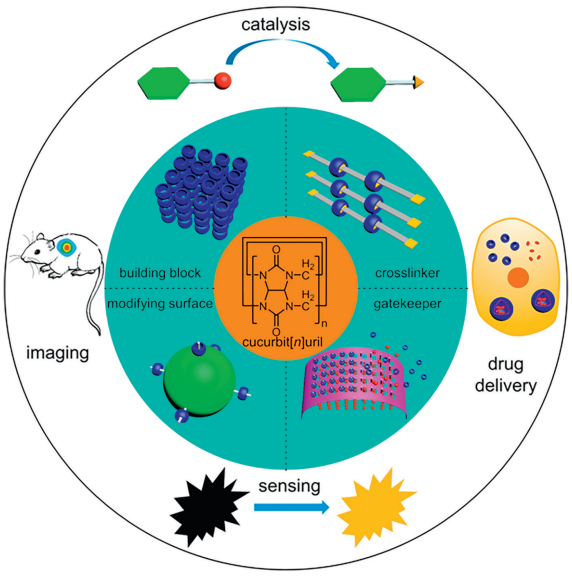

Fig. 1. Strategies for CB[*n*]-based nanostructure construction and modification, and their applications.

ify nanostructure surface; (4) as gatekeepers to control the release of cargo. Applications have been developed based on these nanostructures. While there are no universal rule to choose the construction strategy, the optimal approach is often determined based on the desired nanostructure stability, surface property and cargo release characteristics.

2. CB[*n*]-type host molecules

Since the discovery of CB[*n*]s in 1905, CB[*n*] family has expanded to a large variety of hosts. As shown in Fig. 2, CB[5], CB[6], CB[7], CB[8] and CB[10] are some of the first isolated macrocyclic CB[*n*]s [27–29]. Inverted CB[*n*]s, ns-CB[10] and bis-ns-CB[6] are macrocyclic CB[*n*]s with unique structures [30–33]. Large-sized macrocyclic CB[*n*]s were later discovered and isolated as twisted CB[*n*]s [34]. All the above CB[*n*]s are composed of glycoluril building blocks. The syntheses of CB[*n*] analogues are based on one-pot cyclization reactions, which generally yield CB[*n*] mixtures. The distribution of CB[*n*] products is controlled by reactant ratio and reaction conditions.

To further diversify CB[*n*] structures and improve their properties, CB[*n*] derivatives and analogues have been developed. Examples include macrocyclic CB[*n*] derivatives based on substituted glycoluril [35], and CB[*n*] analogues based on glycoluril and bis(phthalhydrazide) [36]. The chemical modification of CB[*n*]s is generally considered to be challenging. It was discovered that glycoluril oligomers were able to retain a rigid C-shape structure, and acyclic CB[*n*]s were designed and synthesized [37]. Acyclic CB[*n*]s retain the excellent binding property of macrocyclic CB[*n*]s. Different from macrocyclic CB[*n*]s, acyclic CB[*n*]s are convenient to modify, and the multistep synthesis renders them to be prepared in a large scale.

The above CB[*n*]s, CB[*n*] derivatives and CB[*n*] analogues generally possess high binding affinity and selectivity towards suitable guests, since these hosts feature restrictive and hydrophobic cavities, and electron-rich carbonyl portals. The structural characteristics render some driving forces for binding, including hydrophobicity, electrostatic interactions, hydrogen bonding and chaotropic effect. Among them, chaotropic effect is a unique driving force, which is orthogonal to the hydrophobic effect and most effective for very large ions that extend beyond the classical Hofmeister scale [38].

The above wide array of CB[*n*]-type molecular containers offer a variety of hosts to choose from. Three types of CB[*n*]-based supramolecular interaction are most frequently used to build nanoarchitectures: (1) CB[*n*]-based high affinity inclusion complexation with 1:1 stoichiometry, which may reach up to picomolar dissociation constant; (2) CB[8]-based ternary complexation with a 1:2 host-guest stoichiometry; (3) the binding between CB[*n*] carbonyl fringe and nanoparticle surface. CB[*n*]s could also be used as the key building blocks to construct nanostructures *via* covalent bonds. The diverse CB[*n*]s and multiple ways to construct nanoarchitectures render these hosts acting as powerful tools in nanoscience and nanotechnology. Their unique structures and ultra-high binding affinity with suitable guests allow them to be the optimal or even the sole option for some applications.

3. As building blocks of nanoarchitectures

CB[*n*]-type hosts could serve as building blocks to construct nanoarchitectures. The oxidation of peripheral hydrogens on macrocyclic CB[*n*]s could be used to introduce hydroxyl groups, which may be further functionalized *via* thiol-ene "click" reaction or other synthetic methodology. Acyclic CB[*n*]s could be conveniently modified with functional groups. These chemical modified CB[*n*]-type hosts could be used as the key building blocks. The hosts are either crosslinked by covalent bonds to prepare nanocapsules, or self-assembled into supramolecular nanoarchitectures. The host cavity of these nanoarchitectures may be used to encapsulate cargo for drug delivery and other applications.

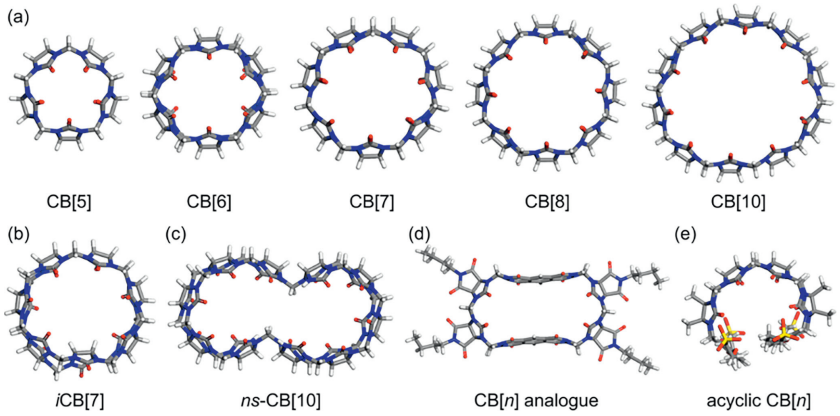

Fig. 2. Chemical structures of macrocyclic CB[*n*]s, CB[*n*] analogue and acyclic CB[*n*].

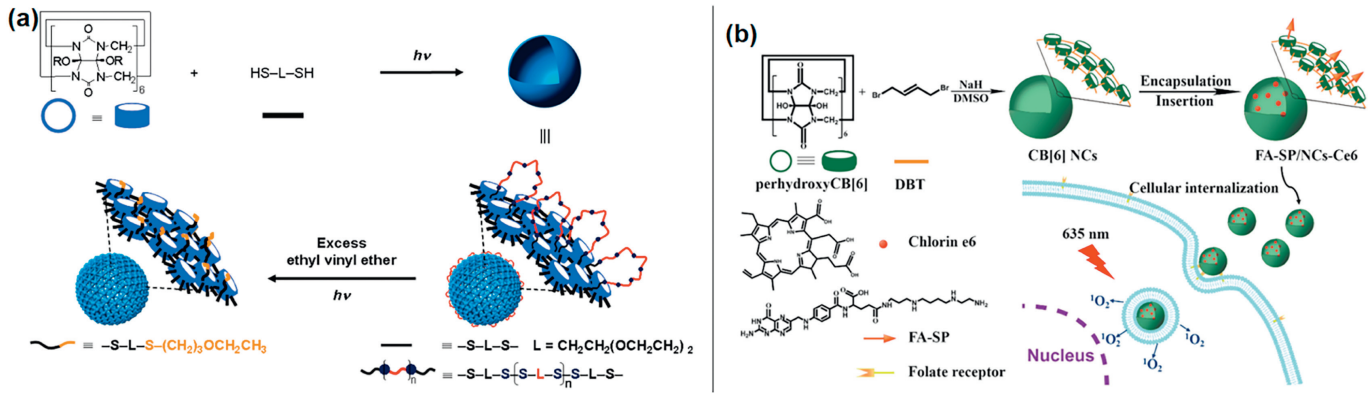

Fig. 3. (a) Synthesis of CB[6]-based polymer nanocapsules. Adapted with permission [35]. Copyright 2010, American Chemical Society. (b) Schematic illustration of polymer nanocapsule preparation and construction of the drug delivery system. Adapted with permission [37]. Copyright 2019, American Chemical Society.

3.1. CB[n]-based nanocapsules

Kim, Sung and coworkers developed direct synthesis of CB[6]-based polymer nanocapsules [39,40]. The synthesis started from $(allyloxy)_{12}$CB[6], a synthetic host molecule with 12 reactive allyloxy groups at the periphery (Fig. 3a). The CB[6] derivative was reacting with dithiol crosslinkers with various length to undergo an irreversible covalent formation. It was confirmed that 2D oligomeric patches turned into a hollow sphere to give the resulting polymers nanocapsule architectures. It was discovered that appropriate reaction conditions could be used to control the size of nanocapsules. Nanocapsules were capable of encapsulating model dye in the interior of the nanostructures. CB[6] cavities were exposed to further encapsulate cargo *via* host-guest interactions. This method was later applied to the preparation of free standing and single-monomer-thick 2D polymers [41].

This nanocapsule preparation method was applied for drug delivery purpose. Wang and coworkers used a ditopic linker, 1,4-dibromobut-2-ene, to crosslink perhydroxyCB[6] (Fig. 3b) [42]. The covalent bond formation led to the construction of CB[6]-based nanocapsules, which were used for the loading of photodynamic therapeutic drug chlorin e6 (Ce6). Surface CB[6] cavities were used to incorporate folate targeting groups *via* host-guest interaction. The nanocapsules were capable of targeted deliver Ce6 to tumor cells *in vitro*. A similar methodology was used to prepare nanocapsules with azobenzene crosslinker, which were confirmed to release payload under hypoxia conditions [43]. The nanocapsules were able to targeted deliver doxorubicin to hypoxia cells on zebrafish animal model.

3.2. CB[n]-based self-assembly

Another strategy to construct CB[*n*]-based nanoparticles is by supramolecular interactions. Self-assembly is a simple and efficient way to build nanoarchitectures. Stimuli responsiveness could often be conveniently introduced into the design of self-assembly systems.

Kim and coworkers synthesized CB[*n*] derivatives, and introduced hydrophilic chains to give amphiphilic CB[*n*]s, which were assembled into vesicles [44]. Kim, Park and coworkers developed a mono-allyloxylated CB[7] into an unconventional amphiphile [45]. It was discovered that this mono-allyloxylated CB[7] acted as a surfactant, and self-assembled into well-dispersed colloidal particles. Mono-allyloxylated CB[7] could react with glutathione under UV irradiation *via* a thiol-ene conjugation, which led to a morphological change. This unconventional amphiphile was used to encapsulate cargo drug. Light-triggered intracellular cargo release was achieved with two photon absorption by the reaction between the allyloxy group and cytosolic thiol molecules.

Wang and coworkers designed and fabricated a safe, biocompatible, and stimuli-responsive CB[7]-mediated supramolecular bactericidal nanoparticle (Fig. 4a) [46]. The nanoparticle was fabricated by encapsulating a highly bioactive carbazole-decorated imidazolium salt into CB[7], which led to self-assembled topographies from microsheets to nanospheroidal architectures. *In vivo* antibacterial trials against rice bacterial blight were carried out, and confirmed that the bactericidal nanoparticle was capable of relieving the disease symptoms after being triggered by 1-adamantanamine hydrochloride.

Liu and coworkers used four macrocyclic hosts, CB[7], CB[8], water soluble pillar[5]arene and tetrasulfonated crown ether, to mediate the host-guest assembly, which generate various nanoscale and microscale architectures (Fig. 4b) [47]. Bipyridinium-modified diphenylalanine derivative was used as the guest. The high affinity binding between host and bipyridinium-guest led to topological aggregates from nanofibers to nanorods, octahedron-like nanostructure, helical nanowires, and rectangular nanosheets. This work demonstrates that CB[*n*] is a powerful tool to fine-tune the nanoarchitectures by supramolecular encapsulation, which is also reported by other research groups [48–50].

CB[*n*]-based nanoscale self-assembly was developed for biomedical applications. Ma and coworkers developed supramolecular vesicles based on acid-labile acyclic CB[*n*] and doxorubicin prodrug [51]. The supramolecular vesicles were assembled by the inclusion complex formed between acyclic CB[*n*] host and doxorubicin moiety. The negatively-charged supramolecular vesicles could convert to positively-charged micelles with smaller sizes under mildly acidic conditions, which was due to the degradation of acid-labile host. Cell study demonstrated the pH-responsive supramolecular vesicles could targeted-deliver doxorubicin to cancer cells under acidic condition.

Wang and coworkers used the chaotropic effect to design and prepare supramolecular organic frameworks (SOFs) based on CB[8], methylene blue and closo–dodecaborate cluster (B_{12}) [52]. A uniform NanoSOF was conveniently prepared with excellent water dispersibility and bioavailability by simple mixing. The *in vivo* study confirmed that NanoSOF was a smart nanomedicine for targeted tumor imaging and photodynamic therapy of tumor.

Other smart drug delivery systems (DDSs) based on CB[*n*] nanoscale self-assembly were reported [53–56]. These reports show that CB[*n*]s are excellent host molecules to construct versatile nanoarchitectures with great stability under complex physiological or pathological conditions. Other CB[*n*]-based nanoscale imaging systems were investigated [57–60]. The outstanding recog-

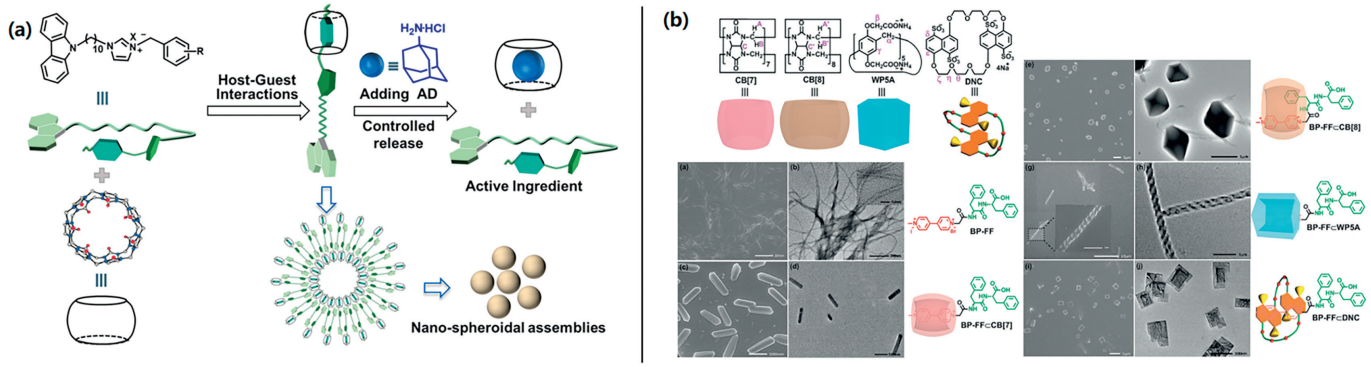

Fig. 4. (a) Schematic presentation of using the stimuli-responsive host-guest system for phytopathogen management. Adapted with permission [41]. Copyright 2022, American Chemical Society. (b) Chemical structures of hosts, and microscopic images of supramolecular assemblies. Adapted with permission [42]. Copyright 2016, John Wiley and Sons.

nition property of CB[*n*]s renders them great candidates as building blocks for sophisticated nanoarchitectures.

4. As supramolecular crosslinker

When constructing nanostructures, CB[*n*]s are widely used as supramolecular "crosslinkers". CB[8] is the most frequently used host molecule due to its ability to form highly stable 1:2 inclusion complex. Ns-CB[10] is another host to form 1:2 inclusion complex as a supramolecular crosslinker. CB[*n*]s are used as supramolecular crosslinkers to build polymeric nanoparticles, self-assembly nanostructures and nanoscale supramolecular organic frameworks (SOFs).

4.1. Polymeric nanoarchitectures

The crosslinking of polymeric chains is a common strategy to fabricate nanoparticles. CB[*n*]s can be used as supramolecular crosslinkers to construct polymeric nanoarchitectures due to the highly stable host-guest complexation. CB[8]-based ternary complexation is the most frequently used supramolecular interaction. To control the size and morphology of polymeric architectures, either "bottom up" or "top down" method is applied.

Abell, Scherman and coworkers developed a simple one-step approach based on CB[8] ternary complexes for the fabrication of microcapsules (Fig. 5a) [61]. Microfluidic droplets were used as "top down" template to produce highly uniform microcapsules with a continuous production. This supramolecular fabrication method produced dynamic and highly stable microcapsules, which could be loaded in one step during the formation of microscale structures and were amenable to on-demand cargo release. Later, this microfluidic fabrication method was used to produce ultrathin polymer microcapsules by electrostatically directed self-assembly [62]. The "top down" method was further applied to form patterned arrays of supramolecular microcapsule (Fig. 5b) [63]. The hydrogel material was formed by CB[8] ternary complexation, and patterned by sessile microdroplets on plasma-treated solid surface. The dynamic host-guest interaction yielded well-defined microcapsule skins, which were potentially responsive to a wide variety of stimuli.

Another way to control the size of polymeric nanoparticle is the "bottom up" strategy. Scherman and coworkers developed single chain polymer nanoparticles mediated by CB[8] ternary complexation [64]. The side chains of the water-soluble polymer were functionalized with naphthalene and viologen groups, which would be simultaneously encapsulated by CB[8] to form high affinity inclusion complexes. The polymeric materials were "collapsed" at the molecular level due to the intramolecular CB[8]-mediated crosslinking to yield nanoparticles. Similarly, ns-CB[10] was used to crosslink polymeric chain to form nanoparticles [65].

4.2. Supramolecular nanoscale self-assembly

When using small organic molecules or other non-polymeric compounds as building blocks, the crosslinking by CB[8] may be used to construct supramolecular nanoscale self-assembly [66–68].

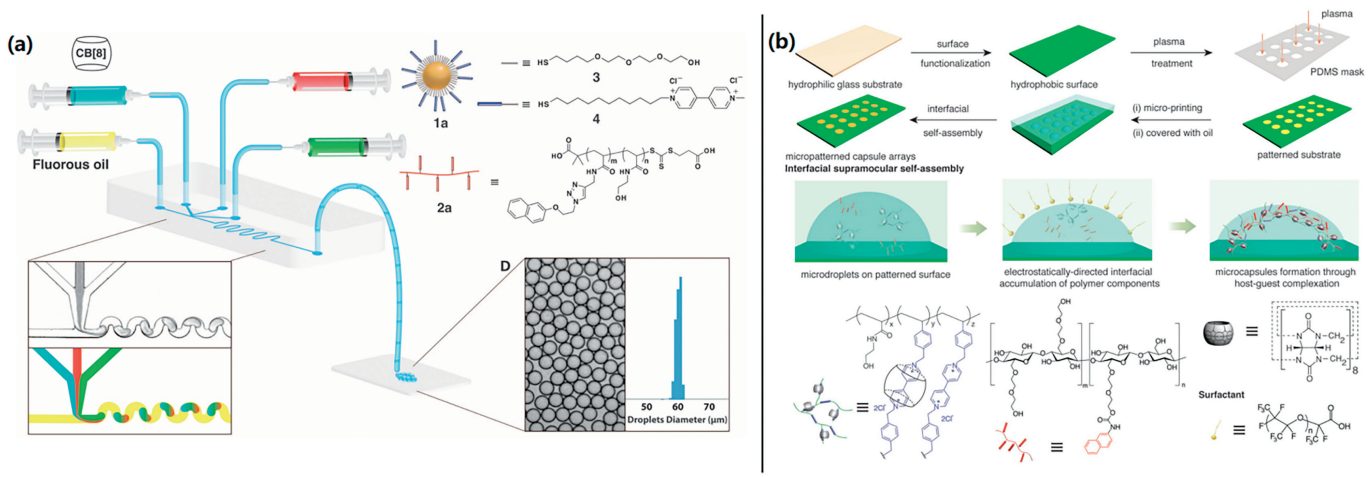

Fig. 5. (a) Schematic representation of the microcapsule fabrication mediated by microfluidic droplets. Adapted with permission [56]. Copyright 2022, American Association for the Advancement of Science. (b) Schematic illustration for preparing the patterned arrays of supramolecular hydrogel-based microcapsules.

The self-assembly is often achieved by supramolecular aggregation. The nanoscale supramolecular self-assembly is used for drug delivery, imaging and other applications.

Scherman, Barrio and coworkers investigated the two-dimensional crystallization of CB[8] complexes [69]. The imidazolium guest formed a supramolecular complex with CB[8], which subsequently underwent an aggregation process. The stepwise self-assembly yielded anisotropic crystalline aggregates, which were identified to be micron-sized two-dimensional fibers with a thickness of a single CB[8] macrocycle. This investigation implied that the macroscopic properties of the material might be illustrated by the characterization of the nanofibers.

Luo, Huang and coworkers developed CB[8]-based giant supramolecular vesicles [70]. The supramolecular amphiphiles were constructed by the heteroternary complexation of CB[8], *trans*-azobenzene and methyl viologen. The supramolecular vesicles had a large diameter of more than 800 nm. The vesicles were discovered to be stable and versatile platforms, which could be designed as multifunctional nanocarriers. Model drug could be loaded and released upon photoexcitation *in vitro*.

Xu, Yang and coworkers designed and prepared rodlike supramolecular nanoassemblies based on poly(aspartic acid) derivatives-grafted cellulose and hydroxyl–rich polycations, which were crosslinked *via* CB[8]-based heteroternary complexation [71]. The supramolecular nanoassemblies were used to deliver tumor-suppressive noncoding RNAs. Cell and animal investigations revealed that nanoassembly-delivered noncoding RNAs showed a much better tumor suppressive effect compared to control groups.

The CB[8]-based nanoscale self-assembly achieved interesting agricultural applications. Wang and coworkers developed a user-friendly herbicide based on photo-responsive supramolecular vesicles (Fig. 6a) [72]. Paraquat, an highly toxic herbicide, formed a ternary complex with a *trans*-azobenzene derivative and CB[8]. The three components self-assembled into supramolecular vesicles. The stable supramolecular vesicles sequestered the toxicity of paraquat. When UV irradiation or sunlight was applied, the azobenzene derivative underwent *trans* to *cis* isomerization, and supramolecular vesicles broke down to release the paraquat payload.

CB[8]-mediated ternary complexation has important applications in the building of photoluminescence systems for imaging purposes. Liu and coworkers used an anthracyl pyridinium derivative (ENDT), a weakly fluorescent compound, and two macrocyclic hosts, CB[8] and *p*-sulfonatocalix[4]arene, to construct supramolecular assemblies [73]. ENDT was encapsulated by CB[8], and stacked into rodlike supramolecular nanoassemblies. The further addition of *p*-sulfonatocalix[4]arene converted nanorods into nanoparticles. Both stages of supramolecular assembly led to an enhancement in photoluminescence. The resulting nanoparticles had strong near-infrared emission, and were used for lysosome-targeted cell imaging.

Liu and coworkers used supramolecular assembly to build an artificial light harvesting system (Fig. 6b) [74]. The artificial light harvesting system was based on racemic 1,2-diaminocyclohexan-derived 6-bromoisoquinoline, CB[8] and sulfonatocalix[4]arene. The components sequentially assembled into nanoparticles in aqueous solution. The CB[8] confinement effect greatly enhanced the phosphorescent emission. The resulting nanoassembly possessed a remarkable ultralarge Strokes shift and long-lived NIR photoluminescence emission, which rendered it to be used as imaging agent for NIR cell labeling.

Tang, Jin, Wang and coworkers explored the use of CB[8]-based host-guest chemistry to fabricate well-defined and controllable multiblock nanostructures (Fig. 6c) [75]. Three types of supramolecular complexation were utilized: (1) The encapsulation of different numbers of AIEgen guests by CB[8]; (2) the competitive displacement caused by the binding of Na cation to the CB[8] carbonyl portals; (3) the reversible assembly of cationic guests. By using the CB[8]-based hierarchical supramolecular self-assembly, fluorescent multiblock microcolumns with 1 to 7 blocks were successfully fabricated, visualized and regulated.

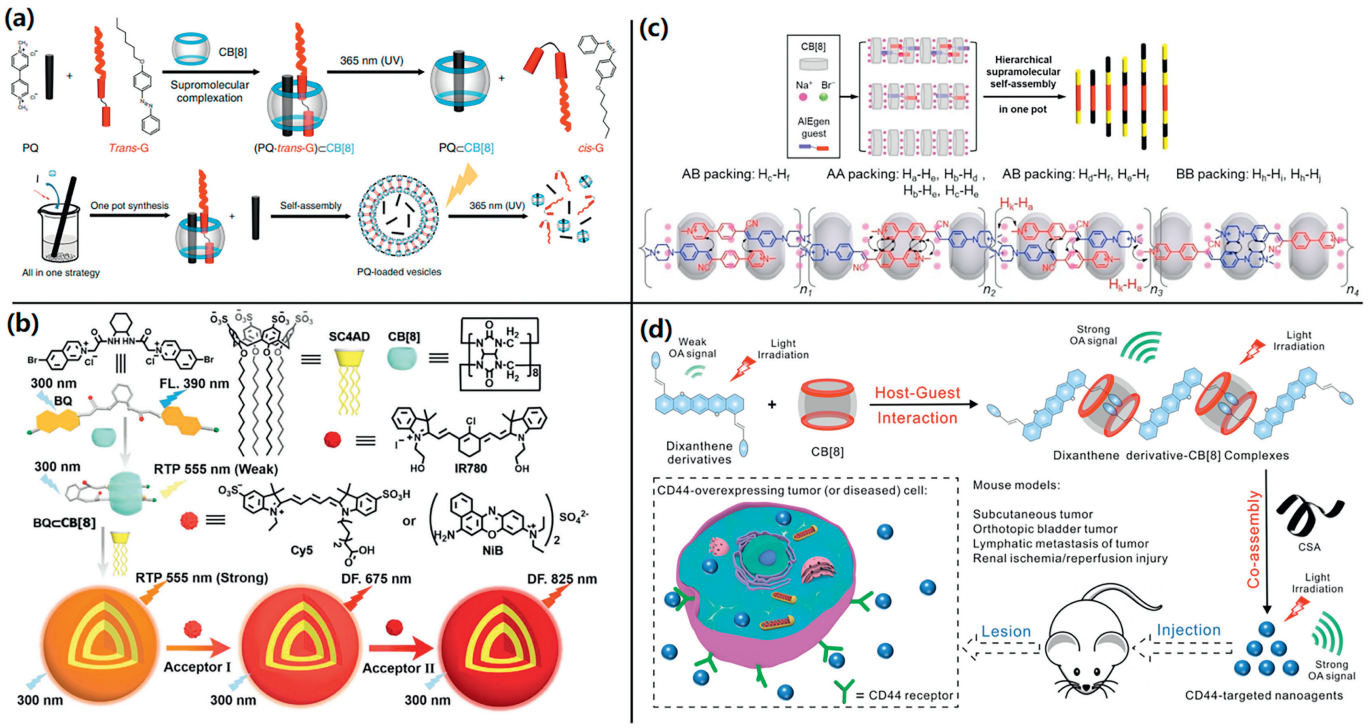

Fig. 6. (a) Preparation of photo-responsive nanoparticles. (b) Illustration of the construction of two-step sequential phosphorescence harvesting system. (c) Schematic illustration of the fabrication of fluorescent multi-block microcolumns from CB[8], NaBr and AIEgen guest. Adapted with permission [70]. Copyright 2022, John Wiley and Sons. (d) Construction of CB[8]-based water-dispersible assemblies as contrast agents with enhanced optoacoustic performance.

Photoacoustic, magnetic and other new imaging modalities have emerged as promising diagnostic methods. Zhao, Wu, Chen and coworkers developed a photoacoustic imaging system based on CB[8] ternary complexation (Fig. 6d) [76]. Two dixanthene-based chromophores were used as guest chromophores, which were encapsulated by CB[8]. The chromophore, CB[8] and chondroitin sulfate A (CSA) co-assembled into water-dispersible CD44-targeted nanoagents. Compared to the chromophores, the nanoagents exhibited a significant enhancement in the optoacoustic signal. The reasons for this improved performance include an increased absorption coefficient, and intensified non-radiative relaxation of the excited state due to the suppression of the competitive radiative transition. These nanoagents were proved to be highly effective optoacoustic imaging system *in vivo*.

4.3. Nanoscale supramolecular organic frameworks

In addition to the above two types of CB[*n*]-crosslinked nanoassemblies, CB[8]-based ternary complexation is a powerful tool to construct SOFs. As a highly ordered material, CB[8]-based SOFs are used in various applications, including drug delivery, catalysis and chemical sensing.

Li, Liu, Zhang and coworkers developed the first three-dimensional SOFs based on CB[8]-mediated ternary complexation (Fig. 7a) [77]. Building blocks were composed of tetratopic 4-(4-methoxyphenyl)pyridin-1-ium) unit. CB[8] was capable of enhancing the homodimerization of the building blocks by forming 1:2 inclusion complexes. The co-assembly between the building block and CB[8] led to the formation of a highly soluble periodic 3D SOF in water. These SOFs were found to be in nanoscale diameter. The SOFs were highly ordered and porous, which were capable of encapsulating anionic dyes and drugs. This method was applied to construct homogeneous supramolecular metal-organic framework by incorporating Ru catalytic centers based on CB[8]-mediated ternary complexation [78]. The framework material was able to efficiently produce hydrogen upon irradiation of visible light. Nanoscale SOFs were also used to deliver chemotherapeutics and overcome multidrug resistance *in vitro* and *in vivo* [79].

The CB[8]-mediated ternary complexation was used to construct two-dimensional SOFs. Li, Liu, Zhao and coworkers designed and synthesized a rigid stacking-forbidden 1,3,5-triphenylbenzene compound with three 4,4′-bipyridin-1-ium units on the peripheral benzene rings (Fig. 7b) [80]. The introduction of hydrophilic bis(2-hydroxyethyl)carbamoyl groups to the central benzene ring suppressed 1D stacking and improved solubility in water. The 2D SOF was confirmed to be highly ordered and single layered. Feng and coworkers developed a free-standing monolayer 2D SOF with good internal order. The 2D SOF self-assembled at a liquid-liquid interface, and yielded exceptionally large-area, insoluble films [81]. Liu and coworkers constructed CB[8]-mediated 2D supramolecular nanoarchitectures for efficient electrochemical nitrogen reduction [82].

Cao and coworkers designed and prepared two types of shape-controllable and fluorescent SOFs based on CB[8]-mediated 1:2 host-guest complexation [83]. These two SOFs were co-assembled by CB[8] and tetraphenyl ethylene-bearing building blocks. The microscopic morphology of these two SOFs were cuboids and spheroids, respectively, and demonstrated aggregation-induced emission. They also prepared fluorescent achiral SOFs, which were capable of chirality induction in water [84,85]. Suitable guests, including phenylalanine and dipeptides, could induce chirality of SOFs.

5. To modify nanostructure surface

As summarized above, CB[*n*]s could be used to construct nanoarchitectures. Besides, these hosts could be applied to modify the surface of preformed nanoarchitectures, and regulate the surface characteristics. The modification of nanostructures by CB[*n*]s is important for two reasons: (1) The regulation of nanostructure characteristics to improve transmembrane efficiency and other property; (2) Supramolecular conjugation of nanostructures to form hierarchical architectures. The surface modification of nanostructure could also regulate the release of encapsulated cargo, which will be discussed in the next section.

5.1. Nanoparticle surface regulation

Due to the high affinity and selective binding of CB[*n*]s towards suitable guests, nanoparticle surface could be conveniently modified with targeting groups and other functional groups. CB[*n*]s may also be introduced onto nanoparticle surface for analytical or catalytic purposes.

CB[*n*]-modified nanoparticles have been applied for drug delivery. Zhao, Wang and coworkers developed a cryo-shocked platelet coupled with reactive oxygen specie (ROS)-responsive nanomedicine, which was conjugated *via* CB[7]-based supramolecular interaction [86]. To prepare the non-covalently conjugated system, CB[7] was surface modified onto platelet *via* a ligand insertion approach, and adamantane amine was introduced into the liposomal ROS nanomedicine. Subsequently, platelet and nanomedicine were linked *via* the host-guest interaction between CB[7] and adamantane amine. Due to the ultra high stability of the CB[7]-adamantane amine complexation, platelet and nanomedicine would remain stable under the complex physiological environment. *In vitro* and *in vivo* assay showed that the system exhibited a high thrombus-targeting efficiency and anti-inflammation efficacy. In addition, Pan and coworkers used CB[6]-capped nanocarbon for the sustained inhibition of cancer [87]. Wang, Lee, Yang and coworkers

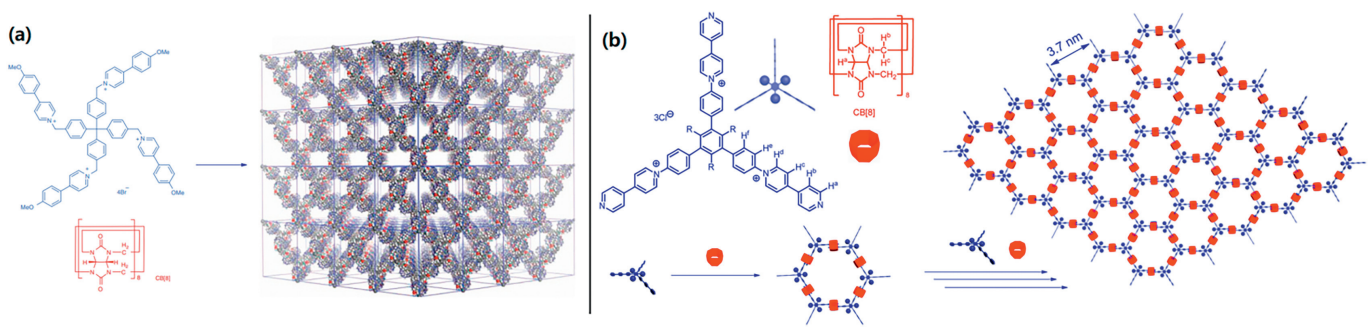

Fig. 7. (a) Construction of CB[8]-mediated 3D SOF. (b) Self-assembly of different building blocks with CB[8] to form 2D SOF. Adapted with permission [75]. Copyright 2013, American Chemical Society.

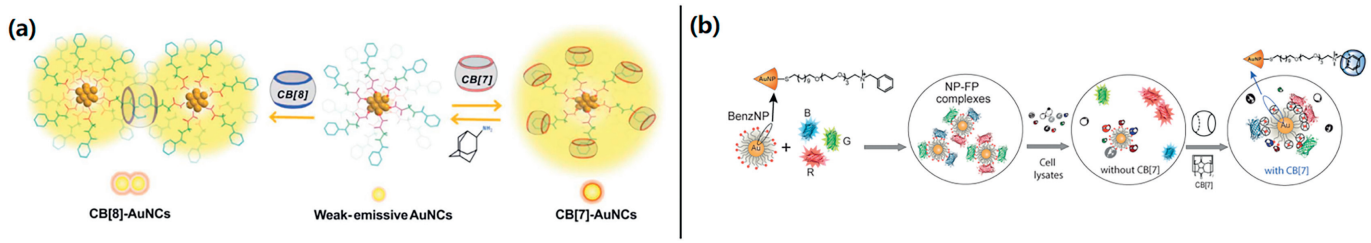

Fig. 8. (a) Host-guest assembly of CB[7] and CB[8] with FGGC-Au Nanoclusters. Adapted with permission [85]. Copyright 2020, Royal Society of Chemistry. (b) Design strategy of the CB[7]-based nanosensors. Adapted with permission [90]. Copyright 2017, American Chemical Society.

developed CB[8]-based supramolecularly coated nanoparticles with selective decoating-induced activation for multiple applications [88]. Gao, Yang and coworkers prepared CB[7]-based supramolecular nanoassembly for antimicrobial treatment and bacterial detection [89].

Imaging and diagnostic uses have been developed with CB[*n*]-modified nanostructures. Ma and coworkers developed CB[*n*] surface modified Au nanoclusters with enhanced photoluminescence intensity (Fig. 8a) [90]. Unmodified Au nanoclusters suffer from relatively low luminescence efficiency in solution. To solve this issue, Au nanoclusters were surface modified with a tetrapeptide with a sequence of FGGC or Phe-Gly-Gly-Cys. The Phenylalanine terminus of the peptide was capped with CB[7] or CB[8] by 1:1 or 1:2 host-guest supramolecular complexation. The supramolecular surface modification rigidified the Au nanoclusters, and dramatically improved the red phosphorescence emission with a quantum yield of 51% for CB[7] and 39% for CB[8], respectively. The CB[7]-brightened Au nanoclusters were confirmed to show strong luminescence in A549 cancer cells. Pérez-Prieto, González-Béjar and coworkers developed CB[*n*]-capped upconversion nanoparticles as highly emissive scaffolds for energy acceptors [91]. Ni and coworkers used CB[7] and CB[8] to assist the formation of carbon dots with a tunable particle size, which were prepared by a hydrothermal reaction from a single organic precursor in water [92].

Ling and coworkers used a supramolecular approach to mediate the nanoparticle surface and regulate the biological effect [93]. Diverse types of nanoparticles were used in this study, including oleic acid coated iron oxide nanoparticles, manganese oxide nanoparticles and cetyltrimethylammonium bromide-capped gold nanorods. An acyclic CB[*n*] was used to noncovalently modify the nanoparticle surface *via* a bilateral host-guest interaction, and targeting group RGD was introduced onto the nanoparticle surface. *In vivo* experiments confirmed that the RGD-modified nanoparticles demonstrated significant biological targeting effect.

Kim, Ryu and coworkers used the ultrastable host-guest binding pair to separate and purify proteins. They prepared CB[7]-modified beads to isolate plasma membrane proteins *via* supramolecular fishing [94]. Proteins were labeled with 1-trimethylammoniumethylferrocene, a guest with ultra-high binding affinity with CB[7]. CB[7]-conjugated beads were capable of capturing labelled proteins from heterogeneous protein mixtures *via* host-guest interaction. The treatment with competitive guest 1,1′-bis(trimethylammoniumethyl)ferrocene would displace and recover captured proteins. This supramolecular approach for the purification of membrane proteins demonstrated its potential as an alternative strategy to streptavidin-biotin for membrane proteomics. This supramolecular strategy was later applied to the purification of protein therapeutics [95]. A monoclonal antibody drug, Herceptin, and cytokine interferon α-2a were labeled with adamantylammonium guest by using the enzyme sortase A. CB[7]-conjugated agarose beads were used to fish the guest-labelled protein therapeutics *via* host-guest interaction. A competitive displacement resulted in the recovery of protein therapeutics. This supramolecular method was proved to be scalable, recyclable and low cost.

Nanosensors based on CB[*n*]-capped Au nanoparticles were developed by Rotello and coworkers (Fig. 8b) [96]. Cationic benzylammonium-functionalized Au nanoparticles were used as substrates, which were encapsulated by CB[7]. Au nanoparticles with or without CB[7] would have different binding interactions with the biomolecules in cell lysates, and generate "fingerprints" fluorescence outputs by using three fluorescent proteins. These nanosensors could be used to discriminate lysates from different cell types by linear discriminant analysis. Assay validation confirmed that the sensing was highly reproducible, and required minimal sample quantity (200 ng of total proteins). Liang and coworkers reported CB[7]-based Au nanoassemblies for electrochemical detection of amino acids [97]. Du and coworkers developed CB[7]-enhanced electrochemiluminescence of Au nanoclusters for D-dimer sensing [98].

CB[*n*]-modified Au nanostructures have demonstrated great potential in interface photochemistry and biosensing. Ha and coworkers used CB[7] for the *in situ* reversible tuning of chemical interface damping (CID) [99]. Monoamine-functionalized CB[7] was conjugated to the surface of single Au nanorods. *In situ* tuning of CID on single Au nanorods was achieved by complexing CB[7] and oxaliplatin, which led to the change of the chemical nature and electronic characteristics. Subsequently, spermine was added as a competitive guest to displace oxaliplatin. It was proved that the CB[7] modified Au nanorods acted as a recyclable platform with repeated encapsulation and release of the guest.

Surface-enhanced Raman scattering (SERS) spectroscopy is a powerful tool for chemical sensing by identifying molecules by their unique "fingerprints" [100,101]. CB[*n*]s have proved their great value to serve as "hot spots", or nanogaps between two or more closely spaced Ag or Au nanoparticles, to achieve a high SERS enhancement. Kim, Moskovits, Baek and coworkers developed smart SERS hot spots, which placed single molecules in a plasmonic nanojunction using host-guest chemistry [102]. Thiol-CB[6] was used as a dual-function building block. This building block served as a molecular spacer to form a nanogap between Ag nanoparticle and Ag substrate, and a host to encapsulate the target molecule with a high binding affinity. The length of the polymethylene linker was adjusted to control the position of the target analyte, perylene bisimide. This smart SERS hot spot was used to investigate the position of the single analyte molecule, and its SERS enhancement in the hot spots. Scherman, Baumberg, Mahajan and coworkers achieved *in situ* SERS monitoring of photochemistry within a nanojunction reactor [103]. Au nanoparticles were linked by CB[*n*]. The CB[*n*] molecule served as a nanoscale reaction vessel for a photoreaction. It also functioned as a powerful SERS transducer by a large field enhancement. The real-time SERS-monitoring of a stilbene photoreaction was achieved

by the enhanced Raman fingerprint. This CB[*n*]-based nanoreactor could be applied to monitor and study selective photoreaction *in situ*.

5.2. Controlled self-assembly of nanostructures

The controlled self-assembly of nanostructures is of great importance to construct complex nanoarchitectures as well as to achieve applications.

Tian, Qu and coworkers designed and prepared controlled self-assembly system of TiO_2 nanoparticles *via* CB[8]-mediated radical cation dimerization (Fig. 9a) [104]. The surface of TiO_2 nanoparticles was modified with methyl viologen. When CB[8] was added, nanoparticles were capped with CB[8] *via* host-guest interaction. The charge repulsion of nanoparticles ensured the dispersion. Either photo irradiation or chemical reduction resulted in the formation of methyl viologen radical cations. The CB[8]-enhanced dimerization of methyl viologen radical cations led to the aggregation of nanoparticles. The process could be reversed by the use of oxidation condition. The reversible dual-stimuli-responsive self-assembly was confirmed to switch on and switch off the photocatalytic activity of TiO_2 nanoparticles. Scherman and coworkers designed and prepared hybrid raspberry-like colloids, where CB[8] was used as a supramolecular linker to conjugate silica nanoparticles and polymeric nanoparticles [105].

Yan and coworkers developed an ultrafast laser plasmonic fabrication method of nanocrystals by using CB[5] or cetyltrimethylammonium (CTAB) as glue (Fig. 9b) [106]. This direct-printing process used nanocrystal as "inks", which were deposited on substrates and glued by CB[5] or CTAB. The irradiation of ultrafast laser would decompose the glue molecules, leading to the decreasing of interparticle distance and coalescence of nanocrystals. The resulting bridged nanocrystals showed enhanced photothermal conversion capacity, and could be used for photoresponse information encryption and soft actuator.

Cao and coworkers prepared a hierarchical nanoarchitecture composed of Ru nanoparticles, CB[6] and multiwalled carbon nanotubes (MWCNs), and used this nanostructure for hydrogen evolution electrocatalyst [107]. The nanoarchitecture was synthesized with a facile one-pot reaction approach by heating and sonication. The unique alignment of Ru nanoparticles, CB[6] and MWCNs resulted in good electronic conductivity and abundant catalytic sites. Therefore, enhanced catalytic activity and stability were achieved. Guenin, Trabolsi and coworkers reported a similar nanoassembly with Pd-loaded CB[7]-modified iron oxide nanoparticles for cross-coupling reactions [108].

CB[*n*]-mediated nanoparticle self-assembly could be used for biomedical applications. Wang and coworkers developed aggregated nanoparticles mediated by CB[7] for tumor-specific bioimaging and photothermal therapy [109]. They also constructed CB[7]-capped Au nanocages, and used their spermine-induced self-aggregation for enhanced chemotherapy and photothermal therapy [110].

6. As gatekeepers

Nanostructures are often used to load cargo and deliver the payload with on-demand release. This is especially important for drug delivery applications. CB[*n*]s have been used to surface modify nanostructures for "gatekeeping" purpose, by which the encapsulation and release of cargo are regulated by CB[*n*]s.

6.1. Nanovalves on mesoporous silica

Zink and coworkers introduced the concept of "nanovalves", which were based on channels in porous materials, such as mechanized mesoporous silica nanoparticles (MSNs). These channels served as reservoir to encapsulate cargo. Stimuli-responsive nanovalves were installed on the tunnels to controlled release cargo. Host-guest interaction based on CB[*n*]s was found to be highly effective for the design of nanovalves.

Several types of external stimuli were applied to trigger the opening of nanovalves and the release of encapsulated cargo, including pH, magnetism and light [111–113]. Nanoparticles consisting of gold cores and mesoporous silica spheres were used. The mesoporous silica possessed pore openings with approximately 2 nm width. Nanovalves based on CB[6] encircling stalks were installed onto the pores. The plasmonic heating of the gold core would raise the temperature of nanoparticles, which reduced the binding strength between CB[6] and the stalk. Therefore, plasmonic heating led to the opening of nanovalves to release the cargo loaded inside pores. Later, a multi-stimuli-responsive magnetic supramolecular nanoplatform was developed to co-deliver large and low molecular weight drugs, which were used for synergistic eradication of pathogenic biofilms (Fig. 10a) [114]. This co-delivery platform was composed of two parts: (1) MSNs with large pores capped by cyclodextrin-modified polyethylenimine; (2) adamantane-decorated mesoporous silica nanoparticles with a magnetic core capped by CB[6]. The host-guest interaction between cyclodextrin and adamantane co-assemble the two types of MSNs. Large molecular weight antimicrobial peptide melittin and low molecular weight antibiotic ofloxacin were loaded into the two types of MSNs, respectively. Under the stimulus of pathogen cells and heating generated by an alternating magnetic field, nanovalves were opened to release both types of drugs. *In vivo* implantation model revealed that the coassemblies eradicated the pathogenic biofilms from the implants, which helped prevent host tissue damage and inflammation. In addition, Hu, Xu, Di and coworkers reported a CB[8]-capped MSN to combat colitis and improve intestinal homeostasis *in vivo* [115]. Hu, Di, Chen and coworkers developed CB[8]-capped MSNs for enzyme-triggered targeted drug delivery [116].

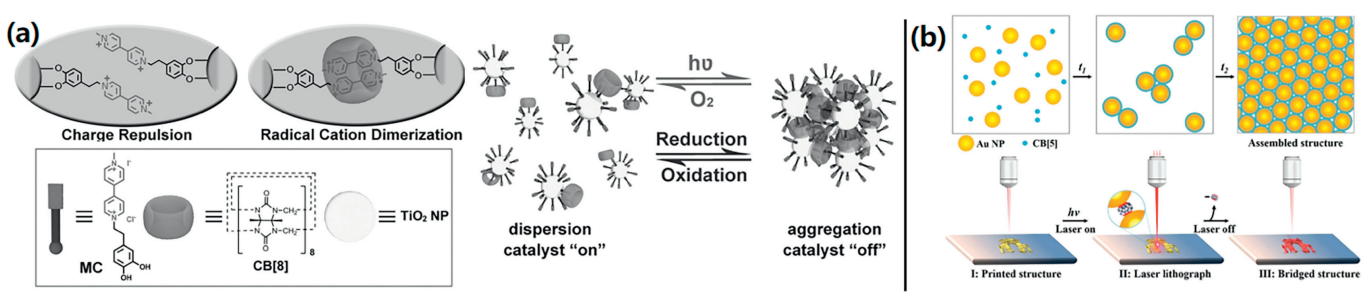

Fig. 9. (a) Self-assembly of MV^{2+}-TiO_2 nanoparticles through photochemical and chemical-reduction. Adapted with permission [98]. Copyright 2015, John Wiley and Sons. (b) Light controlled fabrication of plasmonic structures. Adapted with permission [100]. Copyright 2023, John Wiley and Sons.

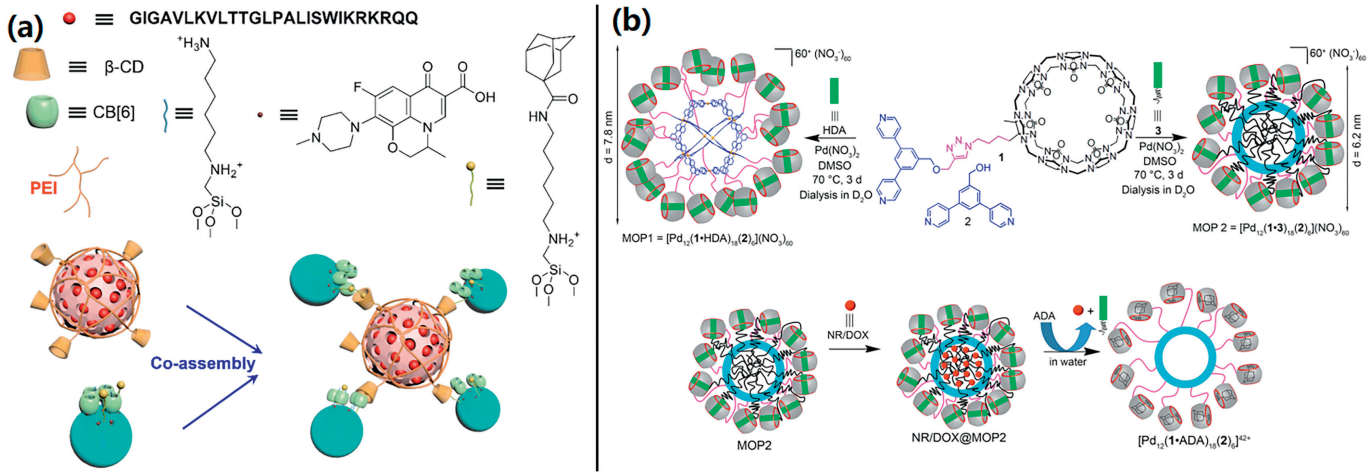

Fig. 10. (a) Schematic representation of the molecular components and synthetic route of supramolecular nanoplatform. Adapted with permission [108]. Copyright 2020, American Chemical Society. (b) Self-assembly of MOPs. Adapted with permission [114]. Copyright 2017, American Chemical Society.

6.2. Gatekeepers on soft nanostructures

CB[*n*]s were employed as gatekeepers on the surface of soft nanomaterials to control the loading and release of encapsulated cargo. CB[*n*]-based host-guest interaction was also used to tune the catalytic reactivity of nanostructures.

Rotello and coworkers developed bioorthogonal catalysis based on supramolecular regulation in cells [117]. The catalyst was a gold nanoparticle with an average size of approximately 2 nm. The nanoparticle consisted of a hydrophobic alkane segment for Ru catalyst encapsulation, a tetra(ethylene glycol) unit to improve the biocompatibility, and a dimethylbenzylammonium group to bind CB[7] as the gatekeeper. Ru-catalyzed deallylation was chosen as a model bioorthogonal process to regenerate the fluorescence in cells. It was discovered that the binding and displacement of gatekeeper CB[7] on the nanoenzyme could be used to reversibly control activity of the catalyst. The potential applications in imaging and therapeutic treatment were showed by the allylcarbamate cleavage for pro-fluorophore activation and propargyl group breaking for prodrug activation in the intracellular environment. This strategy was applied to drug delivery [118]. Diaminohexane-terminated gold nanoparticles were used as model drug. CB[7], a high affinity host for diamino guest, was used to control the delivery of gold nanoparticles. When CB[7] was added, the threading of this macrocyclic host on the particle surface suppressed the cytotoxicity of positively charged gold nanoparticles. When a competitive guest, 1-adamantylamine, was added, CB[7] was removed from the particle surface, and gold nanoparticles were released from the endosomal compartments to trigger the recovery of cytotoxicity. This work explored a new supramolecular strategy based on CB[7]-guest binding to activate intracellular cytotoxicity.

Isaacs, Briken and coworkers developed CB[*n*]-based drug delivery systems. Metal-organic polyhedron or MOP was used as the core of nanoparticles [119]. 24 methyl viologen units were modified on the external surface of nanoparticles. Acid-labile prodrug based on doxorubicin was used with a naphthalene handle. The prodrug was incorporated onto MOP nanoparticles noncovalently *via* CB[8]-mediated ternary complexation. The nanoparticles demonstrated pH-dependent release of doxorubicin, and high *in vitro* cytotoxicity against HeLa tumor cells. The gatekeeping strategy was also applied to MOP nanoparticles for drug delivery purposes. As shown in Fig. 10b, MOP nanoparticles were covalently modified with CB [7,120]. The inner cavity of MOP was modified with octadecyl hexanediamine to render it hydrophobic. The hydrophobic MOP inner cavity was used to encapsulate hydrophobic dye Nile Red or the anti-tumor drug doxorubicin. CB[7] bound with hexanediamine, which served as a gatekeeper and contract the nanoparticle. The existence of gatekeepers rendered these nanoparticle responsive to three types of stimuli: (1) A competitive binder with CB[7]; (2) a dual pH-chemical stimulus leading to the change of adamantane carboxylate protonation state; (3) a dual pH-photochemical stimulus by azobenzene configuration change from *trans*-isomer to *cis*-isomer.

7. Conclusion and perspective

In this review, we summarize the recent advances on CB[*n*]-based nanostructure construction and modification, an important topic on the interface of supramolecular chemistry and nanoscience. Great progress has been achieved on the use of CB[*n*]s to construct sophisticated nanoarchitectures. CB[*n*]s are employed as building blocks of nanostructures, to crosslink nanostructures by host-guest interaction, to modify the surface of nanostructures, or to be used as gatekeepers. Applications have been achieved by CB[*n*]-based nanoscience and nanotechnology, including nanofabrication, drug delivery, chemical sensing and catalysis. CB[*n*]s have demonstrated their unique role in the construction and applications of nanoarchitectures due to their molecular structures and excellent binding property. Compared to cyclodextrin and other hosts, the high binding affinity of CB[*n*]-based complexation ensures the nanostructure stability and prevent premature cargo release.

CB[*n*]s are experiencing a booming period of research since the discovery and isolation of macrocyclic homologues at the beginning of this century. Since the start of the second decade, functions and applications have become the focal points of CB[*n*] research. CB[*n*]-based nanoscience and nanotechnology are the key areas to develop applications. Looking at the recent progress, two types of applications demonstrate the most prominent values: drug delivery and chemical sensing. CB[*n*]s have been applied to construct sophisticated drug delivery systems, and surface modify nanocarriers or nanopharmaceuticals *via* supramolecular interaction [121,122]. CB[*n*]-based high affinity host-guest interaction has proved its enormous value in building complex DDSs. Most importantly, CB[8]-based ternary complexation and other CB[*n*]-based supramolecular interaction are unique to ensure ultra-high stability in complex physiological and pathological environments. In the arena of analytical science, CB[*n*]s have demonstrated their

great potential to enhance SERS effect, and to manipulate single molecule on solid support. CB[n]-based SERS technology may be developed to be a powerful tool for ultrasensitive sensing.

The most notable limitation on CB[n]-based nanoscience and nanotechnology is the lack of clinical or industrial applications. When pursing these applications, cyclodextrins and other macrocycles are often chosen. This preference is most importantly due to the well-established characterization of these hosts, for example, the cyclodextrin biosafety profile. A thorough evaluation on the biocompatibility and other properties of CB[n]s is necessary in order to push forward their clinical and industrial uses. Some of CB[n] limitations, including its limited solubility in water and difficult chemical modification, also restrict its ability to construct nanostructures and achieve the desired applications.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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