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Engineering Responsive Polymer Building Blocks with Host–Guest Molecular Recognition for Functional Applications

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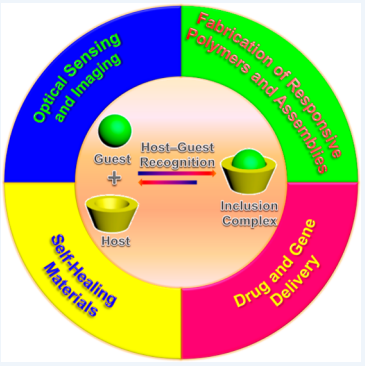
CONSPECTUS: All living organisms and soft matter are intrinsically responsive and adaptive to external stimuli. Inspired by this fact, tremendous effort aiming to emulate subtle responsive features exhibited by nature has spurred the invention of a diverse range of responsive polymeric materials. Conventional stimuli-responsive polymers are constructed via covalent bonds and can undergo reversible or irreversible changes in chemical structures, physicochemical properties, or both in response to a variety of external stimuli. They have been imparted with a variety of emerging applications including drug and gene delivery, optical sensing and imaging, diagnostics and therapies, smart coatings and textiles, and tissue engineering.



On the other hand, in comparison with molecular chemistry held by covalent bonds, supramolecular chemistry built on weak and reversible noncovalent interactions has emerged as a powerful and versatile strategy for materials fabrication due to its facile accessibility, extraordinary reversibility and adaptivity, and potent applications in diverse fields. Typically involving more than one type of noncovalent interactions (e.g., hydrogen bonding, metal coordination, hydrophobic association, electrostatic interactions, van der Waals forces, and $\pi-\pi$ stacking), host–guest recognition refers to the formation of supramolecular inclusion complexes between two or more entities connected together in a highly controlled and cooperative manner. The inherently reversible and adaptive nature of host–guest molecular recognition chemistry, stemming from multiple noncovalent interactions, has opened up a new platform to construct novel types of stimuli-responsive materials. The introduction of host–guest chemistry not only enriches the realm of responsive materials but also confers them with promising new applications. Most intriguingly, the integration of responsive polymer building blocks with host–guest recognition motifs will endow the former with further broadened responsiveness to external stimuli and accordingly more sophisticated functions.

In this Account, we summarize recent progress in the field of responsive polymeric materials containing host–guest recognition motifs with selected examples and highlight their versatile functional applications, whereas small molecule-oriented host–guest supramolecular systems are excluded. We demonstrate how the introduction of host–guest chemistry into conventional polymer systems can modulate their responsive modes to external stimuli. Moreover, the responsive specificity and selectivity of polymeric systems can also be inherited from the host–guest recognition motifs, and these features provide extra advantages in terms of function integration. The following discussions are categorized in terms of design and functions, namely, host–guest chemistry toward the fabrication of responsive polymers and assemblies, optical sensing and imaging, drug and gene delivery, and self-healing materials. A concluding remark on future developments is also presented. We wish this prosperous field would incur more original and evolutionary ideas and benefit fundamental research and our daily life in a more convenient way.

1. INTRODUCTION

Stimuli-responsive polymeric materials have aroused mounting interest in the past few decades due to their emerging applications in diverse fields such as drug and gene delivery, optical sensing and imaging, diagnostics and therapies, smart coatings and textiles, and tissue engineering. Conventional responsive polymers are constructed via covalent linkages, and they undergo reversible or irreversible changes in chemical structures or physical properties in response to a great variety of external stimuli including pH variation, temperature, ionic strength, light irradiation, mechanical force, electric and magnetic fields, and analyte of interest (e.g., ions, bioactive molecules, etc.) or an integration of them.[1−6] The responsiveness of conventional stimuli-responsive polymers typically arises from functional moieties in the side chains or on the backbone. Additionally, they can exist as various forms such as solutions, gels, self-assembled nanoparticles, (multilayer) films, and bulk solids. The field of responsive polymers has nowadays evolved well beyond the demonstration of novel properties. Currently, the exploitation of useful and advanced functions has emerged to be a more relevant subject.[1,7]

The quite mature molecular chemistry is solely based on covalent bonds. On the other hand, supramolecular chemistry, coined as "chemistry beyond the molecule", features weak and reversible noncovalent interactions. Since its discovery, it has

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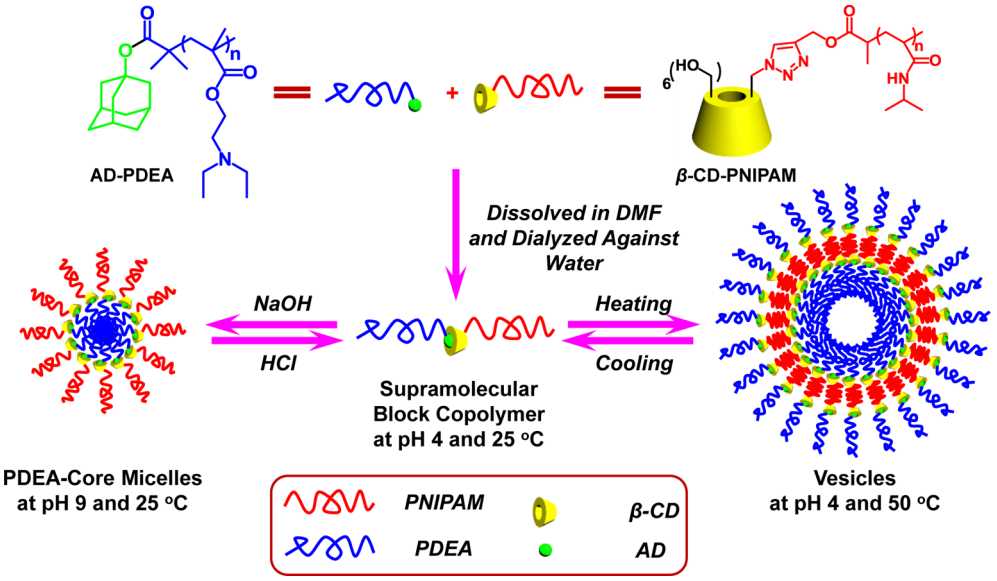

Figure 1. Schematic illustration of the preparation of pH- and thermoresponsive supramolecular DHBC, PNIPAM-*b*-PDEA, via host–guest chemistry and the corresponding stimuli-triggered morphological transitions in aqueous media. Reproduced with permission from ref 27. Copyright 2009 JohnWiley & Sons.

emerged as a powerful and versatile tool for the fabrication of novel types of responsive materials.[8−10] Supramolecular ensembles are built through noncovalent interactions such as hydrogen bonding, metal coordination, hydrophobic association, van der Waals forces, and $\pi-\pi$ stacking.[11−13] In addition, host–guest recognition refers to the formation of supramolecular inclusion complexes consisting of two or more entities connected together via noncovalent interactions in a highly controlled and cooperative manner.[14,15] Due to the dynamic, reversible, and adaptive nature, host–guest recognition has opened up a new platform for the construction of stimuli-responsive materials, especially when integrated with conventional responsive polymer building blocks.

To date, a variety of hosts such as cyclodextrins (CDs), crown ethers, calixarenes, cucurbiturils (CB), and pillararenes have been explored to construct responsive materials, either as supramolecular recognizing motifs or as core building blocks. For instance, as one of the most widely investigated hosts, CDs, containing both primary and secondary hydroxyl groups, were frequently employed as scaffolds for the construction of stimuli-responsive systems by virtue of disparate reaction activities between primary and secondary hydroxyl groups. In this aspect, we previously reported several examples using β-CD as core scaffolds for the synthesis of star copolymers with multifunctional responsive features and explored their functional applications as drug and gene nanocarriers and macromolecular magnetic resonance imaging (MRI) contrast agents.[16−18] Nevertheless, in these systems, the hosts only serve as scaffolds. It can be expected that the introduction of recognizable guests and host–guest recognition events will prominently expand the responsive modes and dynamic ranges.

In this Account, we focus on recent progress in supramolecular systems involving responsive polymer building blocks and host–guest molecular recognition and emphasize their promising functional applications. Small molecule-based host–guest systems are not included; in addition, we do not intend to present an exhaustive survey concerning the fabrication of stimuli-responsive supramolecular polymers because several comprehensive reviews are already available.[19−21] We will highlight the fabrication of stimuli-responsive materials from polymeric building blocks via host–guest molecular recognition. Next, discussions are arranged in terms of functions in the order of optical sensing and imaging, drug and gene delivery, and self-healing materials. These results suggest that the introduction of supramolecular recognition motifs into conventional responsive polymers can play an important role in the design of next-generation functional materials.

2. HOST–GUEST CHEMISTRY FOR THE FABRICATION OF RESPONSIVE POLYMERS AND ASSEMBLIES

Supramolecular inclusion complexes possess specific three-dimensional structures and spatial arrangements for host–guest moieties. Additionally, the noncovalent bonding endows the inclusion complexes with inherent reversibility and adaptivity, allowing for dynamic responses toward external stimuli.[22] Thus, the introduction of supramolecular host–guest recognition into polymeric systems should afford more versatile responsive polymeric materials. In addition, the modular and interchangeable nature of molecular recognition will render the fabrication process less time-consuming and labor-consuming, compared with conventional covalently linked polymer systems.

Supramolecular hosts and guests as well as chemical structures of polymer building blocks can be specifically designed and finely modulated; therefore, numerous possibilities for the construction of supramolecular materials can be achieved. Also note that stimuli-responsive properties can be inherited from both polymer building blocks and host–guest recognition motifs, thus endowing conventional responsive polymers with broadened responsiveness and more intricate functions. We herein highlight supramolecular stimuli-responsive polymers with three sorts of chain topologies, namely, linear block copolymers, hyperbranched polymers, and Janus hyperbranched copolymers. Supramolecular polymers with other diverse architectures can be accessed from additional literature.[21,23−26]

The fabrication of supramolecular diblock copolymers is quite straightforward if polymer building blocks are function-

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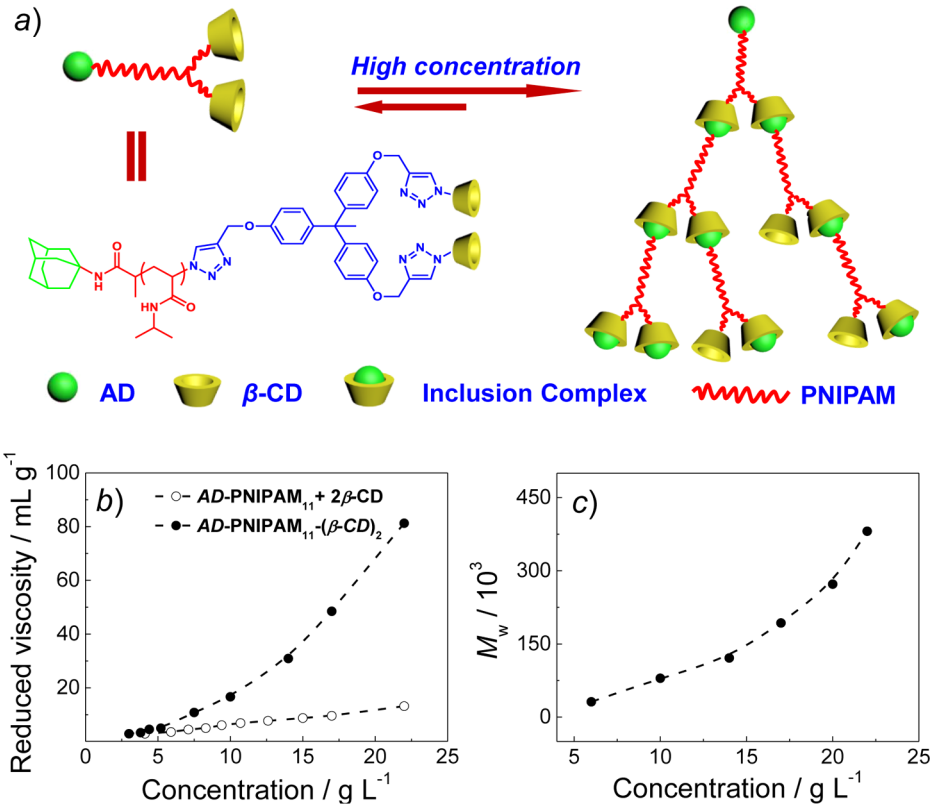

Figure 2. (a) Schematic illustration of the construction of supramolecular hyperbranched thermoresponsive polymers from AD-PNIPAM-(β-CD)$_2$ in aqueous solution via supramolecular host–guest recognition between β-CD and AD moieties. Concentration dependence of (b) reduced viscosity and (c) apparent weight-average molecular weight recorded for the aqueous solution (20 °C) of AD-PNIPAM-(β-CD)$_2$ and AD-PNIPAM/β-CD mixture ([AD]/[β-CD] = 1/2), respectively. Reproduced with permission from ref 29. Copyright 2011 JohnWiley & Sons.

alized with complementary host and guest moieties at the chain ends. We designed multiresponsive double hydrophilic block copolymers (DHBCs) from β-CD-terminated poly(*N*-isopropylacrylamide) (β-CD-PNIPAM) and adamantyl (AD)-terminated poly(2-(diethylamino)ethyl methacrylate) (AD-PDEA) via host–guest recognition between β-CD and AD moieties (Figure 1).[27] The two homopolymers orthogonally self-assembled into supramolecular PNIPAM-*b*-PDEA copolymers, as confirmed by 2D nuclear Overhauser effect spectroscopy (NOESY). The supramolecular DHBC possessed intriguing "schizophrenic" self-assembling behavior in aqueous solution. Specifically, at room temperature and pH < 6, it existed as unimers in water, whereas it formed PDEA core micelles with PNIPAM coronas at pH > 8 due to the deprotonation of the PDEA block. Furthermore, vesicular nanostructures with collapsed PNIPAM bilayers and solvated inner/outer PDEA coronas formed at temperatures above the lower critical solution temperature (LCST) at pH 4. Most significantly, the thermo- and pH-induced morphological transitions were fully reversible.

Linear polymeric building blocks possess relatively small hydrodynamic sizes, and they might be replaced with hyperbranched polymers featuring bulky microstructures and steric hindrance. In a recent example, supramolecular Janus hyperbranched copolymers consisting of two chemically distinct parts were fabricated by mixing hyperbranched polyglycerol functionalized β-CD (β-CD-*g*-HPG) and azobenzene (AZO)-functionalized hyperbranched poly(3-ethyl-3-oxetane methanol) (AZO-*g*-HBPO).[28] The resultant amphiphilic Janus hyperbranched polymer can self-assemble into uniform vesicles in aqueous solution. Although in this case hyperbranched building blocks are chemically inert, the β-CD/AZO inclusion complex is susceptible to UV irradiation owing to the *trans*-to-*cis* isomerization of AZO moieties, thus endowing supramolecular copolymer with the capability of reversibly regulating self-assembled morphologies upon alternated UV and visible light irradiation. This example nicely demonstrated that the introduction of host–guest chemistry into conventional polymeric systems can indeed bring about new responsive motifs and enrich their environmentally adaptive behaviors.

Supramolecular hyperbranched polymers can also be fabricated from well-defined polymeric AB$_2$ precursors (A and B refer to host/guest molecules) via orthogonal host–guest recognition. In this context, we designed a PNIPAM oligomer consisting of a single AD guest and two β-CD host moieties at chain termini, AD-PNIPAM-(β-CD)$_2$ (Figure 2).[29] In aqueous solution, AD-PNIPAM-(β-CD)$_2$ oligomers self-assembled into supramolecular hyperbranched polymers mediated via β-CD/AD inclusion complexation. Interestingly, temperature-dependent optical transmittance measurements revealed a considerable increase in LCST, which might be ascribed to the fact that hydrophobic AD moieties were encapsulated within β-CD cavities. In addition, due to the dynamic and reversible nature of β-CD/AD recognition, the addition of competitive small molecule host or guest moieties can further regulate the solution viscosity, apparent weight-average molecular weight, and LCST. Apart from the construction of supramolecular polymers with varying topologies, supramolecular assemblies can also be fabricated via multivalent host–guest recognition

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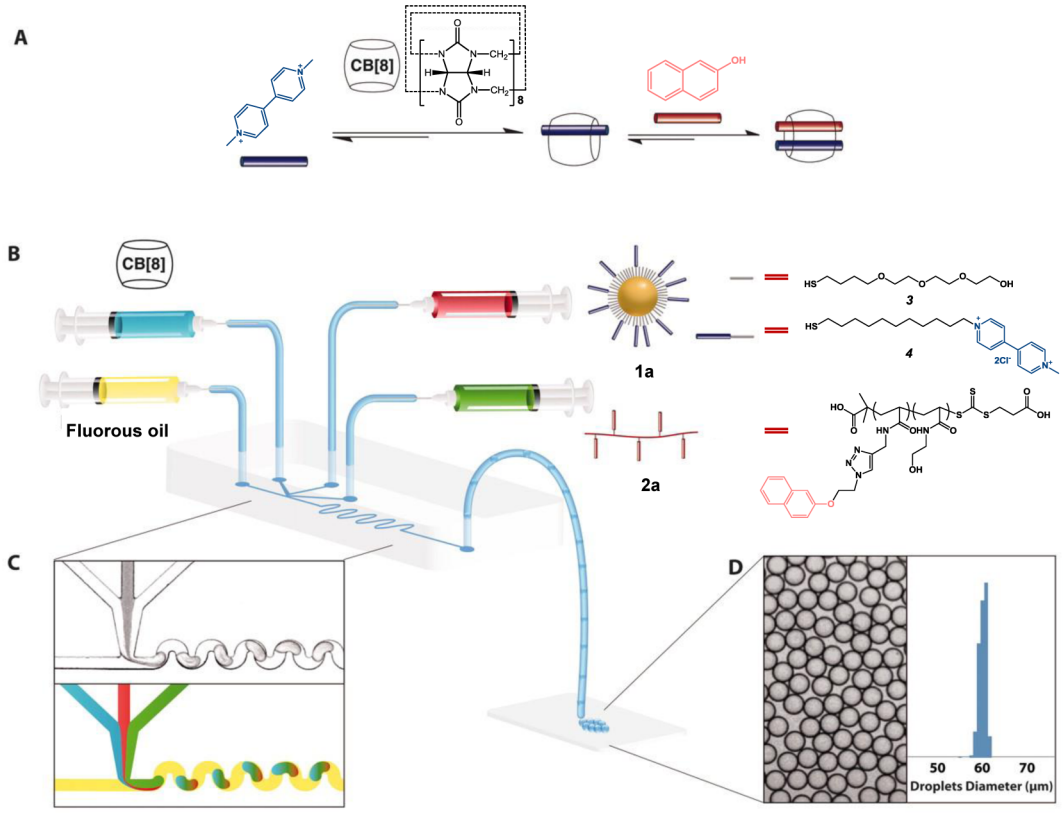

Figure 3. (A) Schematics of the formation of CB[8] ternary complex in aqueous solution with MV^{2+} (blue) and Np (red). (B) Schematic illustration of the microdroplet generation process using a microfluidic T-junction device, comprising a continuous oil phase perpendicular to a combination of three aqueous solutions of CB[8], **1a** (hybrid AuNP decorated with a mixture of neutral and viologen-containing ligands **3** and **4**), and **2a** (Np-containing copolymer) as the dispersed phase. (C) Microscopic image and schematics of the T-junction and a wiggled channel for rapid mixing of reagents online. (D) The microfluidic droplets with a high monodispersity (diameter 59.6 ± 0.8 μm). Reproduced with permission from ref 31. Copyright 2012 AAAS.

between β-CD-based copolymer and AD-functionalized poly(*t*-butyl acrylate).[30]

Moreover, hybrid supramolecular assemblies could also be constructed via host–guest recognition. In a recent contribution, host–guest recognition was applied to fabricate supramolecular hybrid microcapsules in an efficient and scalable manner without compromising functionality and encapsulation efficiency.[31] A simple one-step approach was applied to generate porous microcapsules using four substances including naphthol-functionalized poly(2-hydroxyethyl acrylamide) copolymers, methylviologen (MV^{2+})-modified gold nanoparticles, cucurbit[8]uril (CB[8]), and fluorous oil (Figure 3). Uniform hybrid microcapsules with customizable functionality were obtained by exploiting the fact that the CB host is competent to simultaneously accommodate both electron-deficient MV^{2+} guest and electron-rich naphthol guest. Thus, gold nanoparticle hybrid microcapsules are held together by CB ternary complexes. In this example, the dynamic yet highly stable microcapsules can be loaded in one step during capsule formation and are amenable to on-demand release of loaded substance.

Numerous supramolecular host–guest copolymers with diverse architectures have been explored by virtue of introduction of host/guest moieties to predesigned or post-modified systems.[21] Furthermore, supramolecular assemblies with varying morphologies were achieved via self-assembly followed by the formation of supramolecular copolymers or during the host–guest recognition processes. It remains, however, a tough challenge to fabricate well-defined supramolecular dendrimers by means of noncovalent bonds, although some effort has been dedicated to the functionalization of exteriors of dendrimers by host–guest chemistry. To this end, a predictable solution is the introduction of inclusion complexes with high affinity, while likely resulting in compromised dynamic and adaptive properties.

3. HOST–GUEST CHEMISTRY FOR OPTICAL SENSING AND IMAGING

Host–guest recognition chemistry can also be utilized to regulate colorimetric or fluorometric output for responsive materials; therefore, the design of supramolecular optical sensors can be realized. For instance, by exploiting K^+–crown ether supramolecular recognition, the covalent linkage of a photoinduced electron transfer (PET)-based small molecule K^+ ion-sensing motif to hydroxypropyl cellulose enabled the construction of a commercial portable blood/serum K^+ analyzer in Roche OPTICCA.[32] Supramolecular polymer-based probes can offer extra advantages in terms of detection sensitivity, aqueous dispersibility, and biocompatibility compared with small molecule-based counterparts.[3]

With respect to supramolecular optical probes involving both host–guest chemistry and polymer building blocks, conjugated polythiolphenes functionalized with crown ether pendent groups were employed to detect alkali metal ions.[33] The crown ether-modified polythiolphene was suitable for colorimetric sensing of Li^+, Na^+, and K^+ ions, associated with drastic

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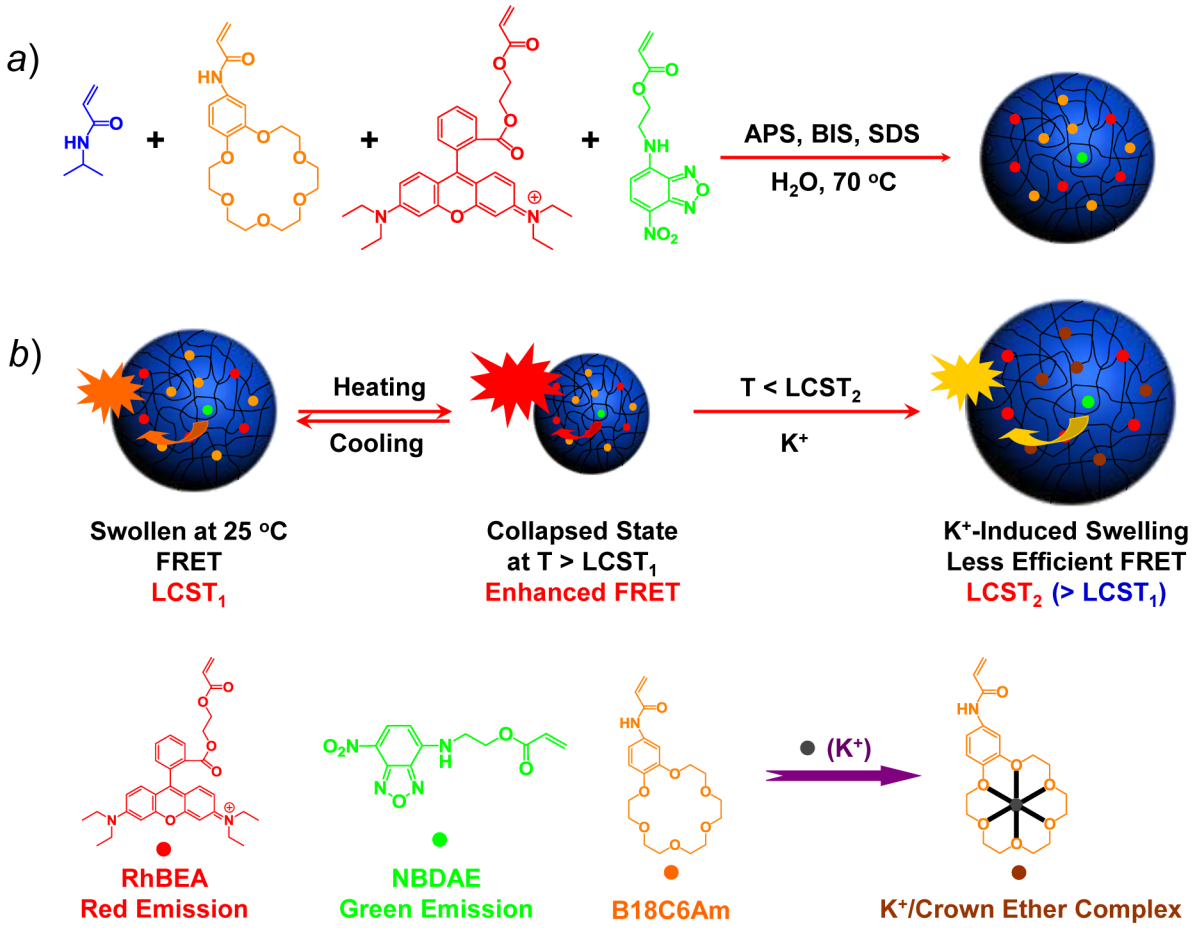

Figure 4. (a) Schematic illustration of the synthesis of thermo- and K^+-responsive P(NIPAM-B18C6Am-NBDAE-RhBEA) microgels via emulsion polymerization. (b) Schematic illustration for tuning the FRET efficiency within microgels by temperature, K^+ ions, and a combination of them. Reproduced with permission from ref 37. Copyright 2010 American Chemical Society.

shift of λ_{max} due to host−guest recognition between crown ether and alkali metal ions, resulting from reduced π-orbital overlap due to rotation of thiophene rings during conformational adaption for maximum metal ion chelation.

In addition to colorimetric variations, fluorometric probes have also drawn much attention owing to their high sensitivity. In the context of supramolecular fluorometric probes, K^+-selective detection capability was assessed on the basis of conjugated poly(*p*-phenylene ethynylene) (PPE) bearing 15-crown-5 (15C5) groups.[34] K^+ was known to form 2:1 sandwich-type complexes with 15C5; in contrast, both Li^+ and Na^+ ions can only form 1:1 complexes. Upon K^+ addition, the absorption spectra red-shifted from 441 to 457 nm, accompanied by significant fluorescence quenching owing to K^+-induced chain aggregation. Nevertheless, neither Li^+ nor Na^+ ions led to evident absorbance or fluorescence changes, thus allowing for highly selective and sensitive detection of K^+ ions. More significantly, the host molecule (e.g., 15C5) can be rationally replaced with other analogues, enabling the detection of other recognizable guests. Huang and co-workers[35] functionalized conjugated PPE with dibenzo[24]crown-8 (DB24C8), which exhibited fluorescence quenching in the presence of bisammonium salt cross-linker due to the formation of cross-linked networks. However, the supramolecular networks were subjected to disintegration by four types of stimuli including K^+ ion addition, Cl^- ion addition, pH increase, and heating, leading to restored fluorescence emission. The supramolecular networks with tunable fluorescence emission can therefore be employed as a multiple fluorescence sensor.

In comparison with fluorescence quenching, an emission turn-on process seems more favorable for sensing and imaging applications owing to increased detection selectivity and optimized imaging contrast. Inspired by specific supramolecular recognition between B15C5 and K^+ ions with the formation of 2:1 sandwich-type complexes, we fabricated a K^+ probe with a fluorescence turn-on feature via the integration of the aggregation-induced emission (AIE) concept.[36] The tetraphenylethene (TPE) core and four outer B15C5 moieties serve as the AIE-active motif and K^+-recognizing moieties, respectively. Initially, TPE−$(B15C5)_4$ molecularly dissolves in THF with negligible emission. However, upon K^+ ion addition, prominently increased fluorescence was observed, in accord with the cross-linking of TPE−$(B15C5)_4$ moieties with K^+ ions. Moreover, ion-selective experiments revealed that both Li^+ and Na^+ ions exhibited negligible effects on the fluorescence intensity, suggesting that TPE−$(B15C5)_4$ could act as a highly sensitive and selective probe for K^+ ions.

The fluorescence resonance energy transfer (FRET) technique with ratiometric detection capability was also involved in designing supramolecular fluorescence probes. We demonstrated a ratiometric fluorescent K^+ sensor based on thermoresponsive PNIPAM microgels covalently incorporated with K^+-recognizing B18C6Am, NBDAE as FRET donor, and rhodamine B-based FRET acceptor (RhBEA) by utilizing K^+-

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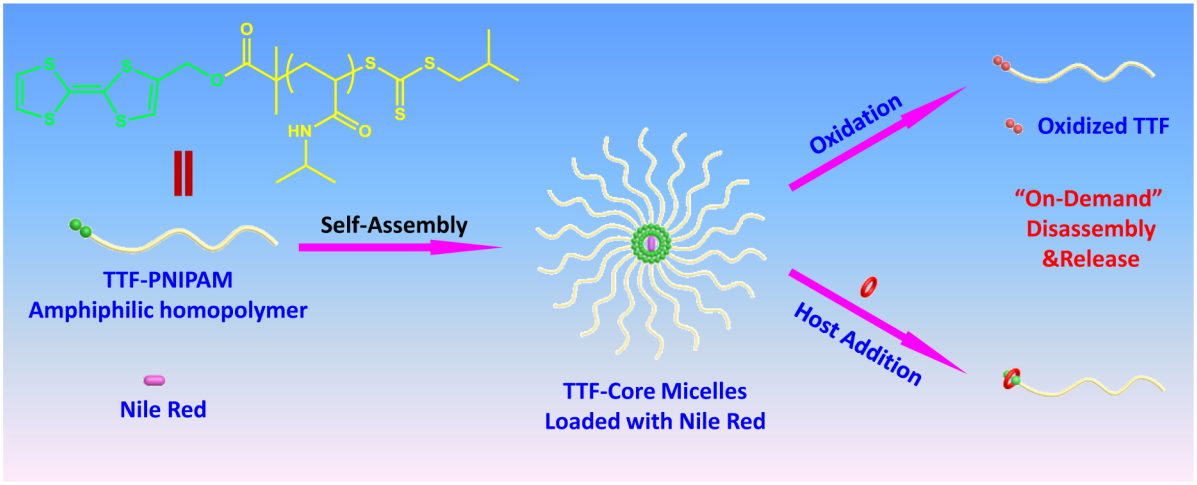

Figure 5. Schematic illustration of the fabrication of micelles from amphiphilic TTF-PNIPAM and their subsequent disassembly in the presence of hosts or oxidants. Reproduced with permission from ref 43. Copyright 2010 American Chemical Society.

induced changes in microgel volume phase transition (VPT) temperatures (Figure 4).[37] The spatial proximity between FRET pairs (i.e., NBDAE and RhBEA) within microgels can be regulated via thermo-induced collapse and swelling of thermoresponsive microgels above and below VPT temperatures, leading to the facile modulation of FRET efficiencies. Moreover, B18C6Am moieties within microgels can preferentially bind K^+ ions via the formation of 1:1 molecular recognition complexes, resulting in increased hydrophilicity and elevated VPT temperatures. Therefore, the gradual addition of K^+ into microgel dispersions at intermediate temperatures, that is, between microgel VPT temperatures with and without K^+ ions, can significantly result in reswelling of initially collapsed microgels. This process can be monitored by changes in fluorescence intensity ratios, that is, FRET efficiencies. This allows for the fluorescent monitoring of thermo- and K^+-induced VPTs of microgels *in situ*. This sensing platform confers a general protocol for designing ratiometric FRET probes for varying analytes by means of specific host–guest interaction-induced shifts in VPT temperatures.[38]

A variety of colorimetric and fluorometric probes have been explored on the basis of polymeric systems involving host–guest chemistry. Nevertheless, it should be noted that most of them are limited to the sensing of alkali metal ions or specific guests. In comparison with versatile strategies for detecting heavy metal ions and bioactive molecules by utilizing chemical reaction-based sensing mechanism or other supramolecular interactions, probes derived from host–guest chemistry are relatively sparse and still in their infancy.

4. HOST–GUEST CHEMISTRY FOR DRUG AND GENE DELIVERY

It is well-established that many host molecules are capable of encapsulating specific guest molecules, resulting in the formation of inclusion complexes. Note that some drugs can also be recognized as a sort of specific supramolecular guest; it is therefore understandable that the host molecules could also be amendable for physical loading, enabling the construction of drug nanocarriers from host-bearing polymers. In this context, CDs are competent to serve as pharmaceutical solubilizers for the controlled release of poorly water-soluble drugs.[39] Besides, a number of drugs were loaded into supramolecular aggregates fabricated from host–guest chemistry by taking advantages of other specific noncovalent interactions (e.g., hydrophobic association and hydrogen bonding). Thus, supramolecular responsive polymer systems can also serve as promising candidates for drug delivery.[40]

Certain drugs, posed as a category of specific guests, can be directly embedded into host molecules owing to specific host–guest recognition, thereby enabling host-containing copolymers as drug carriers. A β-CD labeled DHBC, poly(oligo(ethylene glycol) methyl ether acrylate)-*b*-P(NIPAM-*co*-β-CD), POEGMEA-*b*-P(NIPAM-*co*-β-CD), was used for albendazole (ABZ) delivery.[41] In comparison with native β-CD, the drug loading efficiency increased and the cytotoxicity substantially decreased after covalent attachment of β-CD moieties. Moreover, *in vitro* cellular viability measurement revealed that ABZ-loaded DHBCs were highly toxic to OVCAR-3 ovarian cancer cell lines. After acetylation of β-CD moieties, further increased cytotoxicity was achieved presumably due to elevated drug loading content.

In addition to host encapsulation, those drugs that cannot be directly encapsulated within host molecules can be loaded via the introduction of supramolecular guest linked to the parent drug. For example, 5-fluorocytosine (5-FC) derivative comprising an AD moiety was noncovalently attached to a thermoresponsive copolymer bearing β-CD pendent groups, P(NIPAM-*co*-β-CD), via AD/β-CD recognition, although 5-FC cannot be directly accommodated within the β-CD host.[42] In the presence of α-amylase, the drug-loaded inclusion complexes were digested, followed by the release of embedded 5-fluorocytosine derivative. Notably, this strategy can be applied for intestinal cancer therapy.

On the other hand, host–guest recognition can also be utilized for triggered release of embedded drugs rather than drug loading. Woisel and co-workers[43] fabricated micelles from tetrathiafulvalene (TTF)-terminated PNIPAM (TTF-PNIPAM) by taking advantage of hydrophobic associations of TTF in aqueous solution (Figure 5). Self-assembled micelles encapsulating a hydrophobic model drug could be disintegrated in the presence of specific hosts (e.g., tetracationic macrocycle cyclobis(paraquat-*p*-phenylene) ($CBPQT^{4+}$) or chemical oxidants (e.g., $Fe(ClO_4)_3$), thereby triggering the release of embedded Nile red. In another contribution, Yuan and co-workers[44] constructed a supramolecular amphiphilic PEG-*b*-polystyrene (PEG-*b*-PS) diblock copolymer as a result of

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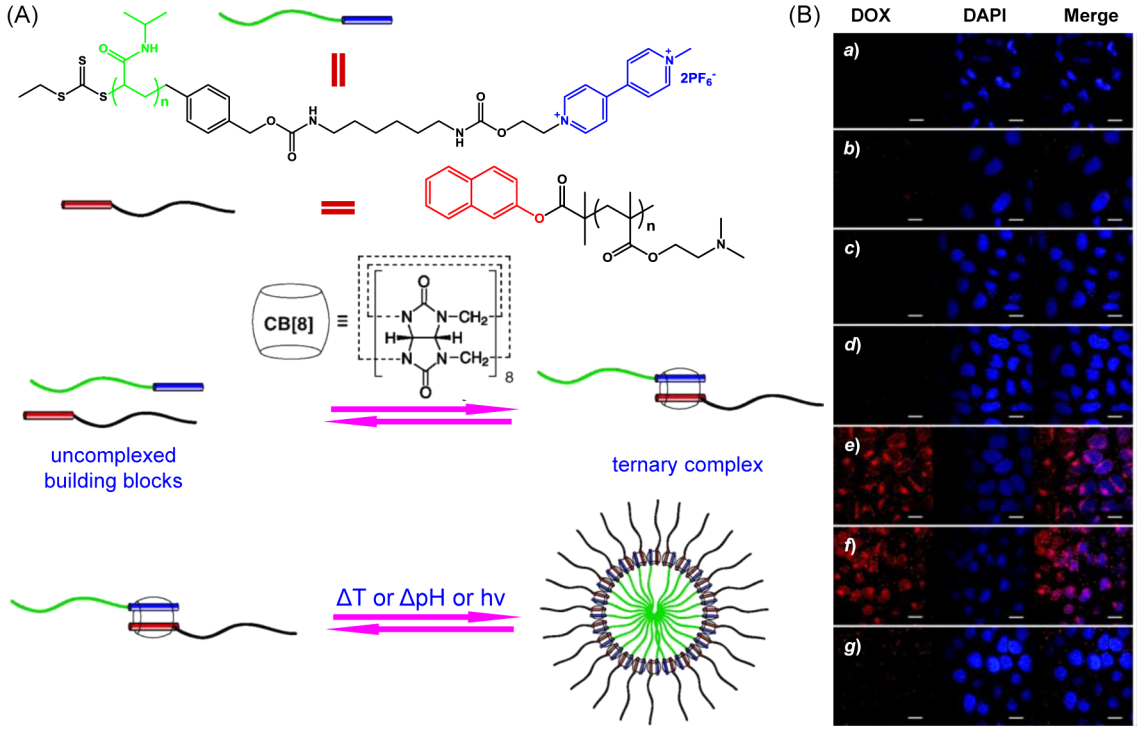

Figure 6. (A) Schematic representation of the formation of CB[8] ternary complex and subsequent assembly into a supramolecular micelle. (B) CLSM images of HeLa cells incubated with supramolecular micelles under different conditions: (a) without micelles, (b) temperature trigger, (c) adamantaneamine trigger, (d) pH trigger, (e) free DOX, (f) combined temperature and adamantaneamine triggers, and (g) no trigger (the scale bar is 20 μm, micelle concentration = 0.5 mg/mL). Reproduced with permission from ref 45. Copyright 2012 American Chemical Society.

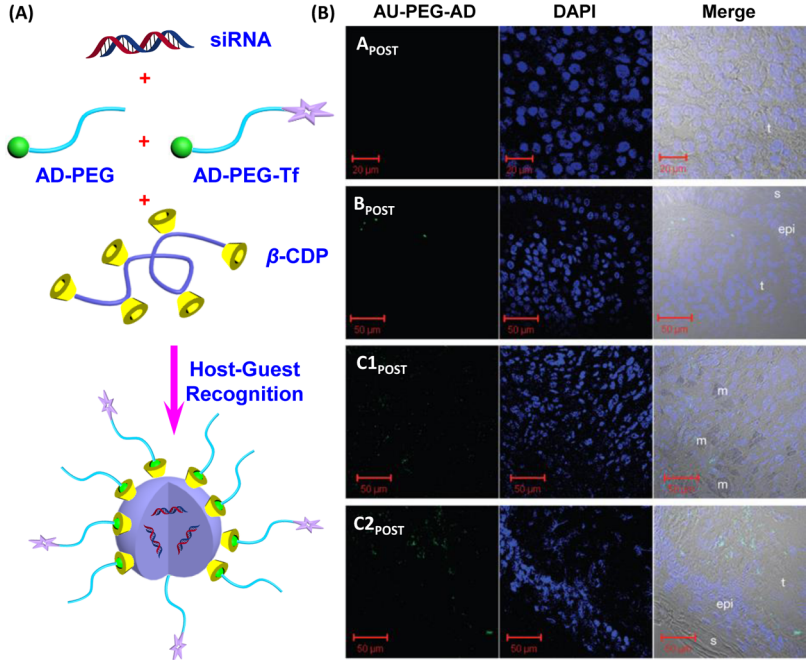

Figure 7. (A) Schematic illustration of the construction of supramolecular nanoparticles encapsulating siRNA from AD-PEG, Tf-AD-PEG, and β-CD polymer via host–guest recognition. (B) CLSM images of post-treatment biopsy sections from patients A, B, and C: (left) Au-PEG-AD stain; (middle) DAPI stain; (right) merged images of the left and right panels with the bright field. Abbreviations: epi, epidermis; m, melanophage; s, skin side; t, tumor side. Reproduced with permission from ref 48. Copyright 2010 Nature Publishing Group.

supramolecular recognition between β-CD and ferrocene (Fc) moieties, starting from β-CD-terminated hydrophobic PS (PS-β-CD) and Fc-functionalized hydrophilic PEG (PEG-Fc). The supramolecular diblock copolymer further self-assembled into vesicles in aqueous solution with PS cores stabilized by PEG bilayers, which can be loaded with both hydrophilic and hydrophobic drugs. Although the hydrophobic PS block and hydrophilic PEO block are inert to external stimuli, vesicular aggregates could be reversibly switched by externally applied voltage with the controlled release of loaded rhodamine B. This

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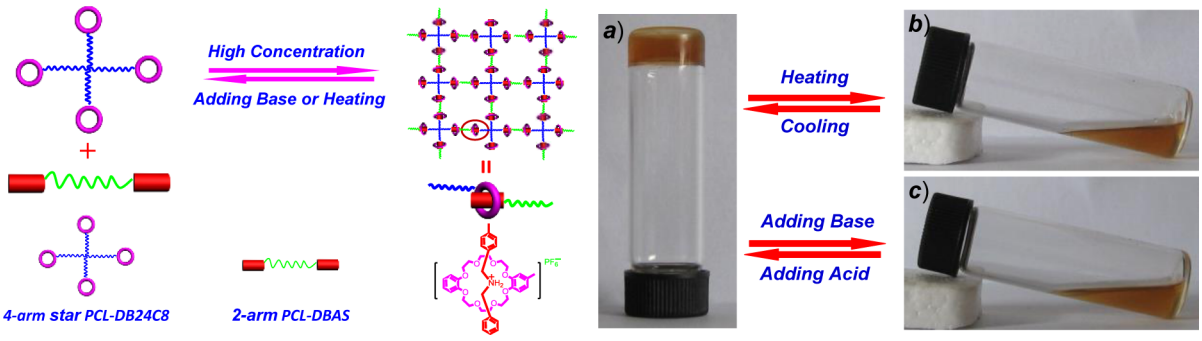

Figure 8. Schematic illustration for the fabrication of supramolecular networks from four-arm star PCL-$(DB24C8)_4$ and two-arm PCL-$(DBAS)_2$ via supramolecular recognition between DB24C8 and DBAS moieties. (a) Supramolecular gel formed from the mixture of four-arm star PCL-$(DB24C8)_4$ and two-arm PCL-$(DBAS)_2$ (DB24C8/DBAS = 1/1) in $CDCl_3$ (150 g L^{-1}, 20 °C); gel−sol transition of the same mixture (b) after heating to 60 °C and (c) after treating with 1.1 equiv of TEA relative to DBAS moieties. Reproduced with permission from ref 8. Copyright 2009 John Wiley & Sons.

is due to reversible association and dissociation of supramolecular β-CD/Fc inclusion complex under alternated redox conditions.

Note that the above examples mainly utilized the dynamic nature of the inclusion complex and do not involve the polymer scaffold. The introduction of stimuli-responsive polymer matrices may endow drug delivery systems with multiple responsive features, thereby delicately regulating drug release profiles. A supramolecular DHBC was synthesized via self-assembly of pH-responsive naphthalene-terminated poly(2-(dimethylamino)ethyl methacrylate) (PDMA) and MV^{2+}-terminated PNIPAM in the presence of CB[8] due to ternary complexation (Figure 6).[45] The as-prepared PDMA-*b*-PNIPAM self-assembled into PNIPAM core micelles in aqueous solution with doxorubicin (DOX) loading at 40 °C. Besides the addition of competitive guests, controlled release of DOX could also be achieved by mediating solution temperature and pH (Figure 6B). The delivery system exhibited prominent inhibition of the proliferation of HeLa cells upon triggered release of DOX from the supramolecular nanocarriers.

In addition to supramolecular assemblies, supramolecular hydrogels can also form via host−guest recognition at relatively high concentrations. For example, supramolecular networks[46] and injectable hydrogels[40] with high drug loading content and sustainable release features can be utilized for controlled drug delivery. In this context, dual-responsive supramolecular polypeptide-based hydrogels and reverse micellar hydrogels were fabricated for the controlled release of DOX.[47] PEG-*b*-poly(L-glutamic acid) (PEG-*b*-PLGA) DHBC was molecularly dissolved in aqueous solution at pH 8.0, whereas it formed micelles with PLGA cores and PEG coronas upon decreasing solution pH to ∼7 owing to the protonation of PLGA block. Since α-CD moieties can simultaneously accommodate two PEG chains in their cavities, the addition of α-CD led to micelle-to-hydrogel transition. On the other hand, reverse micelles with anionic PLGA coronas and physically cross-linked PEG cores formed in the presence of α-CD at pH 8, which experienced hydrogel transition as well upon decreasing solution pH to ∼5 due to intermicellar hydrogen bonding interactions. Reverse micellar hydrogels exhibited high DOX loading (∼10%) and possessed long-term controlled release behavior for up to 45 days. These elegant properties render this platform a potentially useful injectable drug delivery system for cancer therapy.

Host−guest recognition systems can also be utilized for gene delivery. Davis et al.[48,49] designed supramolecular nanoparticles for small interfering RNA (siRNA) delivery, composed of β-CD-based polymer (β-CDP), AD-terminated PEG (Ad-PEG), and transferrin decorated Ad-PEG (Tf-PEG-Ad) (Figure 7A). By mixing the three components with siRNA, they obtained micellar nanoparticles with a diameter of ∼70 nm via AD/β-CD complementary recognition. These nanoparticles can permeate through solid tumors and their accumulation via receptor-mediated endocytosis into tumor cells was proven to be highly dose-dependent, as evidenced by Au-PEG-Ad stain (Figure 7B). Most significantly, based on the first in-human phase I clinical trial for the treatment of melanoma cancer, evidence of inducing RNAi mechanism of action in a human from the delivered siRNA was obtained.

To further improve therapeutic performance, chemotherapy and gene therapy can be integrated to combat multidrug resistance and optimize the sensitivity of chemotherapeutic drugs. In this respect, novel core−shell nanostructures were fabricated via the self-assembly of β-CD functionalized hyperbranched poly(ethylene imine) (PEI) host polymer and hydrophobic poly(β-benzyl-L-aspartate) (PBLA) guest polymer by virtue of specific host−guest recognition between β-CD and benzyl moieties. The supramolecular aggregates could simultaneously serve as drug and gene nanocarriers by taking advantage of hydrophobic cores and hydrophilic PEI coronas, respectively. They might be employed as a new generation of multifunctional nanocarriers for simultaneous drug and gene delivery.[50]

Mounting platforms based on host−guest chemistry have been proven to be potent in drug and gene delivery applications. The dynamic nature and inherently adaptive properties endow these systems with unique multiple stimuli-responsive controlled release features. Most intriguingly, the validity of drug and gene therapies has been ascertained by some profound clinical trials. Albeit potent and promising, some major concerns, that is, specific targeting and accumulation during blood circulation and endosomal escape after cell internalization, should be taken into consideration when designing and optimizing these supramolecular delivery systems.

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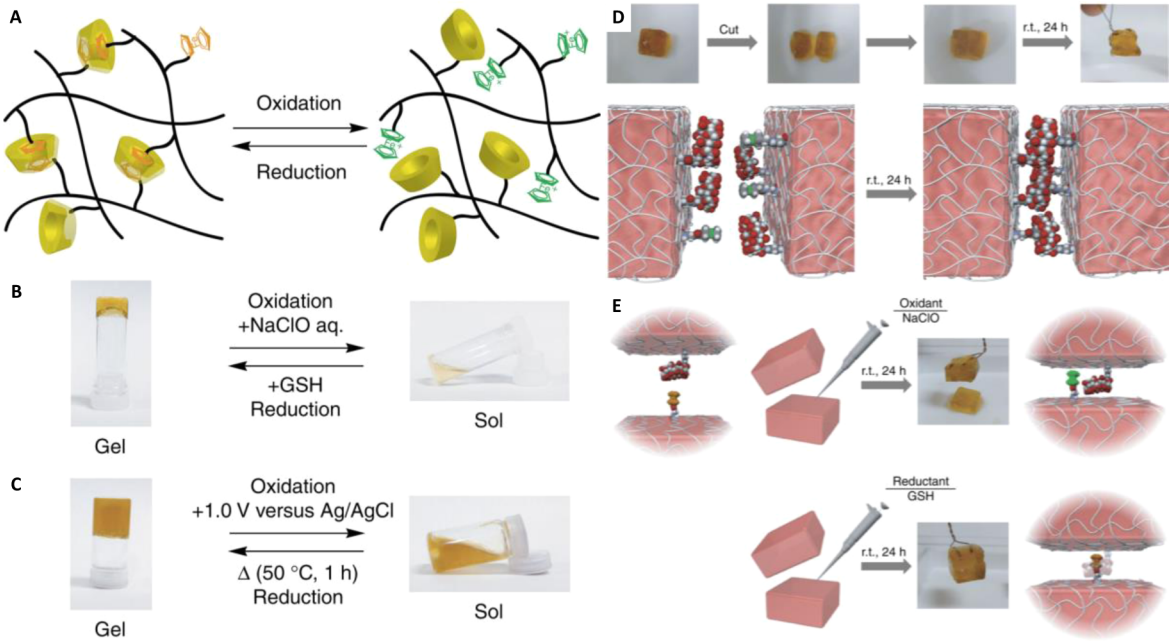

Figure 9. (a) Schematic illustration of sol−gel transition of the supramolecular gel. Macroscopic images of reversible sol−gel transition by using (b) NaClO/GSH and (c) electrochemical reactions. (d) Two cut PAA-β-CD/PAA-Fc hydrogel pieces were self-healed after 24 h standing. (e) Redox-responsive healing experiment of PAA-β-CD/PAA-Fc hydrogel using oxidizing/reducing agents. A PAA-β-CD/PAA-Fc hydrogel was cut in half, and NaClO solution could not heal the cut gels after 24 h standing, whereas self-healing gel was achieved upon addition of GSH solution onto the oxidized cut surface at the same time range. Reproduced with permission from ref 55. Copyright 2011 Nature Publishing Group.

5. HOST−GUEST CHEMISTRY FOR SELF-HEALING MATERIALS

Stimuli-responsive supramolecular gels constructed via noncovalent bonds might retain structural stability and functionality after exposure to externally applied stimuli or shear forces. This feature endows supramolecular gels fabricated from host−guest chemistry with unique self-healing capability. β-CD/AD and β-CD/AZO host−guest chemistry has been applied to fabricate supramolecular gels on the basis of different polymeric backbones.[51−53] We previously demonstrated temperature- and pH-responsive supramolecular gels derived from biodegradable poly(ε-caprolactone) (PCL) segments functionalized with DB24C8 and dibenzylammonium salt (DBAS) moieties (Figure 8).[8] At a polymer concentration of 150 g L^{-1} in $CHCl_3$, the mixture of PCL-$(DB24C8)_4$ and PCL-$(DBAS)_2$ spontaneously form physical gels as a result of supramolecular recognition between DB24C8 and DBAS moieties. Most importantly, the supramolecular interaction can be facilely modulated by changing temperature and pH, thereby conferring reversibility of the sol−gel transition.

Supramolecular recognition between DB24C8 and DBAS moieties was further utilized to fabricate self-healing materials. Huang and co-workers[54] prepared two supramolecular gels by mixing poly(methyl methacrylate) (PMMA) polymer containing pendent DB24C8 units and cross-linkers bearing two bisammonium moieties with disparate end-group sizes. Reversible sol−gel transitions were observed by tuning solution pH owing to pH-responsiveness of the mediating inclusion complexes. The self-healing capability of supramolecular gels can be either discerned visually or further confirmed by rheological measurements.

On the basis of host−guest recognition of β-CD/Fc moieties, Harada et al.[55] demonstrated the construction of supramolecular hydrogels and redox-responsive self-healing behavior (Figure 9). Redox-responsive supramolecular hydrogels were facilely prepared by mixing β-CD-functionalized and Fc-decorated poly(acrylic acid) (PAA), respectively. Because the Fc moiety is redox-responsive, inclusion complexes of β-CD/Fc moieties can be reversibly regulated by redox stimuli, conferring supramolecular gels with self-healing features such as readhesion between cut surfaces.

Self-healing properties represent an outstanding feature of supramolecular host−guest systems by taking advantage of the dynamic nature. Notably, the likelihood to achieve robust self-healing properties yet without compromising the mechanical stiffness seems impractical because strong interactions yield toughness but less self-healing performance and weak interactions afford dynamic healing but low stiffness. Therefore, it is paramount and imperative to balance the dynamic healing capability and mechanical strength for the development of novel self-healing materials in future studies.

6. CONCLUDING REMARKS

In this Account, the fabrication of supramolecular polymeric materials by integrating responsive building blocks with host−guest molecular recognition and their functional applications in optical sensing and imaging, drug and gene delivery, and self-healing materials are discussed. We attempt to elucidate general designing strategies and focus on the functional aspects. Indeed, the potential applications of host−guest chemistry are far beyond the above-mentioned aspects, and further exploration is only limited by our imagination. For instance, applications in wastewater purification,[56] helicity induction and inversion, and fabrication of functional polyrotaxanes[11] have been already demonstrated. Generally, this research field can be further broadened and exploited as described below.

First, although numerous supramolecular polymer architectures and topologies can be achieved via combining host−guest

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chemistry and predesigned polymer building blocks, the function integration aspect is less explored, and it remains a challenge to utilize these supramolecular polymers with robust architectures for unrealized applications.

Second, supramolecular probes relying on the host−guest recognition mechanism mainly focus on the sensing of alkali metal ions or specific guests. The emerging growing point in this aspect might evolve from screening brand new host−guest systems, aiming at extending the range of sensing analytes and detection sensitivity. Meanwhile, the dynamic and adaptive advantages of host−guest chemistry-orientated sensing platforms should be further utilized for reversible and reusable sensing applications. On the other hand, macroscopic self-assembly at the millimeter or centimeter scale based on mesoscopic supramolecular interactions at the molecular level represents a new trend and opens up new directions for this field,[57] which enables the visualization of self-assembly performance. This concept could be also integrated into supramolecular sensors to facilitate the development of new type of sensing devices.

Finally, the functions of host−guest chemistry should further move forward, aimed at meeting the needs of real world circumstances. For instance, host−guest chemistry for drug and gene delivery should be pushed forward further both in fundamental theories and in clinical treatments, and more clinical trials should be encouraged to overcome the bottleneck between *in vitro* results and practical therapies. Self-healing materials fabricated by host−guest chemistry exhibit unprecedented advantages in terms of facile accessibility and speedy response. However, they may lack sufficient mechanical strength when considering their practical applications. Overall, more original and evolutionary concepts are highly desirable for further advancing this intriguing field and extending the practical applications in future studies.

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Notes

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