Cucurbit[*n*]uril-based supramolecular hydrogels: synthesis, properties and applications

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Abstract

Due to their dynamic qualities and potential uses in fields such as biomedicine, tissue engineering, drug delivery, soft materials, and sensing, hydrogels have gained increased attention in recent years. Concurrently, the application of cucurbit[*n*]uril-based host-guest interactions has been crucial in advancing the field of supramolecular chemistry. Given this, there has been a growing number of reports in the literature regarding the formation of hydrogels that are mediated by host-guest interactions between various cucurbit[*n*]urils and their guests. This review aims to present comprehensive insights into the creation and advancement of supramolecular hydrogels utilizing cucurbit[*n*]uril-mediated design strategies. Firstly, supramolecular hydrogels formed via different construction methods with cucurbit[*n*]urils are classified, including (i) outer surface interaction construction and (ii) host-guest construction. Next, the excellent properties possessed by

hydrogels, namely biocompatibility, stimulus responsiveness, and self-healing, are discussed. Finally, the different hydrogels are classified according to their applications, with a focus on their biomedical use. We believe that this review highlights the potential for further research based on host-guest interaction-mediated hydrogels.

1. Introduction

In recent decades, there has been a growing fascination with hydrogels owing to their dynamic characteristics and versatile applications in a plethora of fields, spanning from materials science to bioscience [1-7]. As three-dimensional structures composed of a significant amount of water, hydrogels demonstrate distinct features such as soft material properties, solid-like rheology, and swelling-shrinking behavior. Typically, hydrogels are fabricated by chemically cross-linking polymers, however, they can also be generated through the use of low molecular weight gelling agents (LMWG) or physical cross-linking of polymers [9,13-14], such as supramolecular polymer hydrogels, also known as supramolecular hydrogels [8,10], that rely on LMWG. In general, both types of hydrogels are referred to as supramolecular hydrogels. Significantly, the construction of supramolecular hydrogels hinges on supramolecular interactions, particularly host-guest interactions involving macrocycles. Recently, scholars have been investigating the creation of supramolecular hydrogels using dynamic non-covalent interactions. When juxtaposed with other non-covalent interactions, host-guest interactions are comparatively more stable and simpler to regulate, and the reversible complexation mechanism between host-guest molecules has emerged as a hot research topic in supramolecular chemistry. Thus, integrating the dynamic characteristics of host-guest interactions with hydrogels offers a promising avenue for producing new soft materials featuring exceptional chemical and physical properties, including self-healing, responsiveness to stimuli, and adaptability. Given the aforementioned attributes, supramolecular hydrogels created via host-guest interactions have garnered significant interest. Of all the appropriate supramolecular entities, cucurbit[*n*]urils exhibit immense potential as efficient crosslinkers for the production of supramolecular hydrogels. Cucurbit[*n*]uril is a fourth-generation macrocyclic host compound constructed by linking glyoxal units through methylene bridges [15-17]. The family of Q[*n*]s are named differently according to the number n of glyoxylate units they

possess. Q[*n*]s possess an extremely symmetrical and rigid structure that resembles a pumpkin on the outside and encompasses a hydrophobic cavity on the inside, with hydrophilic groups located at the entrances and a distinct negative charge. Ordinarily, the Q[*n*] height measures 0.9 nm, with the diameter escalating in tandem with the quantity of glyoxal units incorporated. The specific nature of the host-guest interaction of Q[*n*]s arises from this structural characteristic, thereby imparting high binding constants. In general, the solubility of Q[*n*]s in various organic solvents is below 10^{-5} M. As a result, investigations of the chemical properties of Q[*n*] have primarily been conducted in aqueous media. Furthermore, the Q[*n*] family boasts low toxicity [18] and is generally well-suited to various cell cultures, underscoring its potential for deployment in the biomedical sector. Given the robust charge dipole, hydrogen bonding, and hydrophobic/hydrophilic interactions of Q[*n*]s, almost all Q[*n*] studies to-date have focused on supramolecular assemblies and it is evident that different types of Q[*n*]s exhibit different host-guest behavior.

Based on the above, numerous research groups have reported many interesting hydrogels by using cucurbit[*n*]urils complexed with polymers. Furthermore, these endeavors have resulted in the creation of a range of guests with distinct attributes that can interact based on the hydrophobic nature of the cucurbit[*n*]uril cavity and the electro-positivity of the Q[*n*]'s outer surface. Once the cucurbit[*n*]uril is introduced, the engineered guest molecules can be affixed to the polymer chains and subsequently penetrate its cavity, resulting in the formation of a hydrogel centered on the primary guest complex. In addition, the guest molecule can also be cross-linked with the outer surface that is electronically positive through the cucurbit[*n*]uril to form a non-covalent interaction to construct supramolecular hydrogels.

Reviews of supramolecules and hydrogels have been reported previously, but their focus was on hydrogels constructed from a wide range of macrocyclic host compounds [19] or based on the application of a particular class of macrocyclic hosts in the pharmaceutical field [20]. Consequently, there is a pressing need for a review centered on supramolecular hydrogels founded on cucurbit[*n*]uril-based structures to bridge the gap in this field.

The objective of this review is to offer a comprehensive overview of the design and advancement of supramolecular hydrogels mediated by cucurbit[*n*]uril. Firstly, the supramolecular hydrogels

formed based on different construction methods with cucurbit[*n*]urils are classified, including (i) outer surface interaction construction and (ii) host-guest action construction. Next, the excellent properties possessed by hydrogels, such as biocompatibility, self-healing, and stimulus responsiveness, are discussed. Finally, the different hydrogels are classified according to their applications, with a focus on the biomedical field. We anticipate that this review will emphasize the potential of hydrogels mediated by host-guest interactions.

In Chart 1, the polymers used in the review are shown and are classified as follows: acrylamides, polyethylene glycols, acrylics, cellulose, natural polymers, and heterocycles. In Chart 2, the number of occurrences of the polymers used is summarized, and the different properties of supramolecular hydrogels can be obtained by cross-linking these polymers with cucurbit[*n*]urils.

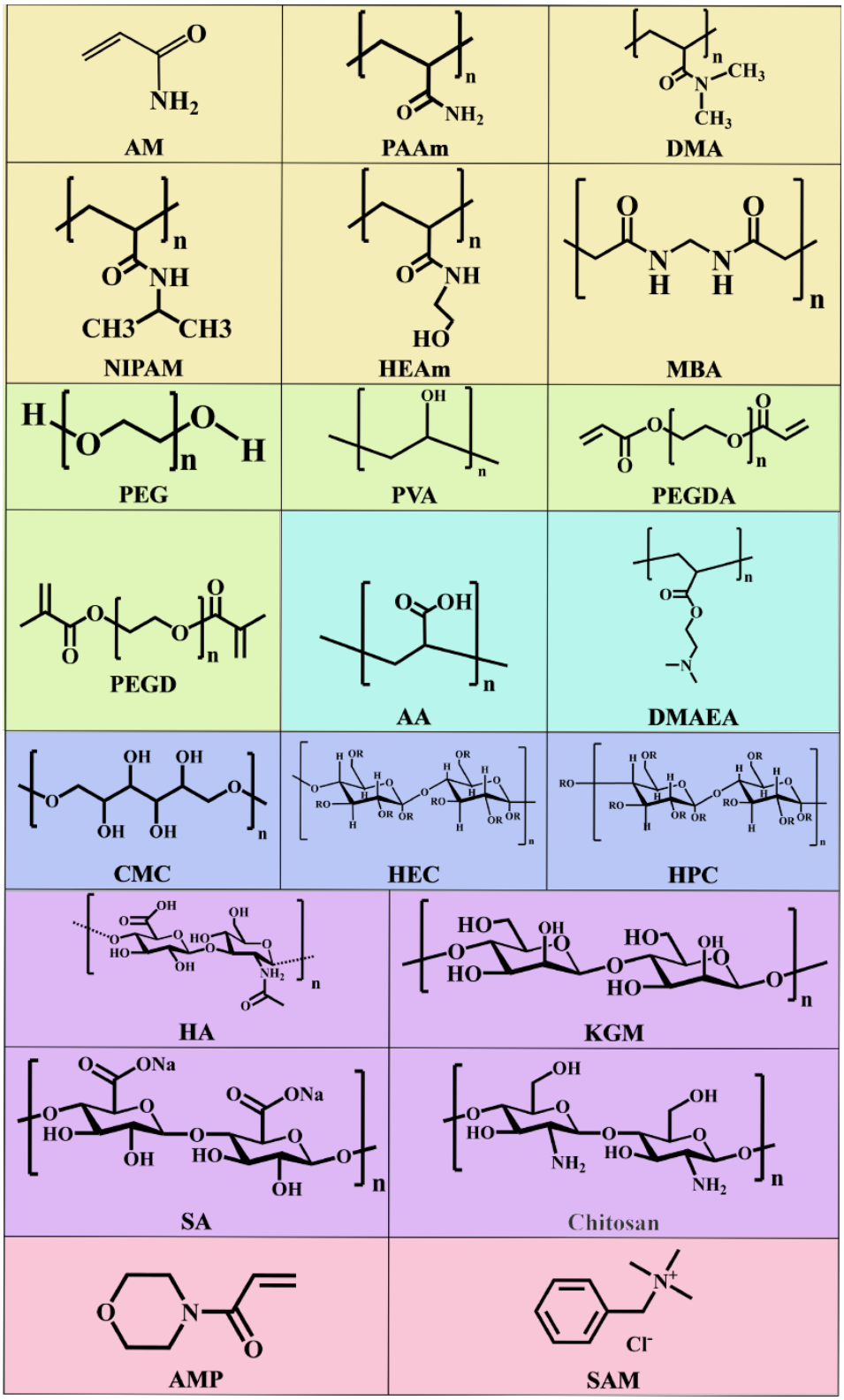

Chart 1. Structures of the Polymers.

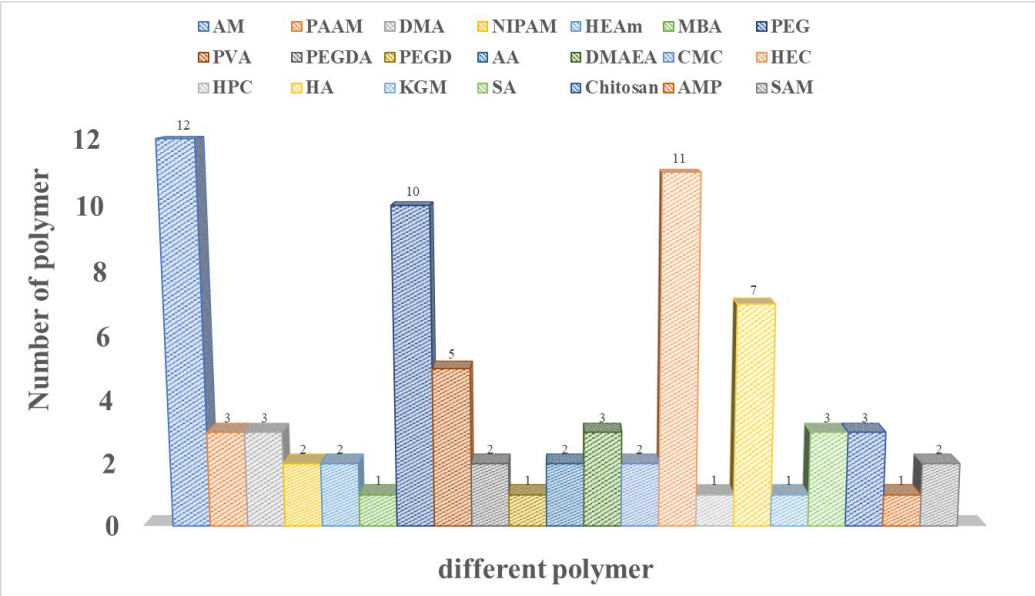

Chart 2. Occurrences of different polymers in the literature.

2. Construction methods

2.1 Outer surface interaction construction

Since 2014, our laboratory and other researchers have been working on supramolecular frameworks based on the outer surface interactions of cucurbit[*n*]urils (OSIQ) [21-26]. When we initially proposed the OSIQ [21], in particular those involving the cucurbit[*n*]urils itself and anion-induced outer surface interactions [22], the positive outer surface of the electrostatic potential of the Q[*n*]s was involved. Subsequent investigations have revealed that coordination polymers based on cucurbit[*n*]urils can serve as efficient agents for the recovery of diverse metal ions [25-26] and for the fabrication of a diverse range of sensors [27-35]. Furthermore, the OSIQ can also be utilized in the construction of supramolecular hydrogels. Kim's group [23] was the first to report the construction of a supramolecular hydrogel by the action of the outer surface of cucurbit[7]uril. In 2021, our group reported the formation of supramolecular hydrogels through external wall interactions between desmethyl pentameric cucurbit[5]uril ($Me_{10}Q[5]$) and *p*-phenylenediamine (*p*-PDA)[36]. The primary force that drives the formation of these gel systems is the utilization of

hydrogen bonding and ionic dipole interactions between the carbonyl oxygen atom of $Me_{10}Q[5]$ and the two amine groups of the *p*-PDA guest. The appropriate concentration of protons facilitates these interactions.

Tan *et al*. have prepared novel alginate physical hydrogel beads [37] and micelle-like nanoclusters [38] for the first time using electrostatic attraction and ionic dipole interactions between sodium alginate and Q[6]. As shown in Figure 1a, a Q[6] can bind to two sodium ions in an aqueous solution via ionic dipole interactions to form a Na^+-Q[6]-Na^+ complex. Each alginate is a long chain of hundreds of carboxyl groups. Two carboxyl groups and one Na^+-Q[6]-Na^+ complex can form a chain of carboxyl-Na^+-Q[6]-Na^+-carboxylate complexes under electrostatic attraction. The interchain complex sites first form a gel at the surface of the alginate/Q[6] gel beads. With the increase of gel time, the Q[6] diffuses to the center of the alginate/Q[6] gel beads. Finally, spherical alginate/Q[6] gels were obtained.

The preparation of polymers (PAM-Q[6]MA-MH) by free radical polymerization with a hydrazinyl monomer (MH) and acrylamide (AM) after derivatization with a monohydroxy-cucurbit[6]uril derivative (Q[6]MA) has been reported [39]. Next, PAM-Q[6]MA-MH was used to create macromolecular complexes with 1-aminopyrine through non-covalent interactions, resulting in novel copolymer systems with unique properties. The resulting PAM-Q[6]MA-MH-1-aminopyrene complexes were then mixed with a glyoxal solution under neutral conditions to form self-healing hydrogels, as illustrated in Figure 1b.

In a similar manner, supramolecular hydrogels can also be fabricated using outer surface interactions of cucurbit[7]uril. Supramolecular hydrogels were constructed by the interaction of dibenzyl ketone with the C-H…O of the Q[7] [40]. Hu *et al.* [41] utilized Q[7] as supramolecular connectors to attach superparamagnetic γ-Fe_2O_3 nanoparticles to chitosan polymer backbones functionalized with catechol. The distinctive barrel-shaped structure of Q[7] not only facilitated the recognition of the catechol derivatives but also established robust electrostatic interactions between its carbonyl entrance and γ-Fe_2O_3 nanoparticles in a supramolecular manner, ultimately leading to the formation of supramolecular hydrogels (depicted in Figure 1c). Similar work has been reported [42]. Liu *et al.* developed a supramolecular hydrogel by utilizing dynamic host-guest interactions between the host molecule Q[8] and the guest unit, while incorporating photonic

crystalline Fe_3O_4@C magnetic nanoparticles (Fe_3O_4@C MNPs) to achieve bright structural colors in the resulting self-healing hydrogel.

In Figure 1d, a novel supramolecular gel was prepared by combining Q[7] with polyacrylamide (PAAm) [43]. Supramolecular gels are formed through the main driving force of hydrogen bonding interaction between the amino and the carbonyl. In addition, novel self-healing supramolecular hydrogels using Q[8] interactions were successfully prepared. The naphthalene group on the side chain of the Q[8] molecule and the copolymer function as cross-linkers, forming 1:2 complexes through supramolecular interactions [44].

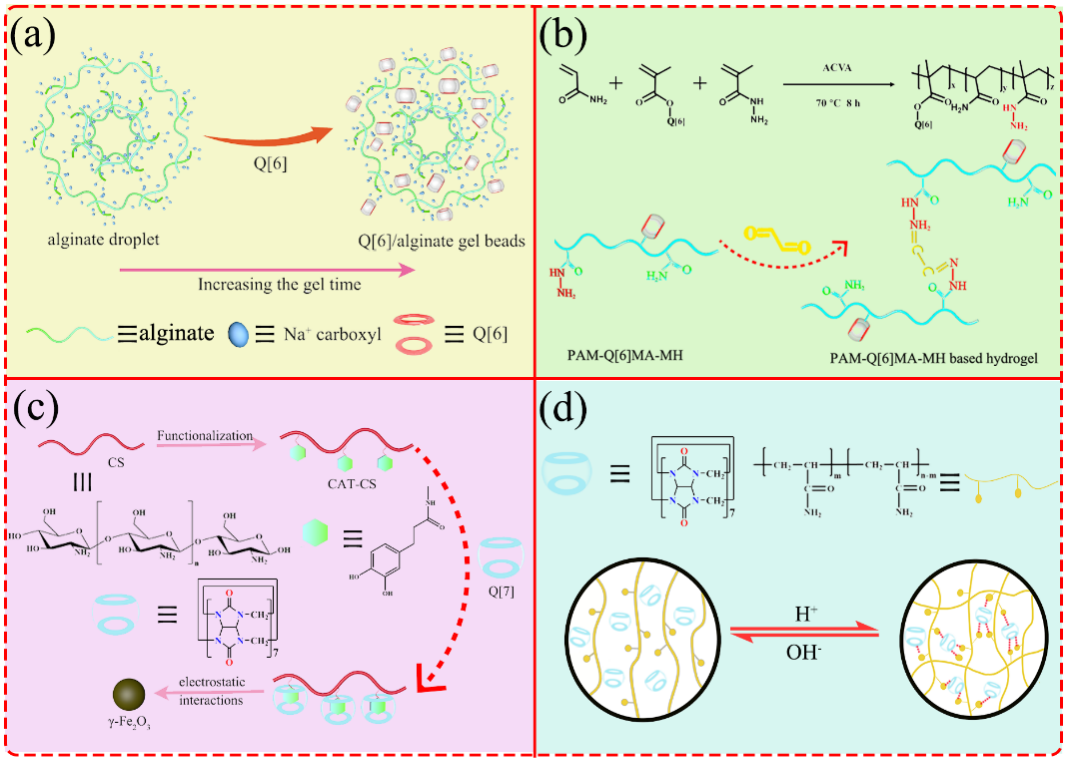

Figure 1. (a) Alginate/Q[6] gel beads are created according to the schematic; (b) A synthetic scheme illustrating the preparation of self-healing hydrogel; (c) Schematic Diagram of hydrogel Prepared by Q[7]-mediated molecular recognition and electrostatic interaction; (d) Schematic illustrating the supramolecular gel's sol-gel phase transition.

2.2 Host-guest interaction construction

2.2.1 Binary complexes constructed based on host-guest interactions

The binary complexes that have been constructed using hosts and guests are mainly based on Q[6]-Q[8], and have different responses to different organic molecules due to their varied cavity sizes. Chujo *et al.* [45] demonstrated the generation of supramolecular hydrogels using Q[6] and silica hybrids. Kim's group reported the use of Q[6]-conjugated hyaluronic acid (Q[6]-HA) and diaminocaprolactone-conjugated hyaluronic acid (da-HA) to form supramolecular hydrogels, which have been applied as three-dimensional artificial extracellular matrices for tissue engineering purposes [46,47]. Tan *et al.* [48] described a novel supramolecular hydrogel that responds to temperature variations, which is based on the interaction between Q[6] and butylamine 4-methyl benzenesulfonate (BAMB). Alexander *et al*. [49] investigated the fluorescence properties of tetra-(2-hydroxyethyl)orthosilicate silica containing *trans*-4-[4-(dimethylamino)styryl]-1-methylpyridine iodinated supramolecular complexes. Organic supramolecular complex-based fluorescent gels were first synthesized through direct addition of Q[7] and Q[8] to the reaction mixture. As shown in Figure 2, cross-linked affinity supramolecular hydrogels spanning five orders of magnitude were able to be obtained by derivatizing Q[7] and then attaching it to polyethylene glycol macromolecules [50-51].

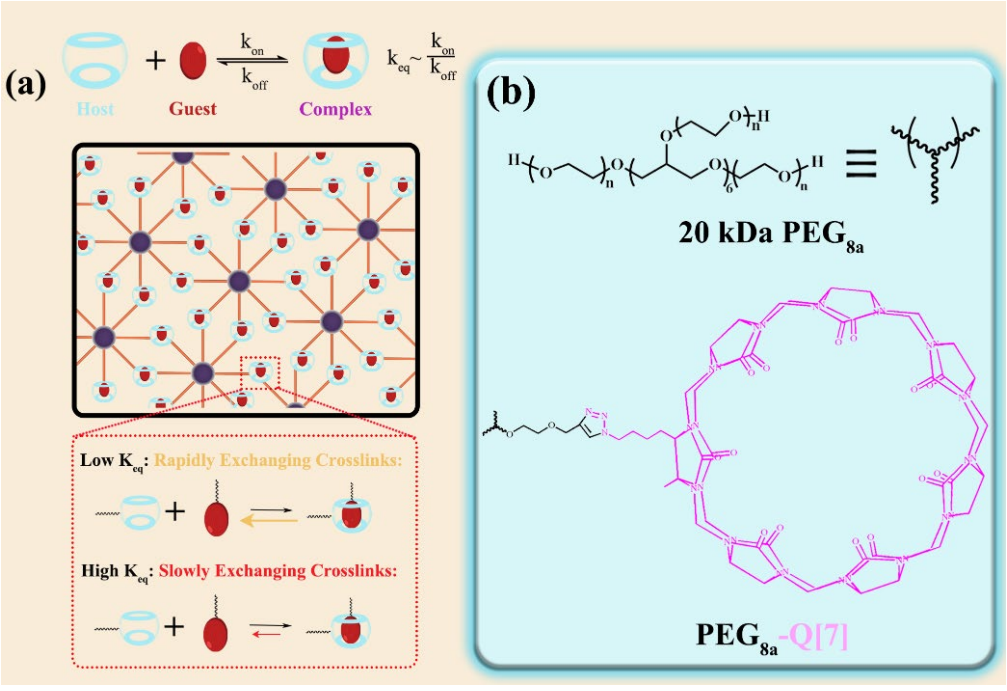

Figure 2. (a) Schematic diagram of host-guest cross-linking; (b) Schematic diagram of hydrogel construction.

In addition, Webber *et al*. also obtained thermally reversible hydrogels by attaching polyethene glycol chains to two Q[7]s and then binding them with functionalized ferrocene (see Figure 3) at a critical temperature (37 ℃) [52]. In other work, polyethene glycol chains were also used to form hydrogels with Q[8] [53].

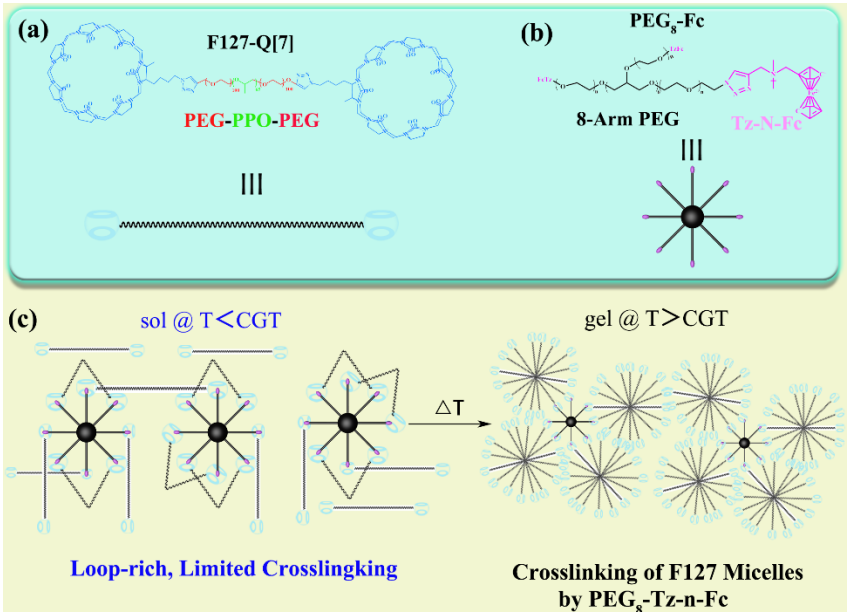

Figure 3. Development of a supramolecular hydrogel with thermo-responsive properties for targeted drug delivery. (a) Modification of Pluronic F127 with cucurbit[7]uril (Q[7]); (b) Schematic diagram of penetration network construction (c) Mechanism of thermal response gelatinization process.

Zheng *et al*. prepared a novel ionic carbazole water-soluble photo-initiator based on a Q[7] to achieve a three-dimensional hydrogel structure in the aqueous phase [54]. Supramolecular hydrogels were also obtained after derivatization of the same guest and 1:1 binding to Q[7] [55].

Wang and colleagues constructed hydrogels in Figure 4a through phenylene violet sperm and Q[7]s in the presence of alginate and $CaCl_2$ [56].

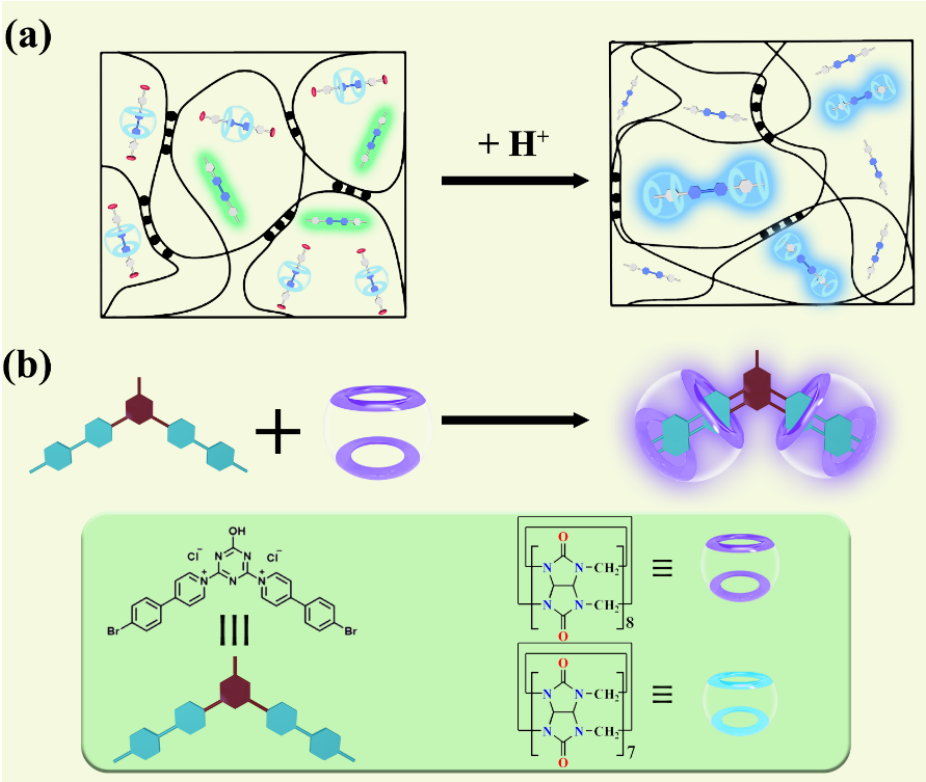

Figure 4. (a) The hydrogels contain a PVP2-Q[7] kinetic trap and DTV; (b) Action Mode of TBP and Q[8].

Wheate *et al*. [57] used gelatin and polyvinyl alcohol (PVA) bases as carriers with Q[7]s to form supramolecular hydrogels for drug retardation, where different levels of PVA exhibited different cytostatic inhibition. Q[8] is a more favorable choice for building supramolecular hydrogels due to its larger cavity when compared to Q[6] and Q[7]. As shown in Figure 4b, the two positively charged pyridine groups of the triazine derivative TBP combine with the Q[8] to form a visible light-excited room-temperature phosphorescent hydrogel [58]. In a comparable manner, non-chiral monomers based on the combination of Q[8] with 4,4'-bipyridine-1-ammonium chloride (BPY^+) salt derivatives were rationally designed and utilized to construct supramolecular helical nanofibers in aqueous solution (Figure 5) [59].

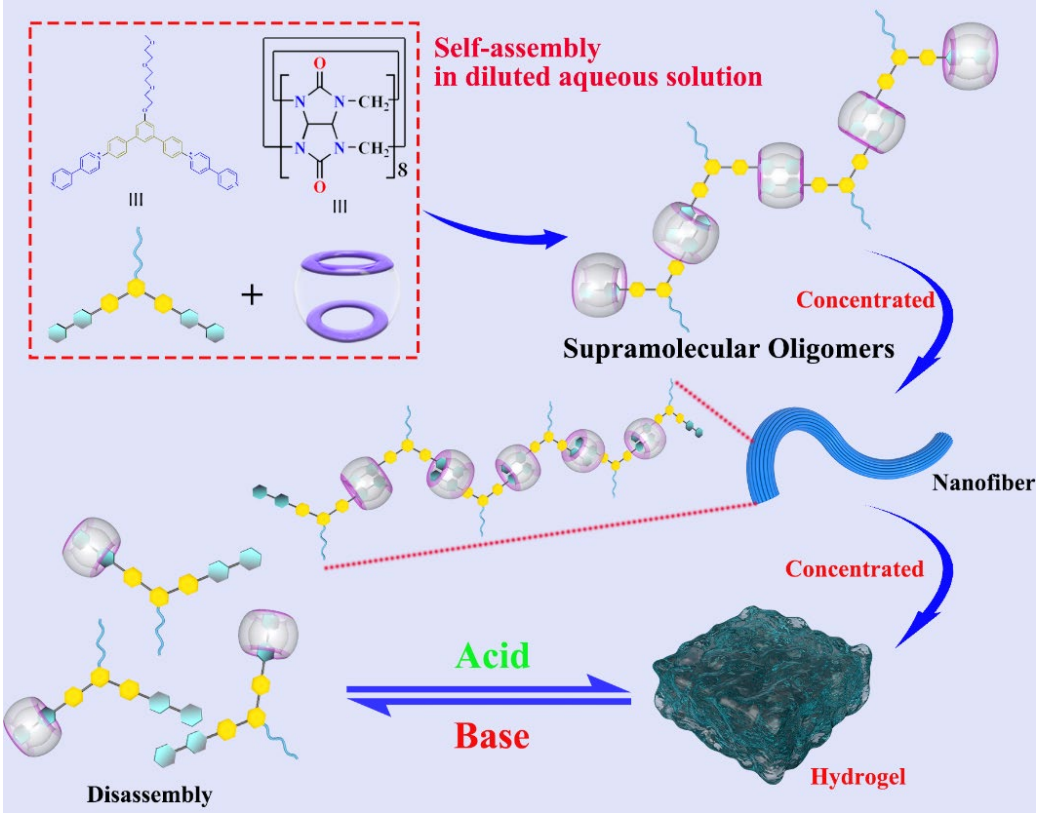

Figure 5. Schematic diagram of supramolecular self-assembly and hydrogel formation process. The hydrogel is responsive to external acid/base additions, allowing for a reversible gel-sol transition.

Poly(vinyl alcohol) was also used with Q[8], and as illustrated in Figure 6, Ji *et al.* [60] initially constructed a lattice using PVA with desirable thermal and chemical stability, high tensile strength, good film-forming ability, and transparency. They then created a second lattice by utilizing allyl-modified 4-(4-bromophenyl)pyridine-1-ammonium bromide (ABP) with Q[8], which was subsequently copolymerized with acrylamide monomer to produce supramolecular hydrogels exhibiting exceptional room temperature phosphorescent properties.

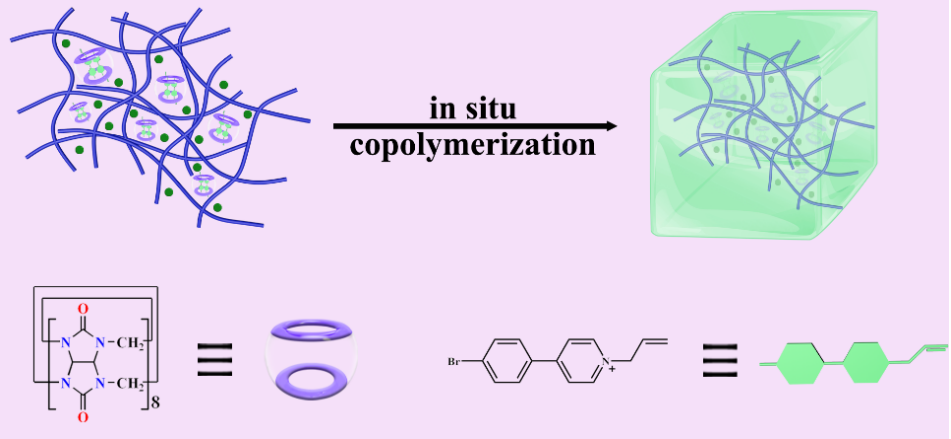

Figure 6. Construction of supramolecular hydrogels and the chemical structure formula of the substances used.

The production of novel supramolecular hydrogels with pH and thermal responsiveness, as depicted in Figure 7 [61], involved the utilization of Q[8] and poly(*N*-(4-vinyl benzyl)-4,4'-bipyridinium dichloride co-acrylamide) (P4VBAM).

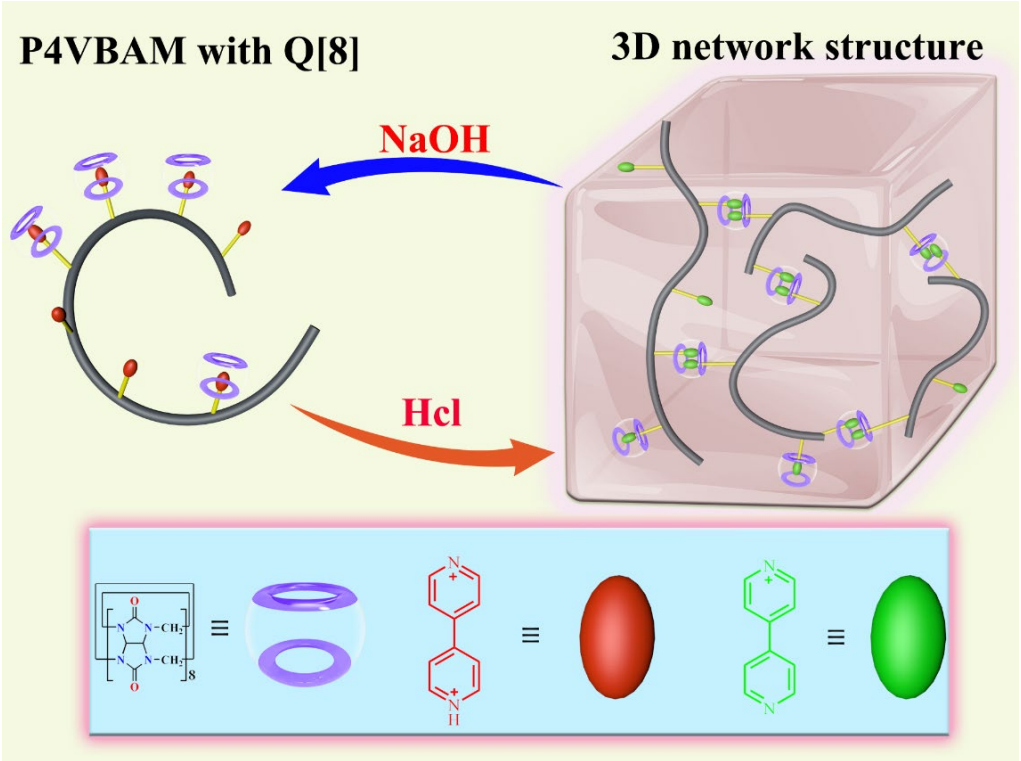

Figure 7. A schematic diagram demonstrates the process of forming supramolecular hydrogels with pH responsiveness by adjusting the pH levels.

Not only that, Tan also modified polylysine with phenylalanine and used it as the polymer backbone of a hydrogel as shown in Figure 8. Through the crosslinking of the phenylalanine and amine groups with Q[8] and a double aldehyde cross-linker, respectively, the resulting double-cross-linked hydrogel exhibited superior mechanical strength, enhanced elongation, and accelerated self-healing properties in comparison to the monoimine cross-linked hydrogel [62].

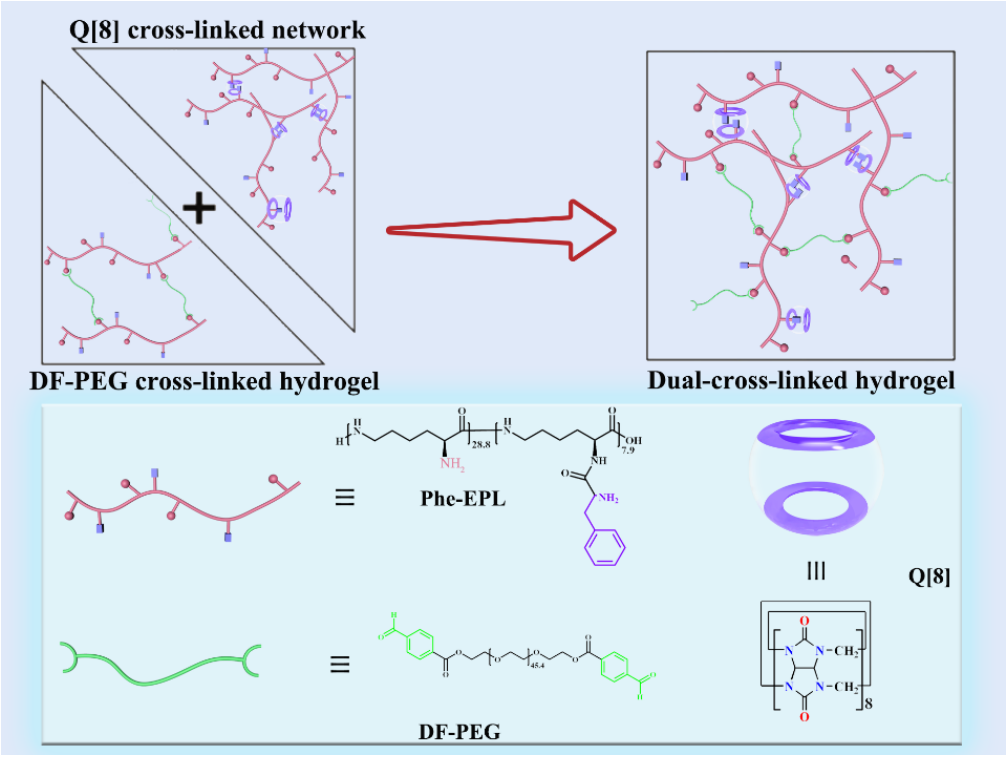

Figure 8. Schematic diagram of double cross-linked hydrogel structure.

In a study by Liu and colleagues [63], an alkyl chain-modified oligo(p-styrene) (Py-OPV) derivative was synthesized, which exhibited J-aggregation upon encapsulation within the cavity of Q[8], and displayed distinct emission properties depending on the monomer used. The fluorescence characteristics of the assemblies could be easily adjusted by manipulating the

concentration of Q[8]. Subsequently, luminescent supramolecular hydrogels were generated via the acrylamide photopolymerization of Py-OPV and Q[8], as shown in Figure 9.

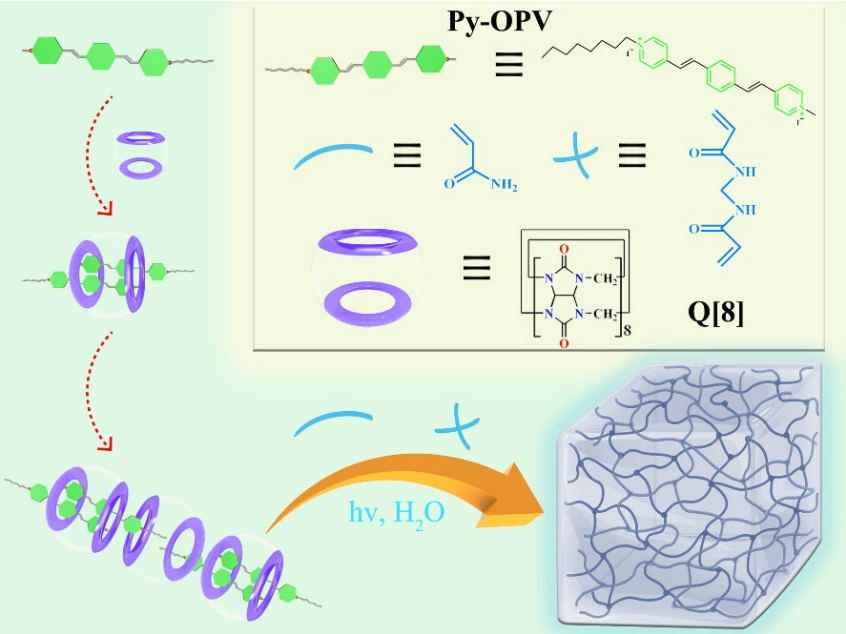

Figure 9. Diagram showing the composition of smart luminous material and the production of hydrogel.

Additionally, a supramolecular hydrogel was successfully created by Liu's group through the non-covalent binding of Q[8] to a tetraphenylene (TPE) derivative (TPE-4Q), as shown in Figure 10 [64]. They have also recently reported on hydrogels with phosphorescent emission [65]. Initially, Q[8] was used to wrap a double cationic bromophenyl pyridine derivative, resulting in weak phosphorescence emission. G/Q[8] was then copolymerized with acrylamide *in situ*, which exhibited enhanced phosphorescent emission. Finally, the copolymer was co-assembled with hyaluronic acid-modified hydroxypropyl-*β*-cyclodextrin (HA-HP-*β*-CD) to form a hydrogel.

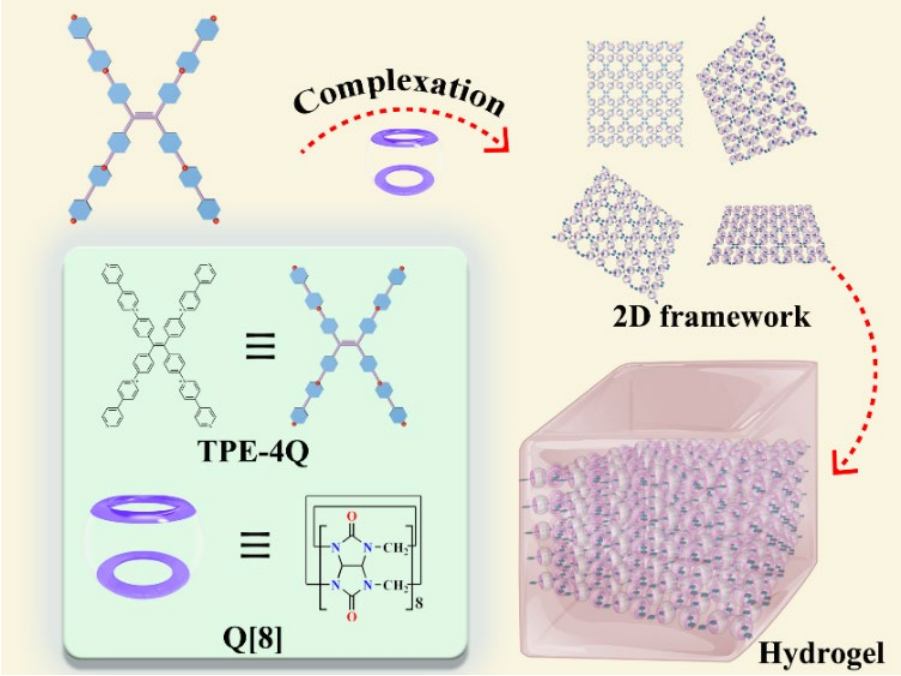

Figure 10. The hydrogel was constructed using the non-covalent binding of Q[8] to a tetraphenylene (TPE) derivative (TPE-4Q).

Figure 11 demonstrates the reversible photodimerization of the guest polymerization with the assistance of Q[8], leading to the transition of hydrogel crosslinking from a physical to a chemical network [66]. Materials with unique characteristics and the ability to be patterned are produced as a result of the photodimerization process, which displays partial reversibility. As a result, hydrogels with network dynamics that are externally controlled have been created.

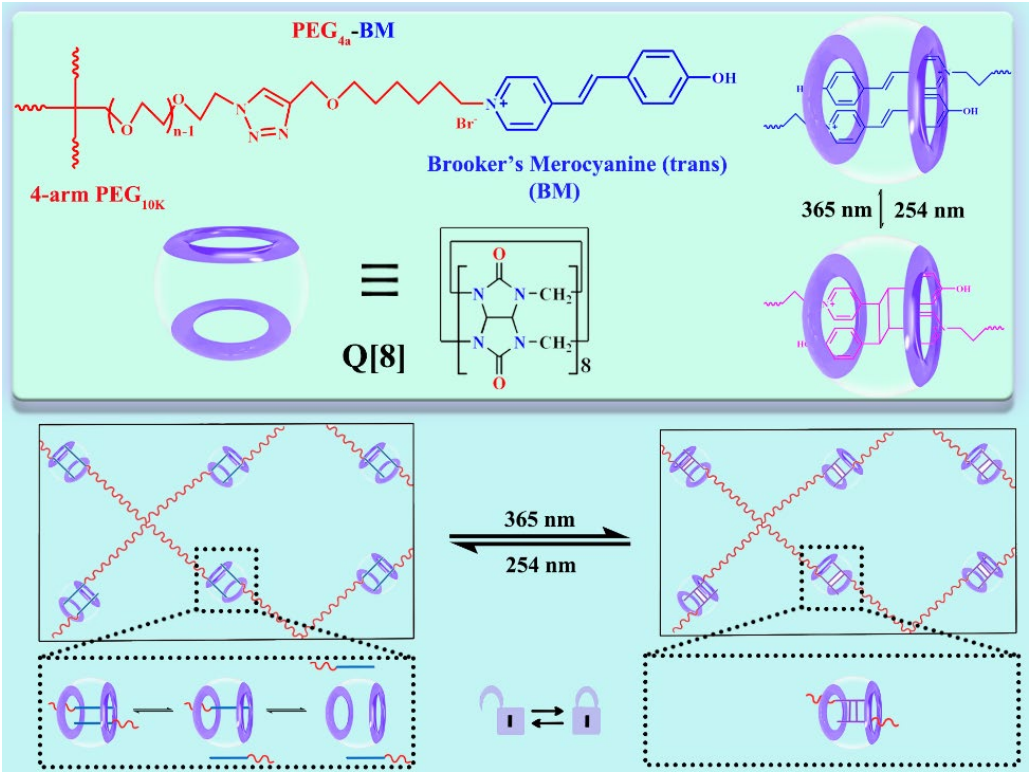

Figure 11. Light-controlled supramolecular hydrogels.

Scherman's group [67-69] has contributed significantly to the field of cucurbit[*n*]urils and hydrogels by synthesizing a range of supramolecular hydrogels based on Q[8] via polymerization in the presence of supramolecular complexes. Figure 12 depicts how different copolymeric monomers are used to create a variety of supramolecular hydrogels.

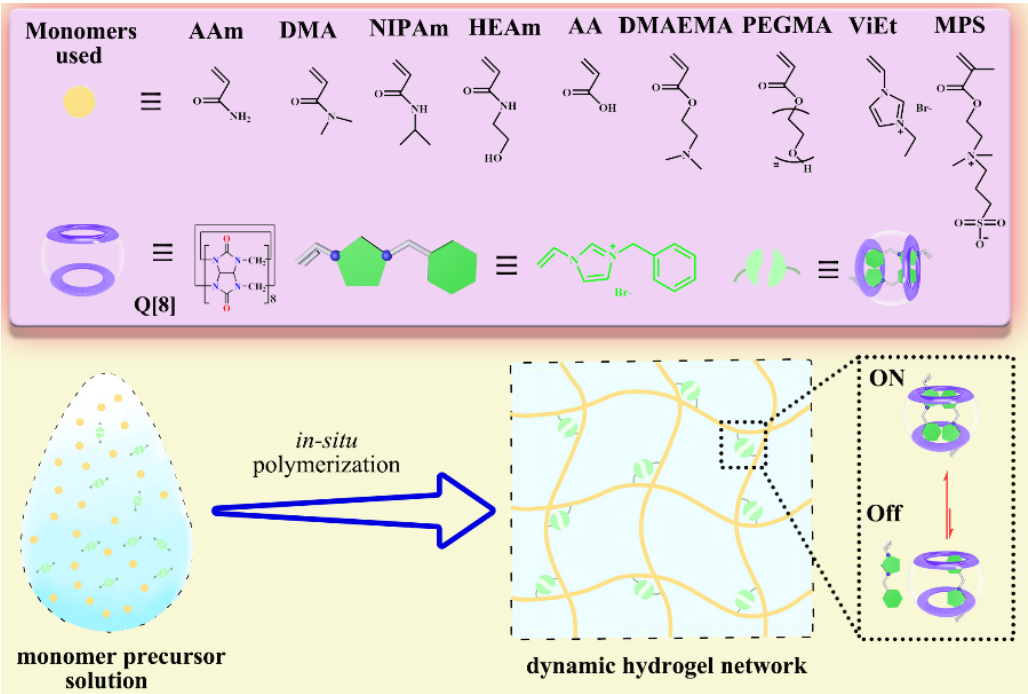

Figure 12. Supramolecular polymer networks are *in situ* polymerized in the presence of a hydrophilic co-monomer, the Q[8], and guest molecules.

Additionally, in Figure 13 Scherman *et al*. prepared guests with different derivatization to show that supramolecular hydrogel networks based on Q[8] can be used as dynamic binders for a variety of non-porous substrates [70].

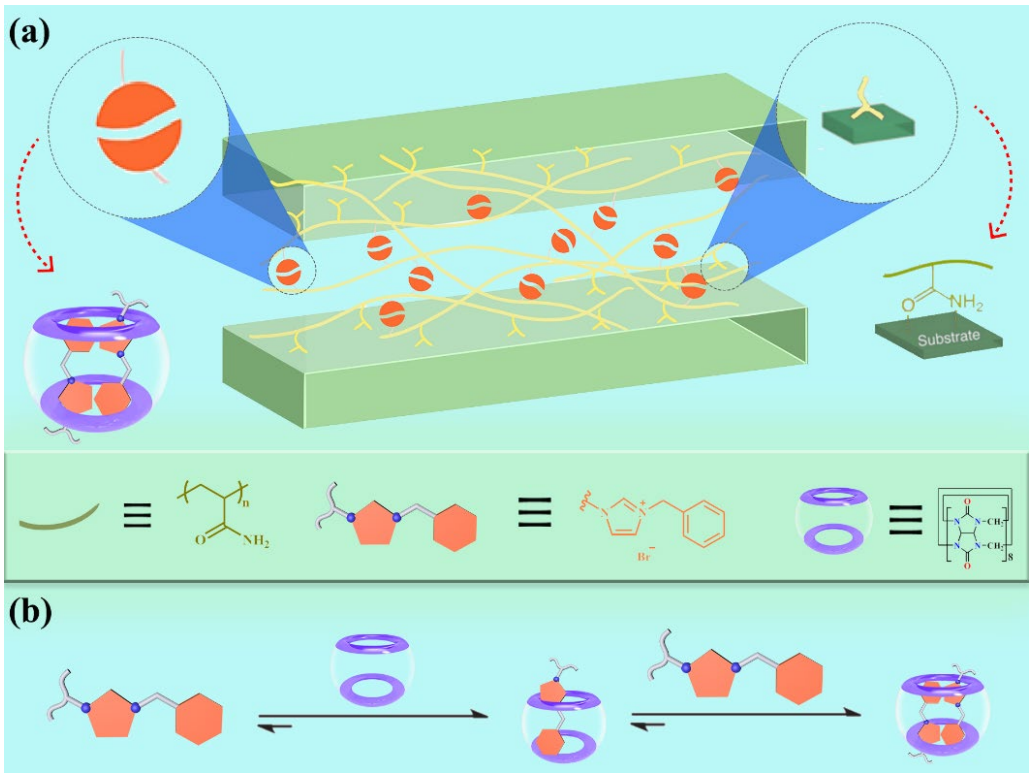

Figure 13. a) The dynamic cross-links of the Q[8] supramolecular ternary complexes are used to create a network structure that can serve as an adhesive between two substrates; b) The construction process of the ternary host-guest complex.

In this system Scherman *et al*. used coumarin-functionalized biopolymers and a host-guest chemical self-assembly of Q[8] to form hydrogels (Figure 14) [71]. Also, they have used similar assemblies in several other reports to construct supramolecular hydrogels and used them in different fields [72-73].

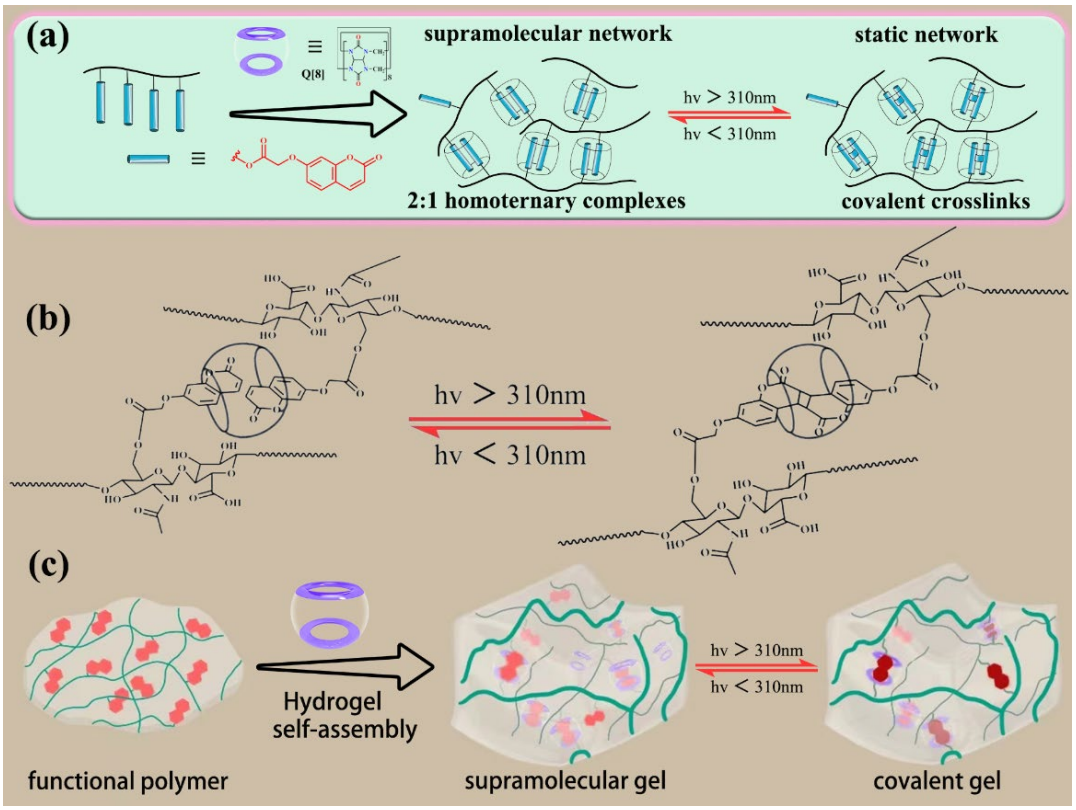

Figure 14. The concept involves using coumarin-functionalized biopolymers and self-assembly with Q[8]. (a) Photogel formation mechanism; (b) Schematic diagram of photogel formation.

Scherman *et al.* [74] demonstrated the continuous production of dual-network hydrogel microfibers with adjustable structural, chemical, and mechanical characteristics by introducing dynamic Q[8] into an agar-based fragile network. Additionally, they created supramolecular hydrogel microcapsules through the utilization of a single emulsion microdrop approach with Q[8] as the host molecule and anthracene-based functionalized hydroxyethylcellulose as the guest polymer in separate research [75]. Liu *et al.* utilized CS-P(AM-G), which is polyacrylamide-1-benzyl-3-vinyl imidazolium bromide functionalized chitosan microspheres, and co-polymerized polyacrylamide in the presence of a guest functional monomer. They achieved the formation of supramolecular hydrogels through the utilization of dynamic host-guest interactions [76] (Figure 15).

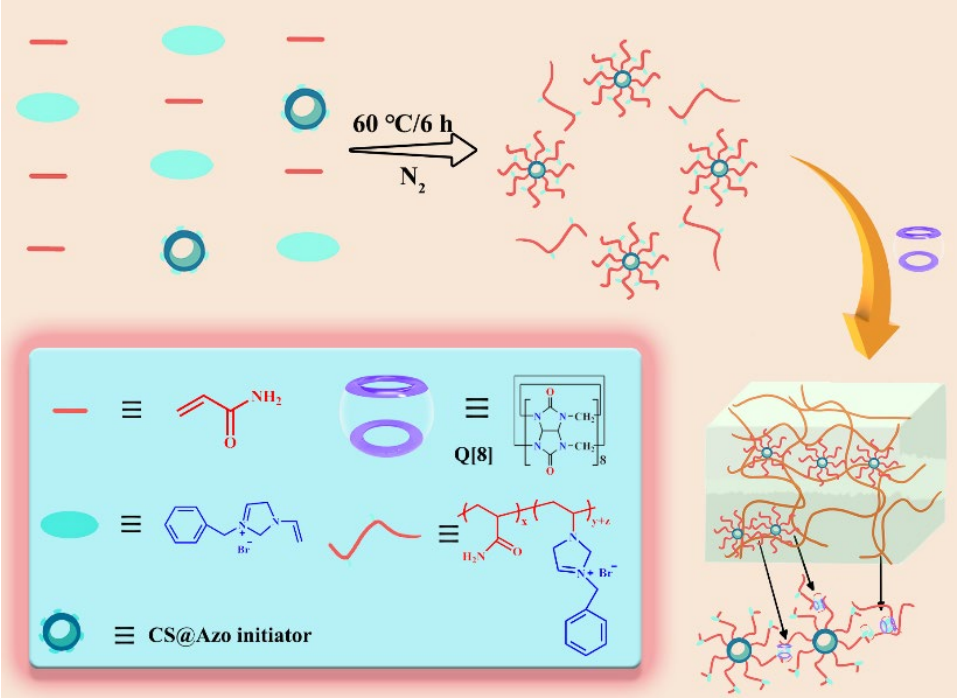

Figure 15. The supramolecular hydrogel consisting of chitosan and Q[8].

Similarly, cross-linked supramolecular hydrogels were generated through host-guest non-covalent interactions and the use of free radical copolymerization of acrylamide with the supramolecular hydrogels [77] (Figure 16). Supramolecular gels can also be formed by complexing Q[8] and *N*-(4-diethylaminobenzyl) chitosan as shown in Figure 17 [78].

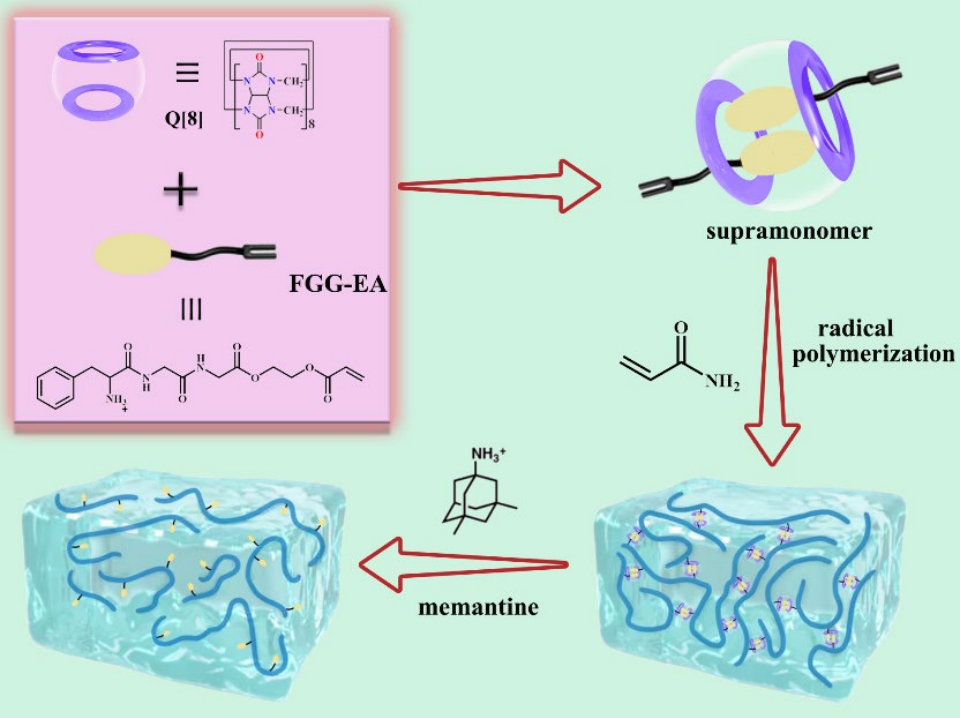

Figure 16. The supramolecular hydrogel consisting of FGG-EA and Q[8].

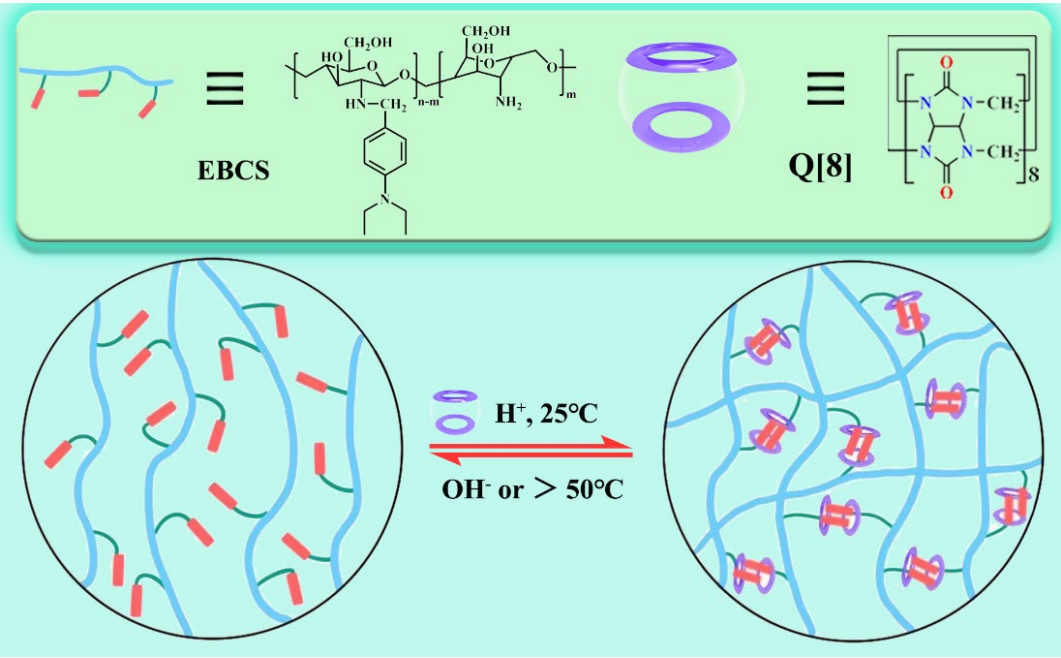

Figure 17. The formation of the Q[8]/EBCS hydrogel.

2.2.2 Ternary complexes constructed based on host-guest interactions

Next, we turn our attention to supramolecular hydrogels constructed from ternary and multi-domain guest complexes. Compared with the host-guest binary complexes, ternary complexes require larger cavities, and therefore the construction of this type of hydrogel is mainly based on the larger polymerization degree cucurbit[*n*]urils (*i.e.* Q[8] and above). Besides, some ternary complexes based on Q[6] and Q[7] are mainly used to change some properties of hydrogels by linking two macrocycle bodies or introducing a third substance.

Kim's group reported an approach for the long-term engineering of mesenchymal stem cell (eMSC) therapy through the *in situ* supramolecular assembly and modular modification of hydrogels. The hydrogels were based on cucurbit[6]uril-coupled hyaluronic acid (Q[6]-HA), diamino hexane-coupled HA (DAH-HA), and drug-coupled Q[6] (drug-Q[6]) [79] (Figure 18).

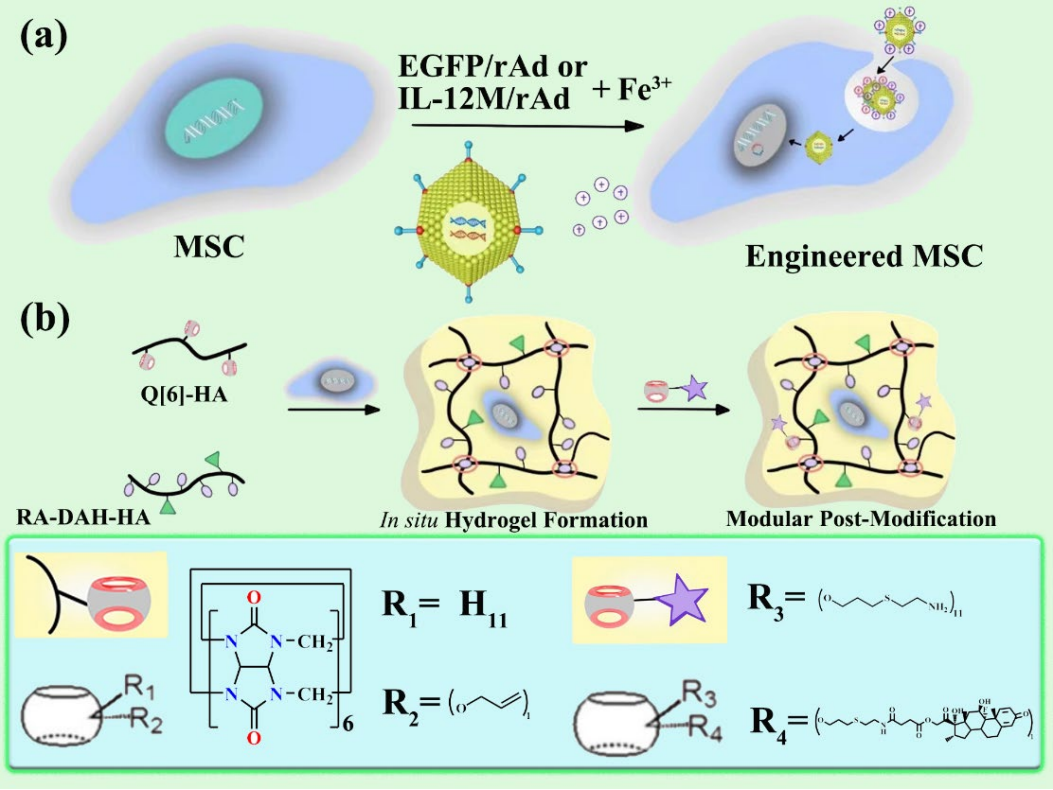

Figure 18. Supramolecular hyaluronic acid hydrogel for bioengineered mesenchymal stem cell processing. (a) In the absence of ferric (Fe^{3+}) ions, MSCs were mediated with recombination adenoviral (rAd) vectors expressing enhanced green fluorescent protein (EGFP) or interleukin-12

mutant (IL-12M) transgenes; (b) A hydrogel called Dexa-Q1[6]/RA-DAH-HA was created for the purpose of cancer treatment. The process involved combining a solution of Q1[6]-HA (2 wt%) and a solution of RA-DAH-HA (2 wt%) in the presence of modified MSCs (MSCs/IL-12M) engineered for this purpose. The Dexa-Q12[6] was also modified in a modular way as part of the process.

Custom-designed cationic copolymers with Q[7] were utilized to achieve enhanced mechanical properties and rapid on-demand dissolution of supramolecular hydrogels, as shown in Figure 19. Host-guest chemistry and electrostatic interactions were employed with clay nanosheets coated with anionic polymers to achieve this goal [80].

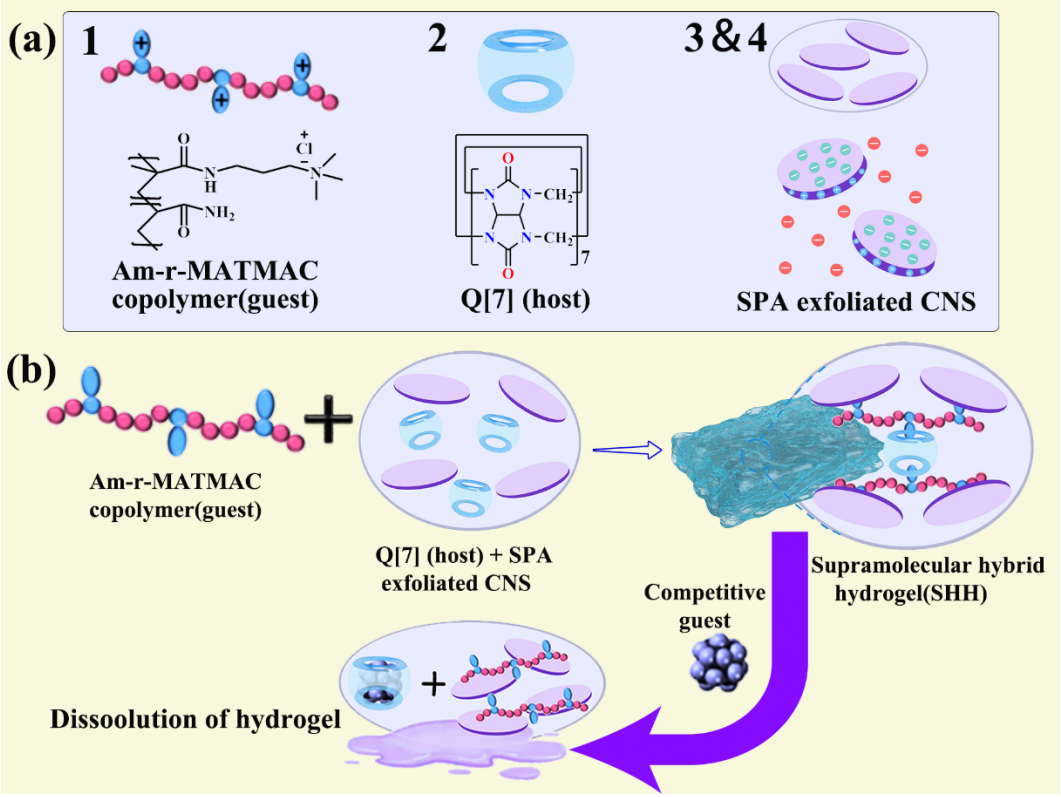

Figure 19. (a) The supramolecular hybrid hydrogel comprises several components, including: 1) Acrylamide-co-(methacryloylamino) propyl] trimethylammonium chloride copolymer (Am-r-MATMAC-CP); 2) Q[7]; 3-4) Sodium polyacrylate (SPA) and Clay nanosheets (CNS); (b) Hydrogel preparation and on-demand dissolution.

Tan *et al*. [81] also constructed an extremely interesting supramolecular hydrogel, as shown in Figure 20, where *N*-isopropyl acrylamide (NIPAM) was first polymerized with ammonium persulfate with *N*-adamantyl-*N*-(4-vinyl benzyl)-*N*-dimethylammonium chloride (AD4VBDMA), and then a Q[7] was introduced to wrap around the adamantyl group of AD4VBDMA to form a supramolecular hydrogel. In addition to this, similar hydrogels with Q[7] competitively inhibited by adamantane were reported [82].

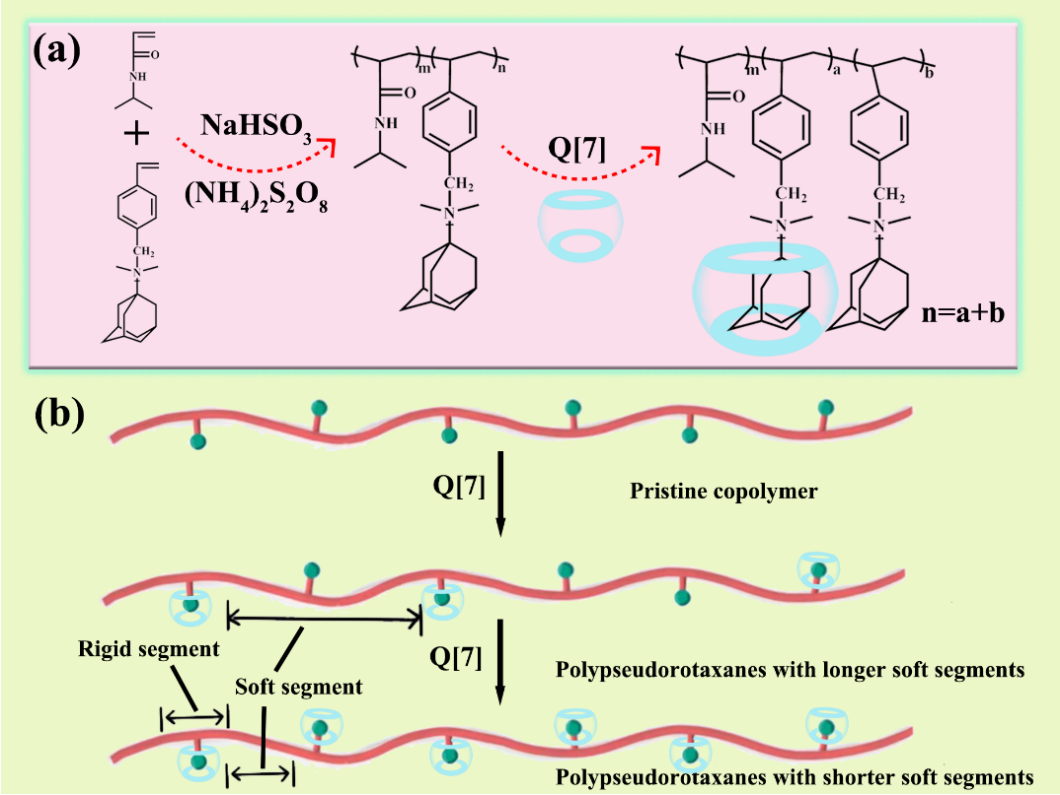

Figure 20. (a) The procedure for preparing NIPAA-based Q[7] poly-pseudorotaxanes involves specific steps, which may vary depending on the specific protocol used; (b) The length of the soft segment can be adjusted by changing the amount of Q[7] added to the system, thus achieving tunability.

Another study by the same group involved the preparation of Ax-HGy hydrogels, which exhibited tunable mechanical and adhesion properties. This was achieved by introducing Q[7], adenine and the guest in acrylamide [83]. A coordinated double cross-linked network is formed

through hydrogen bonding interactions and host-guest interactions. This network allowed for the creation of supramolecular hydrogels with excellent mechanical strength, adhesion strength, and self-healing properties.

In a similar approach, water-soluble polypyrrole was synthesized by incorporating chitosan and water-soluble polypyrrole into an acrylamide matrix containing Q[7]. This was achieved using the one-pot method illustrated in Figure 21. The resulting material was a conformal CxPy conductive hydrogel [84].

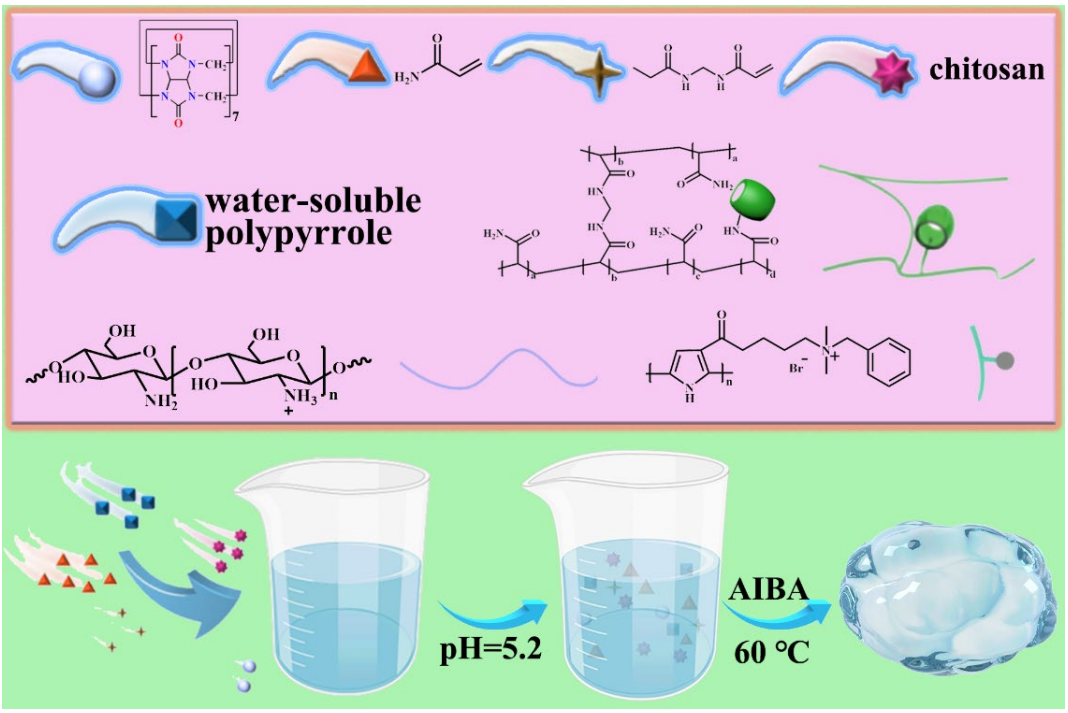

Figure 21. Diagram showing interactions between copolymer and water-soluble polypyrrole during the creation of CxPy hydrogel.

When used in conventional formulations, the peptide-based medication human calcitonin (hCT) has a poor level of therapeutic effectiveness, is unstable, and has a brief half-life. Li *et al.* [85] discovered that by complexing hCT with Q[7] in PLGA-PEG-PLGA, the thermal energy generated during biodegradation can be utilized for the long-term delivery of calcitonin.

In addition, α-cyclodextrin (α-CD) and Q[7] were used as a basis to enable the simple and convenient preparation of light-driven pseudo[4] rotaxane **1** [86]. As shown in Figure 22, a photoisomeric cyanostyrene conjugated cationic surfactant demonstrated AIE behavior when complexed with clay (laponite) and exhibited good thixotropy due to the presence of laponite. [87].

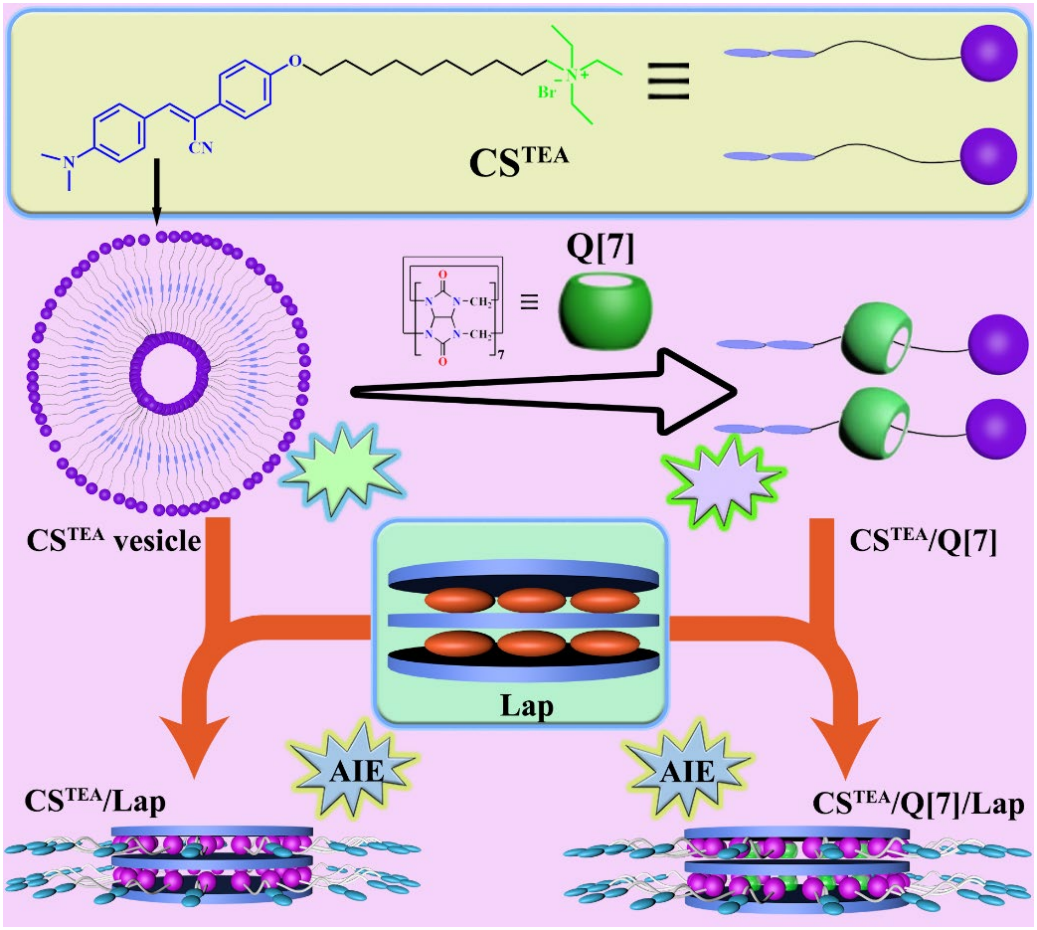

Figure 22. Chemical Composition and Self-Assembly of CS^{TEA} are shown schematically.

The above Q[*n*]s have polymerization degrees less than eight. In the following section, we will discuss supramolecular hydrogels constructed through ternary and multiple host-guest complexes utilizing Q[8]. Let us first discuss the research of Scherman's group. The researchers developed a method to enhance the rheological strain stiffness of Q[8]-based hydrogels by incorporating inorganic nanowires (NWs) into the supramolecular network [88]. In Figure 23, the supramolecular hydrogels consisted of PVA-MV, HEC-Np, and Q[8].

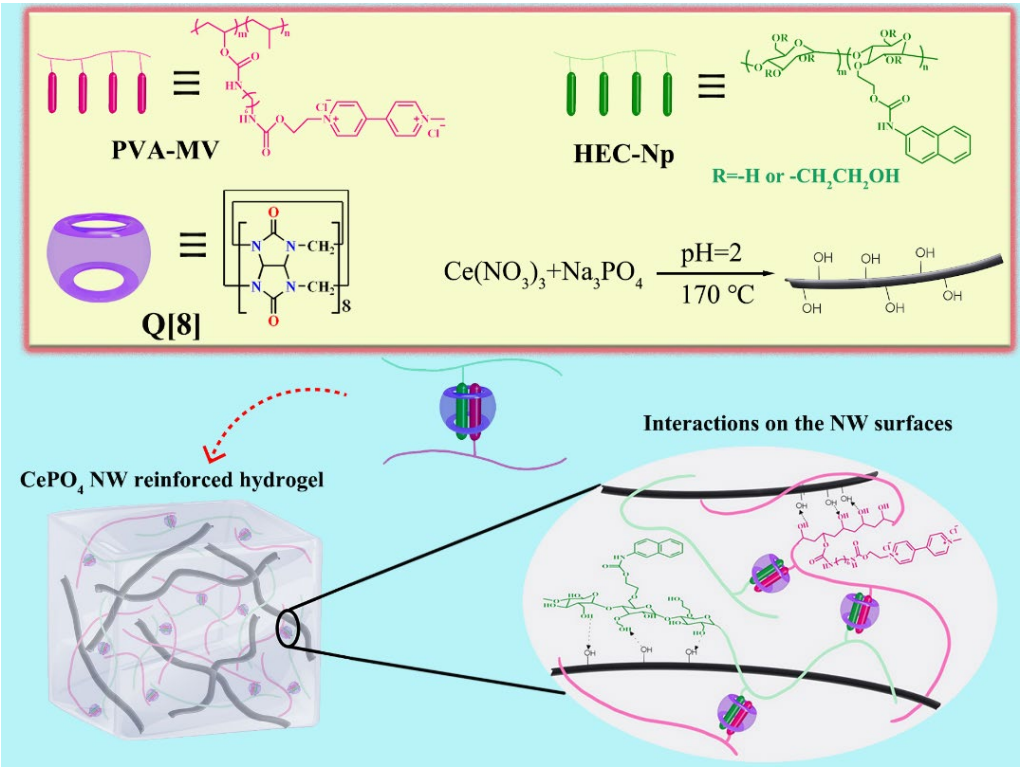

Figure 23. Inorganic nanowires (NWs) were added to the hydrogel based on Q[8] host-guest interactions to enhance its mechanical characteristics.

In another study [89], they combined Q[8] highly branched polywhene (HBP-Q[8]) with HEC-Np. A supramolecular hydrogel was formed through interfacial dynamic complexation between HBP-Q[8], which is positively charged, and HEC-Np in the presence of a negatively charged surfactant. The uniform-sized hydrogel microcapsules were specifically designed to effectively encapsulate the desired cargo in a precisely controlled manner. In addition, this mode of construction has been used in other work [90]. Hydroxyethylcellulose was also used in another study [91] to prepare supramolecular hydrogels using phenylalanine functionalized polysaccharides physically cross-linked with Q[8] in water. Functionalization of polysaccharides was performed in a two-step process to form a 1:2 "homo-ternary" complex with pendant Phe residues through a host-guest interaction with Q[8]. This complexation induced dipeptide Phe-Cys

physical cross-linking, leading to the formation of supramolecular hydrogels (Figure 24). The resulting hydrogels were uniform in size and allowed for targeted encapsulation of cargo.

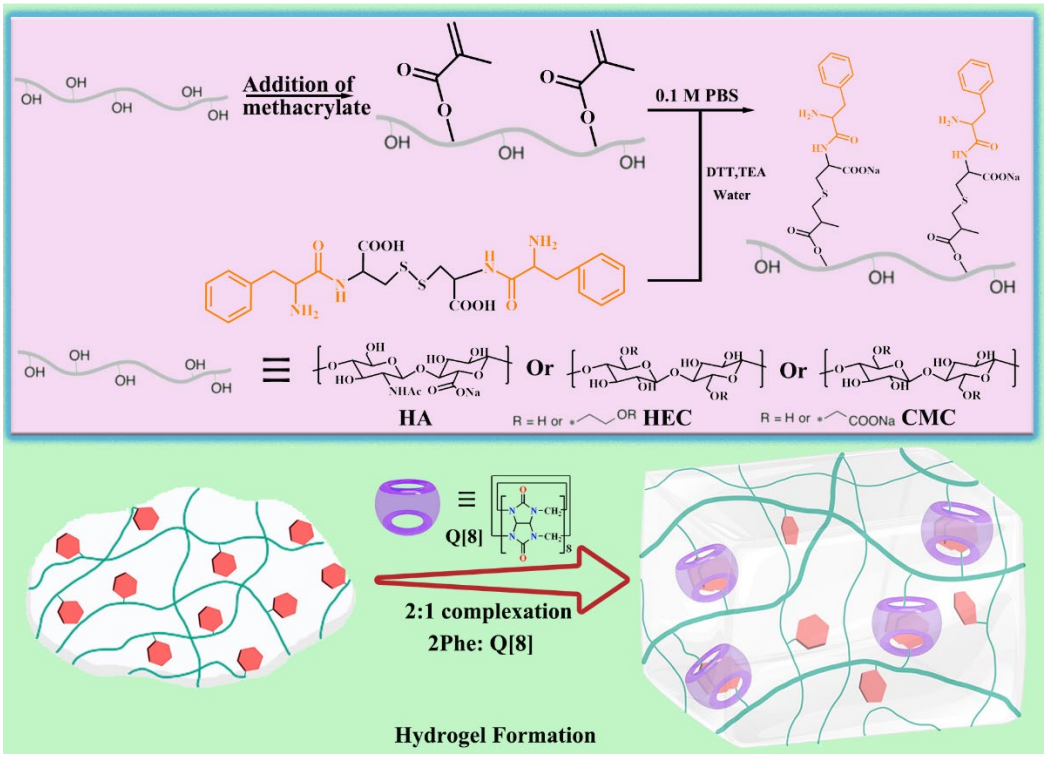

Figure 24. Polysaccharides containing methacrylate groups were created. This process resulted in the production of polysaccharides that feature pendant CF Q[8] binding units. Additionally, a diagram was synthesized to illustrate how hydrogel formation occurs upon Q[8] addition. The pendant CF units, which are denoted by shaded hexagons, contain phenylalanine residues that bind to Q[8] in a 2:1 fashion.

A supramolecular polymer-colloidal hydrogel (SPCH), comprised of 98% water, was developed based on biological systems. This material can be effortlessly stretched into uniform "supramolecular fibers" at room temperature, with a thickness of approximately 6 μm [93]. SPCH was created by self-assembling functionalized polymer-grafted silica nanoparticles and Q[8] in water at various length scales, as shown in Figure 25. This process was facilitated through supramolecular interactions at the molecular level and the formation of nanofibers at the colloidal length scale.

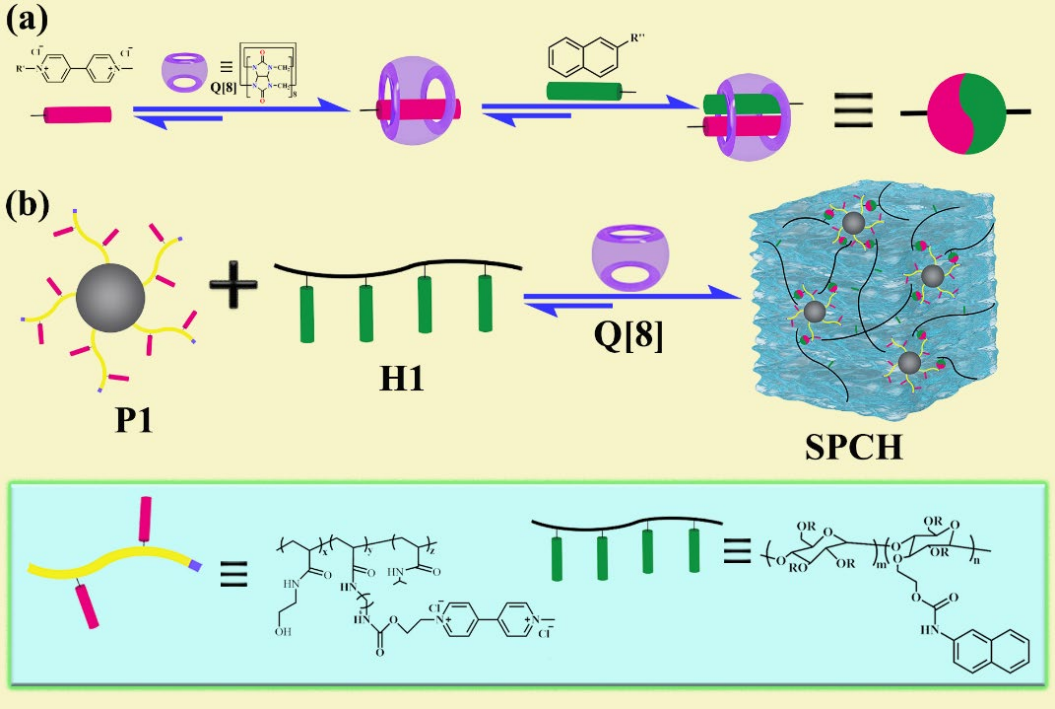

Figure 25. Self-assembly of supramolecular polymer-colloidal hydrogel. (a) The binding of Q[8] in water occurs in a two-step, three-component process, as illustrated in the schematic diagram; (b) The formation of a hierarchical SPCH is depicted in the schematic diagram.

The production of composites with uniformly distributed graphene (GR) at scale continues to be a significant challenge. While it is possible to manufacture GR-polymer nanocomposites on a large scale, there are limitations in the process that lead to poor control over the homogeneity of hydrophobic GR flakes in the matrix. These limitations often result in difficulties in controlling stability and preventing aggregation, which negate the potential benefits of the nano-size of GR. Based on this, Scherman and coworkers reported [94] the exfoliation and stable dispersion of GR in water. By utilizing Q[8]-mediated host-guest chemistry, supramolecular hydrogels were created that contain uniformly distributed graphene (GR) and guest-functionalized macromolecules. The same type of construction approach was also used in other work reported by the same group [95-103]. In addition to their previous work, the researchers reported an example of a fully self-assembled supramolecular two-component network hydrogel [104]. This was achieved by combining two different hydrogel systems: one based on DNA hybridization and the other based

on the host-guest interaction of Q[8] [67,105]. The combination of these two hydrogel formulations results in a new material that consists of two interpenetrating networks that are not cross-linked. In contrast to the two-step polymerization process required to form chemically cross-linked bipartite network hydrogels, this supramolecular system can be prepared using a straightforward "one-pot" mixing method. This is possible due to the highly precise and specific recognition of the motifs involved. A three-stranded guest molecule similar to DNA has also been reported [106].

In addition, many related reports have been made by Tan's group. As shown in Figure 26, they designed an *N*-isopropyl acrylamide (NIPAM)-based thermosensitive copolymer with a naphthalene group on the side chain. The interaction between Q[8] and methyl viologen (MV^{2+}) is enhanced by Q[8]-mediated intermolecular charge transfer (CT) interactions, resulting in positively charged side-chain ternary complexes. The introduction of the ternary complex Q[8]/MV^{2+}/Np onto the side chains of the macromolecular chains causes a change in their microstructure, resulting in a strong tendency towards thermal gelation [107].

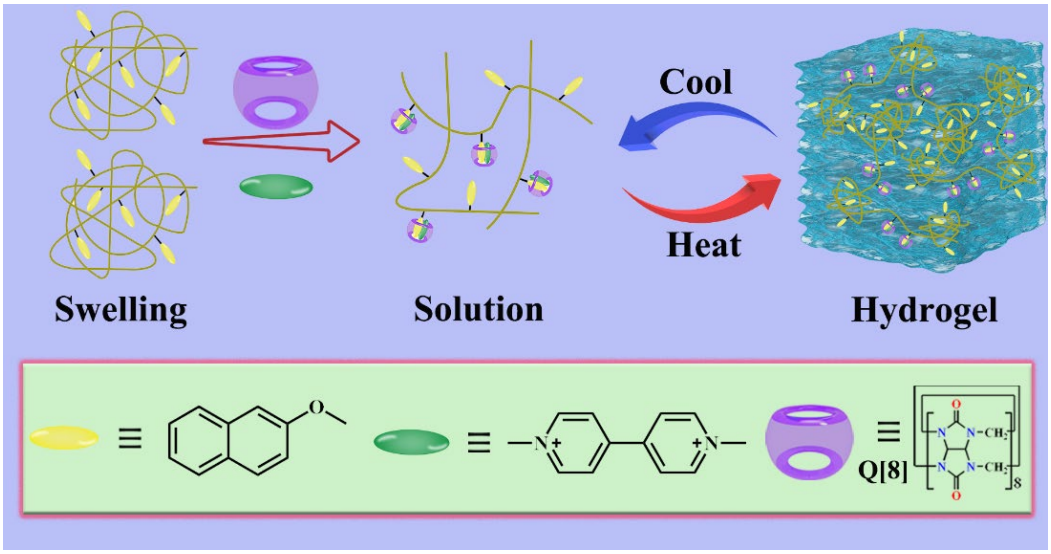

Figure 26. A depiction of the gelation process along with an elucidation of the mechanism for creating thermo-gelling supramolecular hydrogels.

In addition to the work mentioned above, several supramolecular hydrogels based on Q[8] have been prepared by other groups. In one report [108], the ability of an asymmetric azobenzene to form ternary complexes with Q[8] was explored. Initially, copolymers with varying ratios of NIPAM and DMAEA were synthesized. Subsequently, the DMAEA component was post-synthetically modified with asymmetric azobenzene. Upon integration of macrocyclic structures, these polymers undergo gelation to form supramolecular hydrogels. In their study, Liu *et al*. [109] utilized the reverse thermally induced phase separation method to produce self-healing polyethersulfone ultrafiltration membranes (as depicted in Figure 27) using Q[8] as the host and two guest molecules. These membranes exhibited superior self-healing abilities, improved mechanical properties, and increased permeate flux. The efficacy of the membrane was dependent on the concentration of Q[8], and the incorporation of Q[8] hydrogel enhanced the surface hydrophilicity of the resulting membranes.

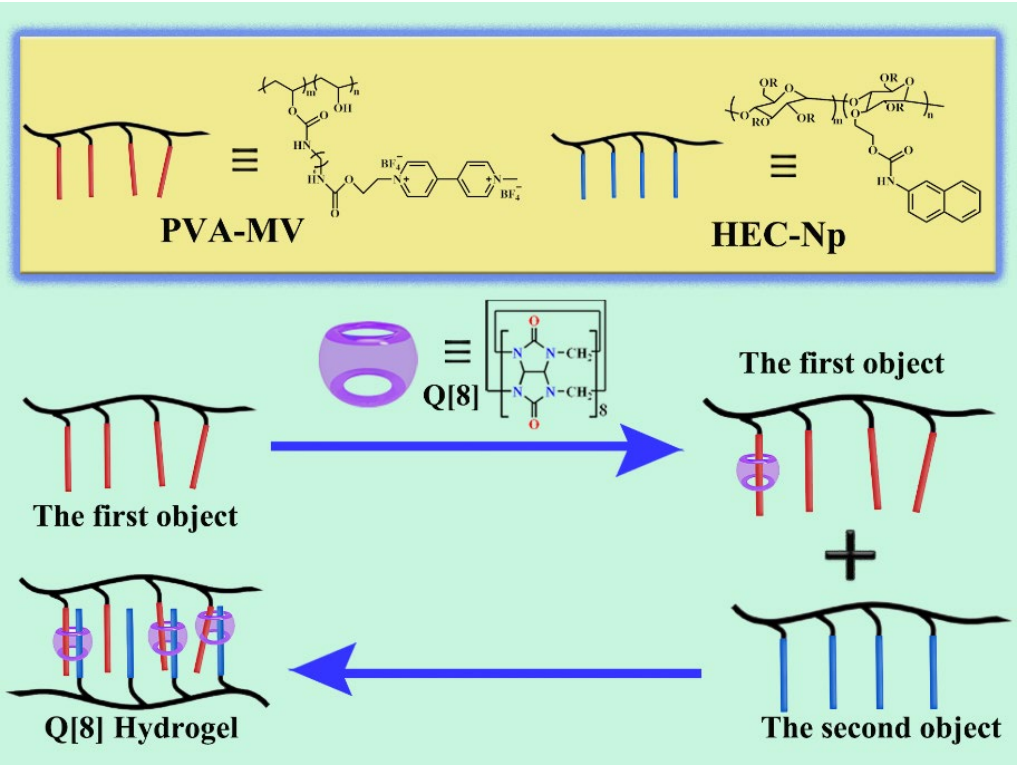

Figure 27. The Q[8] hydrogel is formed through host-guest chemistry, where the Q[8] molecule acts as the host molecule and the guest molecules are functionalized macromolecules.

Methyl viologen and pyrene were grafted onto poly(ethylene glycol) chains containing 4-arm-PEG-BPY^{2+} and 4-arm-PEG-Pyr, respectively. Q[8] was used to create supramolecular host-guest complexes by combining it with the two entities, and they were used to construct hydrogels with desirable homogeneous three-dimensional network structures [110]. In their study, Cornelissen *et al.* [111] produced supramolecular hydrogels through non-covalent cross-linking of cowpea chlorotic mottle virus (CCMV) particles modified with guests and complementary hydroxypropyl cellulose also modified with guests. This was achieved by forming a ternary host-guest complex with Q[8] (see Figure 28).

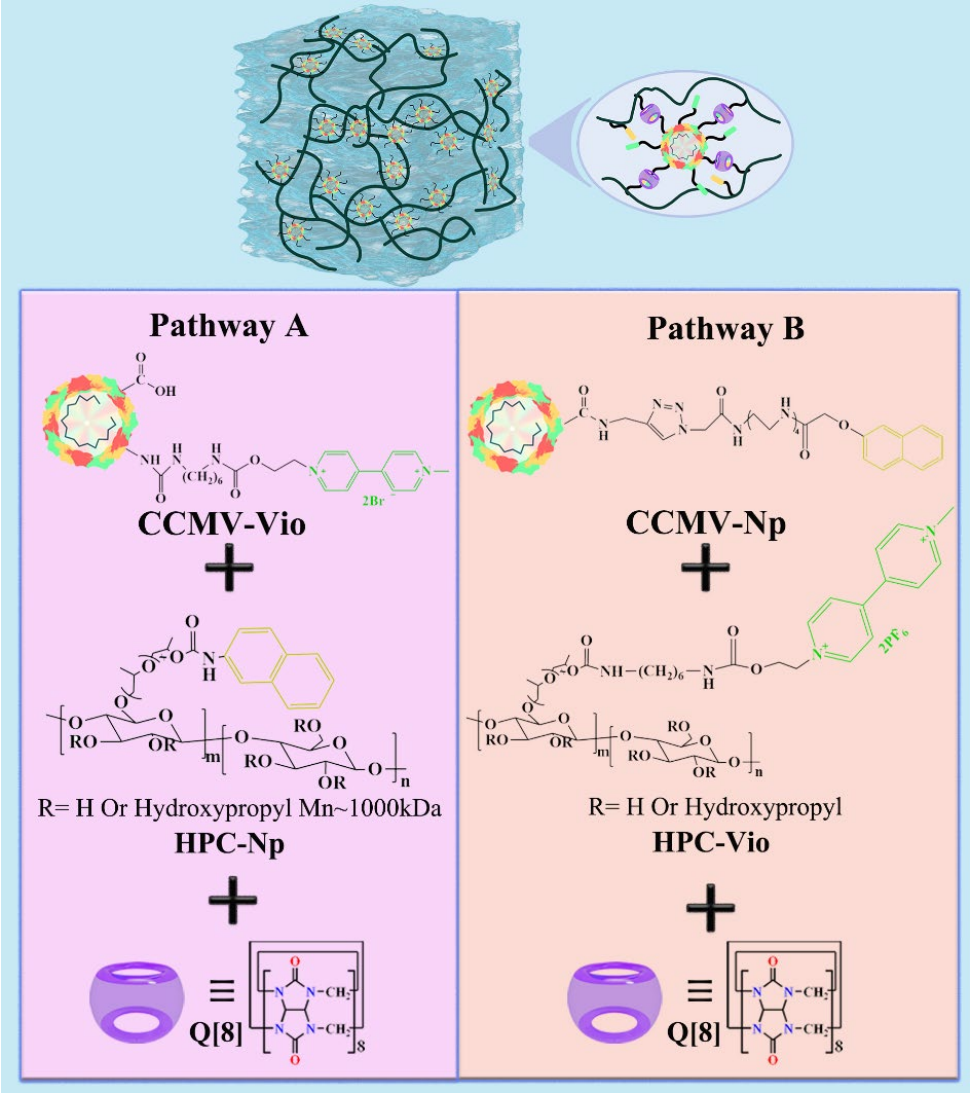

Figure 28. There are two methods available for the production of compartmentalized supramolecular hydrogels using virus nanoparticles. One technique involves the use of the

polymeric material HPC, which is cross-linked with CCMV nanoparticles through host-guest interaction. The other method has not been described in this review.

In their study, Azevedo *et al.* [112] suggested a method for hydrogenating peptide amphiphilic molecules (PA) that involves the formation of host-guest homogeneous ternary complexes with Q[8] and PA nanofibers that contain aromatic amino acids. Compared to their ionic-based counterparts, the host-guest mediated PA hydrogels showed a hierarchical morphology and increased stiffness, which is attributed to the host-guest cross-linking between the PA nanofibers. In a related study [113], researchers introduced a supramolecular function to a bacterial surface through genetic modification of a transmembrane protein that contains a Q[8] binding motif, which is part of a cysteine stabilizing small protein. The work demonstrated that this supramolecular motif on the bacterial surface has a specific binding affinity for Q[8], forming multiple intercellular ternary complexes. As a result, bacterial solutions aggregate, leading to the formation of hydrogels.

In Figure 29, supramolecular hydrogels were prepared using Q[8]-based crosslinking, which was formed by the thiol-ene reaction between the pre-assembled Q[8]-FGGC peptide ternary complex and the grafted norbornene [114].

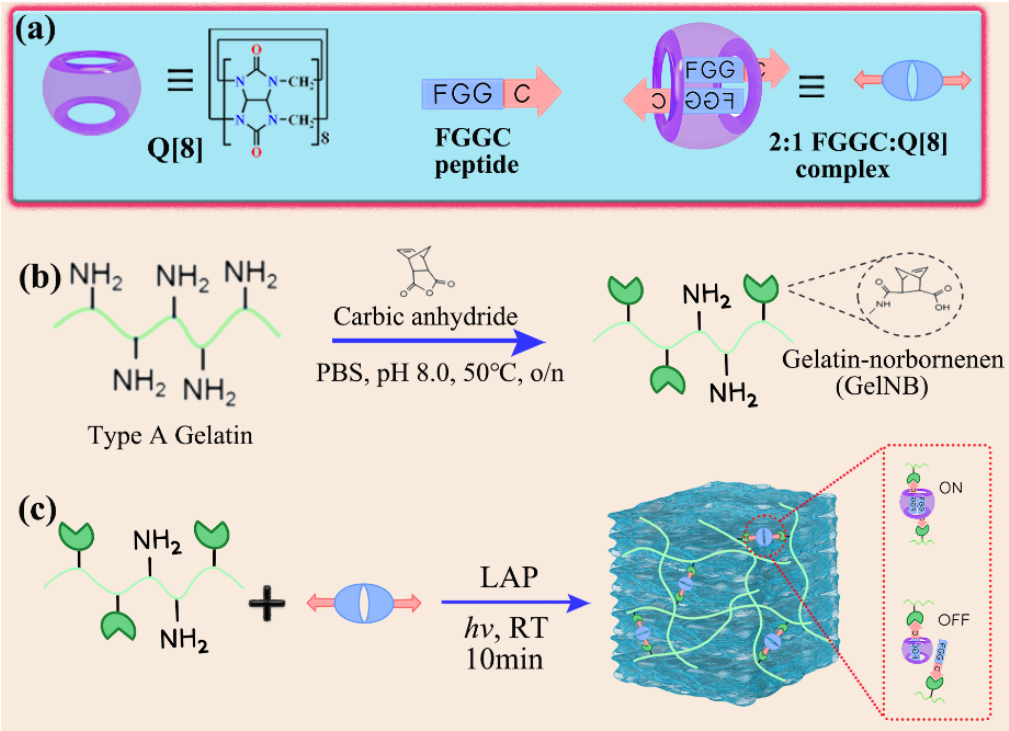

Figure 29. Schematic diagram of the supramolecular hydrogel constructed based on Q [8] (a) Schematic representation of Q[8] forming a 1:2 supramolecular complex with FGGC peptide;(b) Schematic diagram of the reaction to prepare gelatin-norbornene (GelNB); (c) Supramolecular hydrogel formed by cross-linking two substances prepared by (a) and (b).

Figure 30 illustrates the formation of a P(AM-vTPE-G) copolymer, which involves copolymerization of acrylamide (AM), 4-(1,2,2-triphenylvinyl) phenyl acrylate (vTPE), and guest units 1-benzyl-3-vinylimidazolium (G) in the presence of an initiator [115]. Subsequently, supramolecular hydrogels were formed in the presence of Q[8]. During the cross-linking process, the polymerized tetraphenylene (TPE) groups in the polymer chains are clustered together, resulting in high fluorescence enhancement. Furthermore, the luminescence properties of the prepared aqueous light-trapping system were examined using the donor (supramolecular hydrogel) and acceptor (eosin Y disodium salt) systems.

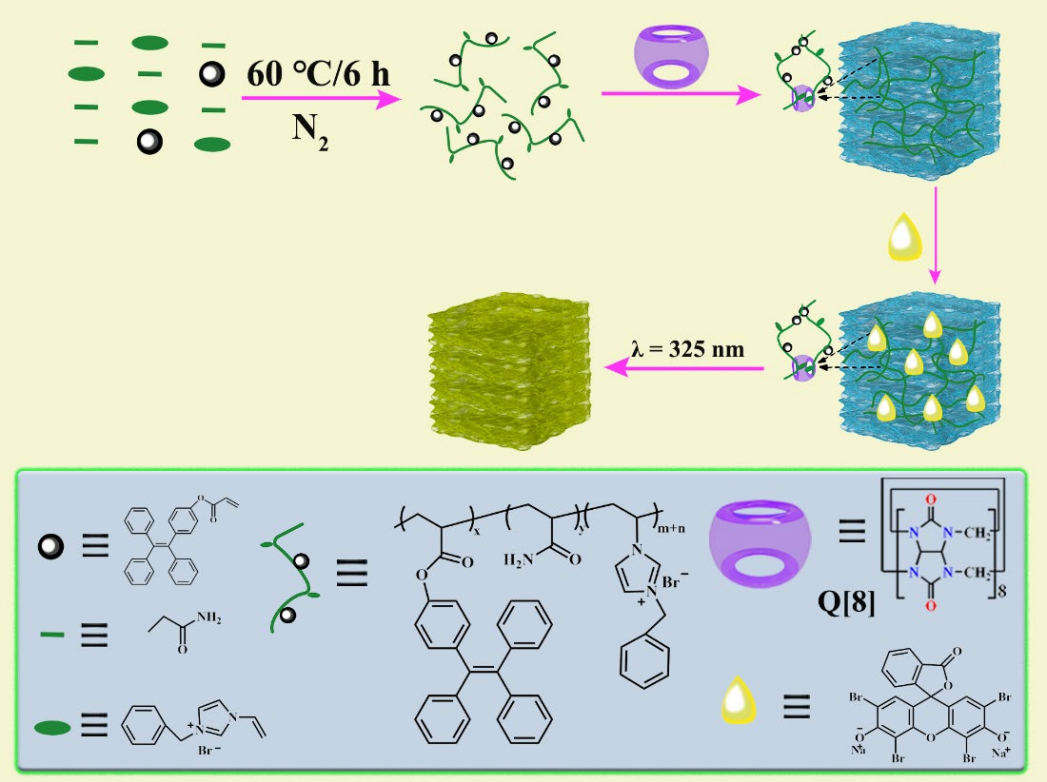

Figure 30. Schematic diagram of supramolecular hydrogel constructed based on tetraphenylene.

A new type of supramolecular hydrogel has been created that can be converted reversibly into its corresponding covalently cross-linked hydrogel under UV lamp [116]. As shown in Figure 31, the development of this supramolecular hydrogel was based on a ternary host-guest interaction involving two anthracene moieties and a host (Q[8] or γ-CD). The anthracene-functionalized poly(*N*-acryloyl morpholine) was synthesized by polymerizing a copolymer composed of modified *N*-acryloyl morpholine and activated ester copolymer monomers. This led to the creation of two distinct polymers: one with neutral anthracene side chains and the other with positively charged anthracene side chains to increase interaction with the host. The binding affinity of the anthracene side chain to the two macrocyclic hosts, Q[8] and γ-CD, was examined using UV-visible spectroscopic titration.

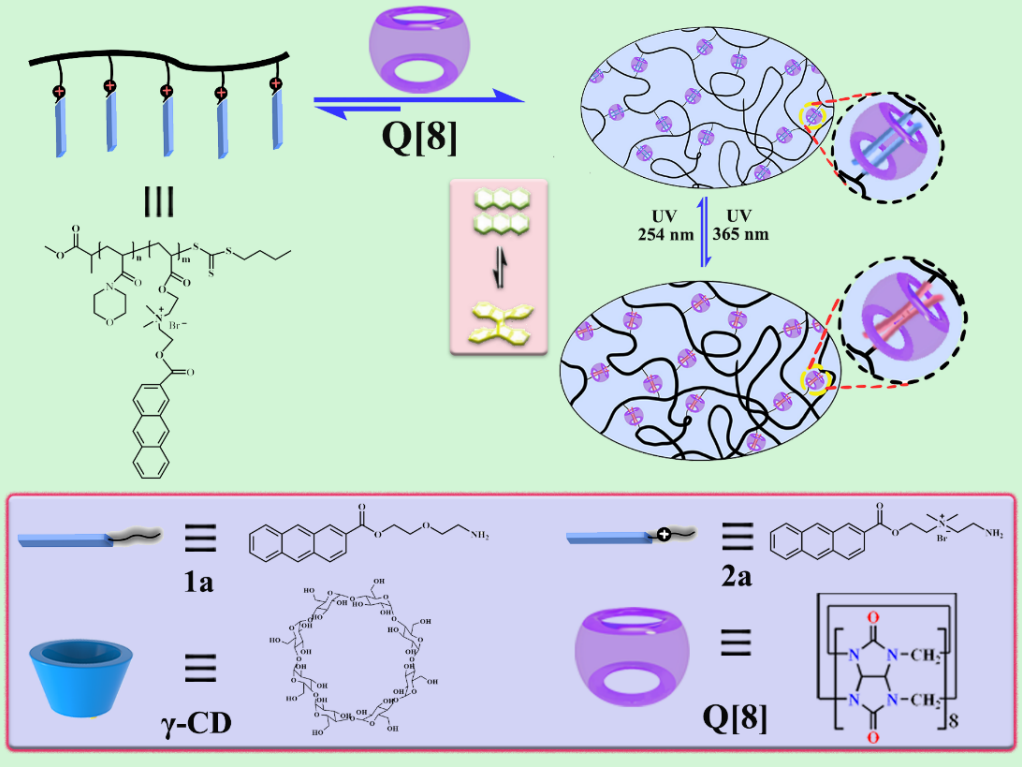

Figure 31. (Top) Schematic diagram of supramolecular hydrogel construction; (bottom) chemical structures of compounds.

In addition to the aforementioned Q[*n*]s, hydrogels have also been prepared using *nor-seco*-cucurbit[10]uril (NS-Q[10]), which possesses double cavities. Kim's group developed a supramolecular hydrogel by mixing NS-Q[10] as a cross-linking agent with a solution of four-armed polyethylene glycol (AdA-4arm-PEG) containing adamantine end groups, as depicted in Figure 32 [117].

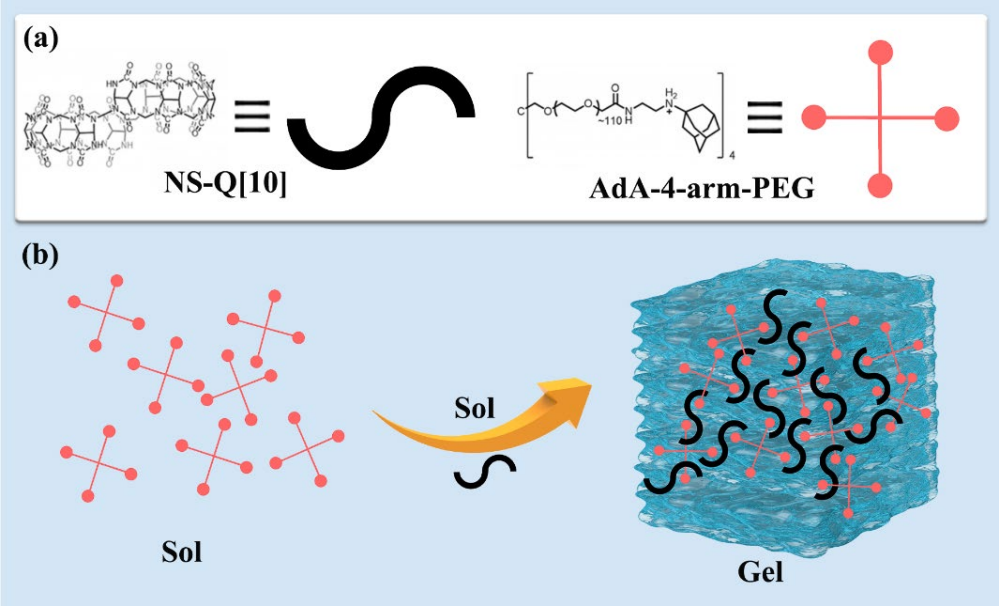

Figure 32. (a) Chemical structures of compounds; (b) Schematic diagram of supramolecular hydrogel formation.

3. Performance Studies

3.1 Self-healing performance

Self-healing capability is a unique property of hydrogels, and therefore, we first investigate the self-healing performance exhibited by different hydrogels. Liu and colleagues [109] reported the preparation of an octa-cyclic water-soluble polyether sulfone ultrafiltration membrane with self-healing properties using the reversible addition-fragmentation chain transfer (RAFT) polymerization and host-guest chemistry method. Figure 46 illustrates the self-healing process of a membrane, which can be influenced by several variables. The swelling ratio is the most critical factor, but there are three additional parameters that impact the efficacy of the healing process. The molecular dispersion of hydrogel chains enhances the self-healing efficiency, while the hydrogen bonds present in the hydrogel species enable them to possess self-healing properties. Additionally, hydrogen bonding between the two hosts facilitates the self-healing process. Research indicates that although hydrogen bonding is crucial in the self-healing process of

hydrogels, the length and flexibility of the hydrogel chains also plays a significant role in achieving optimal self-healing performance.

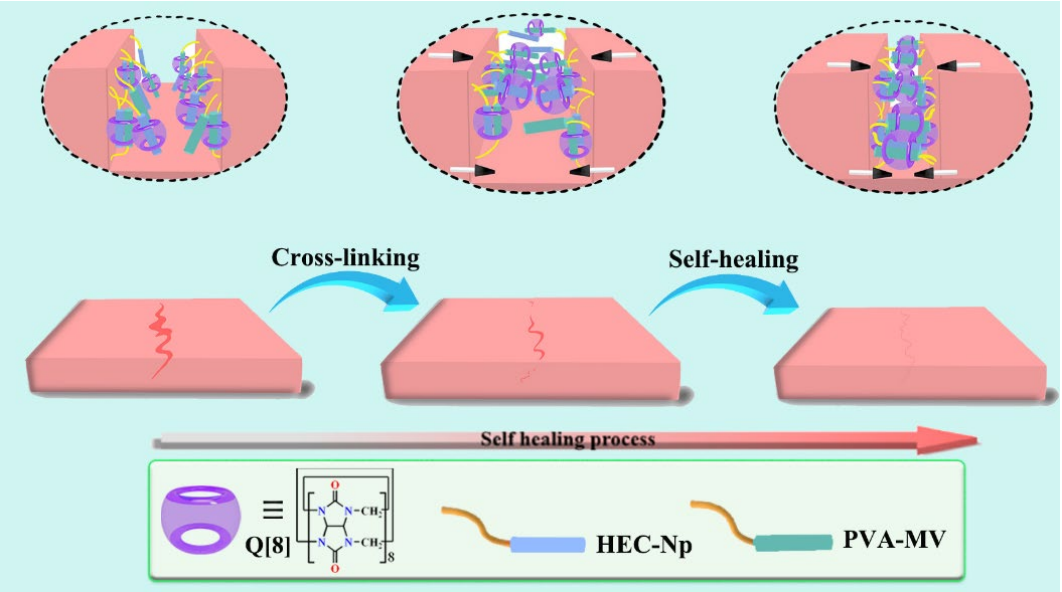

Figure 33. Self healing process of hydrogel.

According to Tan *et al.*, the exceptional self-healing properties of hydrogels can also be attributed to the presence of hydrogen bonding [83]. In contrast, Lv *et al.* [44] demonstrated that the self-healing properties of supramolecular hydrogels were achieved through the robust π-π stacking interaction between two guests included in the Q[8] and the strong π-π stacking interaction between the two guests. The supramolecular hydrogels developed by Zhang and coworkers [42] also exhibited effective self-healing properties. The self-healing properties of hydrogels derived from Q[8] and allyl-modified 4-(4-bromophenyl)pyridine-1-ammonium bromide (ABP) fluorophore via host-guest interactions were suggested by Ji *et al.* [60] to originate from the hydrogen bonding between PVA and polyacrylamide chains and the host-guest interactions between Q[8] and ABP. The supramolecular hydrogel obtained from this method demonstrated fast self-healing ability. In the study conducted by Huang *et al.* [39], the gel was sliced into two pieces, and one piece was stained with rhodamine 6G. After 1 day of incubation, the gel was capable of self-healing and could be stretched along the cut line without rupturing.

During the self-healing process of the gel, the rhodamine 6G dye diffused, resulting in the visualization of the self-healing trajectory as the other part also displayed the color.

The self-healing properties of hydrogels constructed by combining Q[8] highly branched polywhene (HBP-Q[8]) and naphthalene-functionalized hydroxyethylcellulose (HEC-Np) were further investigated by Scherman's group [70,90,100,106]. The hydrogel networks capacity for self-healing was assessed using rheological step strain measurements (20°C), which made it possible to see the networks complete recovery in only a few seconds. Indeed, the full recovery of the viscoelasticity of the network was detected within seconds. Moreover, several cycles showed evidence of rapid self-healing, which was brought on by quick Q[8] host-guest correlation kinetics.

Furthermore, a hydrogel system was developed that synergistically combines three critical but seemingly contradictory criteria by combining a reinforced "hard" nanocrystalline cellulose structural domain with a "soft" supramolecular cross-linked polymer structural domain [95], and utilizing a highly dynamic and selective Q[8]-based ternary complexation that enables rapid exchange interactions. These criteria include fast hydrogel recovery from the processable sol-gel state (in seconds), high storage modulus, and self-healing inhibition passivation facilitated by the specificity of the three-component recognition. The specific three-component recognition allows for rapid self-healing, even when the broken material is exposed to the environment for several months.

3.2 Dynamic properties

3.2.1 Mechanical properties

Different hydrogels also exhibit different mechanical properties, and prepared supramolecular hydrogels can have a mechanical strength of up to 50 kPa [80]. Scherman *et al.* [93] reported a SPCH, and notably the damping capacity of the SPCH exceeds that of biofilaments and fiber-based viscose rayon, highlighting its exceptional mechanical properties. Moreover, in other work [95], they also successfully produced supramolecular nanocomposite hydrogels that fulfill three essential criteria: high storage modulus, fast sol-gel transition, and rapid self-healing. This is driven by equilibrium colloidal enhancement and selectivity and driven by the kinetics of the Q[8] supramolecular interactions. They also synthesized a hydrogel microfibre that has toughness,

stretchability, and fracture stress that are 2-3 orders of magnitude greater, all while preserving mechanical strength and achieving recoverable hysteretic energy dissipation [74]. Not only that, a supramolecular hydrogel reported by Scherman *et al*. [70] that can be used as a dynamic binder for a wide range of porous substrates and nonporous substrates. These Q[8] hydrogel networks may be cured close to the softening temperature without any surface pore functionalization or the addition of curing chemicals to provide a ductile and reparable adhesive interlayer. The supramolecular hydrogels described by Ji *et al.* [60] have the ability to cross-link polyacrylamide chains, increasing the mechanical strength of the resulting supramolecular hydrogels. Supramolecular hydrogels that glow at room temperature and have good tensile and toughness properties were created. Similarly, Wang *et al.* [110] investigated the mechanics of hydrogels. The outcomes demonstrated the excellent mechanical strength of the produced hydrogels. In addition, according to Liu *et al.* [76], adding structural microsphere composites to hydrogels can increase their mechanical strength.

3.2.2 Rheological properties

As previously indicated, a supramolecular hydrogel network made of highly branching Q[8]-threaded polywhene and hydroxyethylcellulose with naphthalene as a functionalizer was constructed [90], and this branching structure can regulate the material dynamics of the hydrogel network through topological and kinetic control. In-depth research was done on the highly branching polywhene hydrogel networks' temperature- and time-dependent rheological characteristics. The rigid complexation of tetraphenylene derivatives with Q[8] allowed access to hydrogels with bright orange fluorescence and high heat resistance even at 200°C [64]. The rheological analysis and microscopic studies confirmed the supramolecular hydrogels' good rheological properties and well-organized lamellar structure.

3.2.3 Adhesive properties

By creating Q[8]-hetero-tetrameric complexes, Scherman *et al.* [100] created a novel class of aqueous binders known as HBP-Q[*n*] that can macroscopically join two wet surfaces, including biological tissues. Even after the interface has mechanically failed, these complexes may rebound

and reversibly attach, creating adhesion with notable tenacity. On-demand activation of adhesion/de-adhesion is made possible by the inclusion of functional guest molecules, such as azo-phenyl groups. This discovery offers a fresh approach for making biomedical devices and tissue adhesives of the future. In other work [102], a supramolecular polymer network was formed by host-guest interactions between Q[8]-assisted naphthalene-functionalized hydroxyethyl cellulose (HEC-Np), styrene-containing copolymers of methyl viologen (PSTMV), Q[8], and photo-isomerized azoimidazole (AzoIm) derivatives. Cellulose-based PRFs are capable of undergoing a quick transition from rigid gels to Newtonian fluids under UV light, resulting in a more than two orders of magnitude drop in zero-shear viscosity. The viscosity reduction rate can be controlled by adjusting the mixture composition and the duration of light exposure. Ternary supramolecular hydrogels constructed through a 3-arm guest molecule and a methyl viologen derivative with a Q[8] (Figure 34) likewise exhibit excellent viscosity [106].

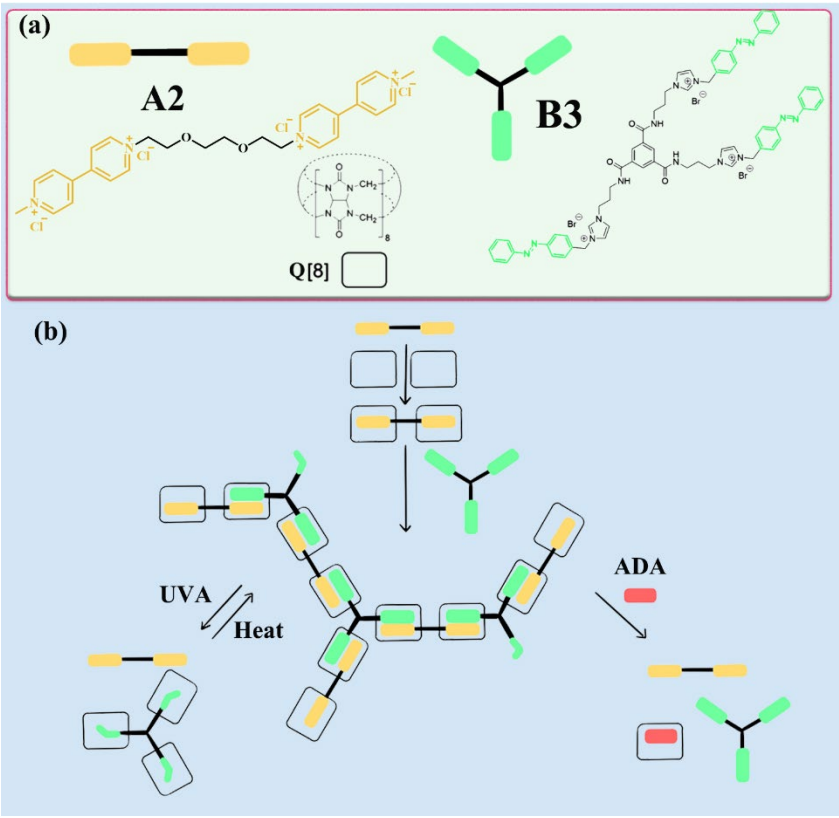

Figure 34. (a) Schematic representations and chemical structures of Q[8], and the guests; (b) Supramolecular assembly process: to create the SHP, A2 is first combined with Q[8] to generate a complex, and then B3 is added. This SHP is susceptible to disassembly in reaction to the

introduction of a competing guest or I reversible photoisomerization of the azobenzene (left) (right).

3.3 Stimulus response properties

3.3.1 pH regulating properties

Supramolecular hydrogels can also demonstrate remarkable pH responsiveness, as evidenced in the work of Huang *et al.* [39]. By mixing supramolecular polymers with a glyoxal solution in the presence of a glacial acetic acid catalyst (pH = 5) or neutral pH conditions, they were able to produce self-healing hydrogels. The obtained hydrogels were pH-reversible responsive. Supramolecular helical nanofibers with non-chiral monomers were constructed in aqueous solution [59]. The nanostructures formed in the supramolecular hydrogels could be modified by adjusting the concentration of monomers, resulting in a range of structures, from helical nanofibers to pH-responsive hydrogels. In addition, the construction of supramolecular hydrogels was controlled by adjusting the pH in the system (Figure 7) [61], and this method has been used by others to adjust the pH [43,56]. The slow-release properties of 5-fluorouracil supramolecular gels under acidic conditions are shown in Figure 17, indicating the potential use of Q[8]/EBCS gels as carriers for pH-sensitive controlled drug release systems. [78].

3.3.2 Thermal properties

By introducing the ternary complex Q[8]/MV^{2+}/Np, the microstructure of the macromolecular chain was altered at the *N*-isopropylacrylamide side chain, leading to a strong tendency to thermal gelation [107]. Modulating the composition of Q[8] and MV^{2+} can modify the formation of positively charged side chain ternary complexes and subsequently influence the gelation temperature. Thus, the introduction of supramolecular interactions gives the hydrogel tunable gelation properties. Furthermore, other studies [48,64] have reported that increasing the concentrations of the guest and Q[*n*] resulted in an increase in the gel-sol transition temperature, and the hydrogels showed sensitivity to thermal stimuli.

Supramolecular hydrogels exhibit excellent thermal stability and reversibility due to their highly branched topology and dynamic host-guest interactions, which prevent phase separation over a wide temperature range [90]. Furthermore [107], these supramolecular hydrogels can undergo microstructural modulation and thermal reversibility when the host is further incorporated and subjected to heat treatment.

The hydrogels obtained by Liu *et al.* [64] emitted a bright orange fluorescence and were highly heat resistant even at 200°C. The rheological analysis and microscopic studies confirmed the supramolecular hydrogels' good rheological properties and well-organized lamellar structure. In Figure 17, *in vitro* drug release studies of 5-fluorouracil supramolecular gels showed that temperature also affects the properties of their gels [78]. Hydrogels for human calcitonin extended release also exhibited thermal sensitivity, with 20 wt% gel solutions exhibiting temperature-sensitive sol-gel transitions in phosphate-buffered solutions at 35°C and slow degradation at neutral pH for over a month [85].

3.3.3 Photosensitive properties

Some supramolecular hydrogels also exhibit photosensitive properties. As shown in Figure 35, the guest in the supramolecular hydrogels reported by Webber's group [108] are of the asymmetric azobenzene type and thus undergo photoisomerization in the presence of UV light, leading to supramolecular motif disruption and prompting a gel-sol transition in the hydrogel. Excitingly, the rapid hydrogel recovery within a few minutes at room temperature is provided by the thermal relaxation of azobenzene to its *trans* state. Similar supramolecular hydrogels can be constructed with olefin double bonds [66].

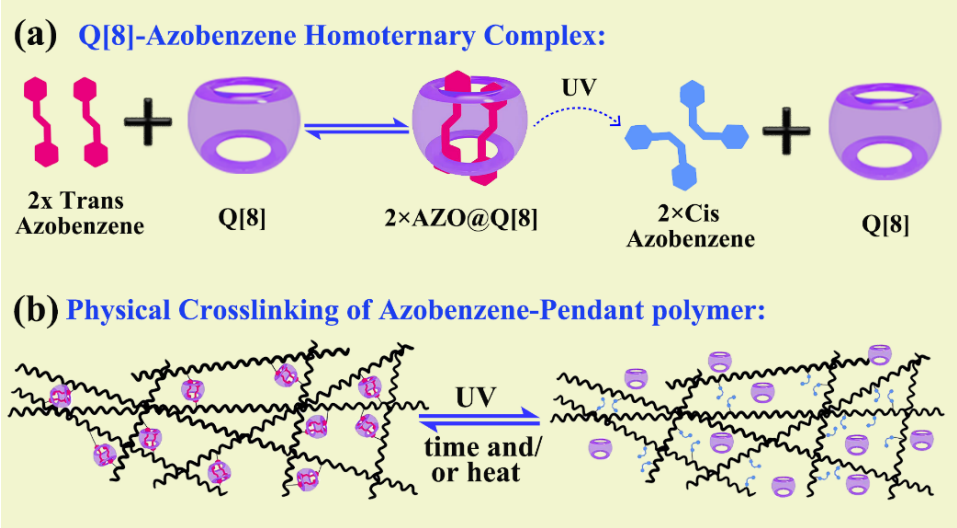

Figure 35. (a) This diagram depicts the proposed approach for creating homo-ternary complexes between Q[8] and asymmetric azobenzene guests; (b) The use of pendant azobenzene guests on polymeric backbones aims to facilitate physical cross-linking through homo-ternary complexation with free Q[8].

3.3.4 Pressure-sensitive properties

In addition, Scherman *et al*. [97] demonstrated the ability of supramolecular hydrogels to associate processes by selectively interfering with external stimuli. Because hydrogels display hitherto unheard-of pressure-sensitive rheological features, the utilization of Q[8]-ternary complexes in hydrogel production is significantly affected by the fact that the binding equilibrium of these complexes rises with increasing stress. As a result, building host-guest systems with changeable kinetic and thermodynamic characteristics that may be customized for applications in a wide variety of sectors offers a great degree of freedom. Similarly, supramolecular hydrogels with photoconvertible isomers were prepared by azobenzene [102,105-106]. In addition [71], they used hydroxyethylcellulose-coumarin-Q[8] to construct supramolecular hydrogels that are also photosensitive by the mechanism that the double bond on the coumarin pyrone undergoes

photoisomerization, leading to a change in the supramolecular hydrogel motif, and that the hydrogel can be switched between the two forms by light modulation.

Hoogenboom and colleagues [116] developed a hydrogel through a ternary host-guest interaction involving two anthracene moieties and a macrocyclic. This hydrogel also suffers from photoisomerization, specifically the reversible conversion of the hydrogel into the corresponding covalent cross-linked hydrogel under near-UV irradiation. The host cavity facilitates the photodimerization of the anthracene molecule, and subsequent far-UV irradiation induces photochemical cleavage of the resulting anthracene dimer.

3.4 Biocompatible properties

To verify the biocompatibility of supramolecular hydrogels, cell proliferation and viability were measured by the MTT method and double fluorescence staining, and it was concluded that supramolecular hydrogels are non-toxic and biocompatible [110]. In addition, NIH-3T3 fibroblasts were studied *in vitro* in culture. After 1 day of culture, both the supramolecular hydrogels and the ionic hydrogels showed high cellular activity, which is consistent with the tissue culture plastic results [112]. Moreover, NIH-3T3 fibroblasts were employed, and they were suspended in a supramolecular crosslinking or photodimer crosslinking solution before being injected by syringe into a warm medium bath at room temperature [53]. The gels were dyed after 0.5 hours utilizing a live/dead activity. Using fluorescence microscopy, the gels were dyed and cell encapsulation was evaluated. In both instances, cell densities were comparable, and the great majority of cells were still alive. This result implies that shearing did not have a negative impact on cell survival. Q[6]/DAH-HA hydrogels were formed *in situ* subcutaneously in nude mice by continuous subcutaneous injection of Q[6]-HA and DAH-HA solutions [45]. Fluorescence of modularly modified fluorescein isothiocyanate-Q[6] in the hydrogel can be maintained for 11 days, reflecting the feasibility of delivering appropriate cell proliferation and differentiation *in vivo*. In addition, this system has been used for long-term engineered mesenchymal stem cell (eMSC) therapy [80]. Duan *et al*. [55] prepared low-toxicity, biocompatible three-dimensional engineered hydrogel scaffold microstructures and co-cultured them with HeLa cells, showing their potential for further applications. Encapsulating human fibroblasts in hydrogels, they remain highly viable in culture and exhibit good swelling morphology [114].

4. Applications

In the final section, we discuss the applications of these constructed supramolecular hydrogels. Hydrogels as a class of polymeric materials have received a lot of attention in recent years, and their application areas are even more diverse, including biomedicine [120,121], tissue engineering [69], drug delivery [96], soft materials [122,123], and sensing [124-126]. Supramolecular hydrogels based on Q[*n*]s have also been reported to have a variety of fascinating uses.

4.1 Biological applications

Biological applications have long been a popular area of supramolecular research and have received even more attention in the last few decades.

A technique for creating sessile microdroplet-derived hollow microcapsule arrays has been develped. The liquid can self-distribute into microdroplet arrays that act as microbins filled with complementary functionalized host-guest polymers to produce hydrogel microcapsules thanks to the difference in wettability between hydrophilic and hydrophobic surfaces [75,89]. Such microcapsules are designed to enclose the desired payload in a certain manner and are homogenous in size. This microcapsule substrate was also used to detect loaded gold nanoparticles using surface-enhanced Raman spectroscopy. These microcapsule arrays simple construction has the potential to be used for biosensing, controlled cargo delivery, sorting and high-throughput analysis. Scherman *et al*. have prepared uniformly sized supramolecular hydrogel beads [98]. Fluorescein-labeled dextran was utilized to assess the efficacy of hydrogel beads as a controlled release drug carrier and revealed that they followed a paradoxical (non-fiction) transport mechanism. Microdroplets containing diluted hydrogel precursors were created in a microfluidic device. The release mechanism of therapeutic carriers in hydrogels is strongly influenced by network dynamics, and the slow-release properties can be tailored by designing the molecular processes responsible for cross-linking in carrier hydrogels [99].

Scherman's group used machine learning to predict the binding of TAK-580 and selumetinib in a recent study [118]. The algorithm accurately predicted the strong binding of TAK-580 and the weak binding of selumetinib, and experimental validation confirmed these results. This indicates that release can be controlled by varying the concentrations of Q[7] or Q[8] in the hydrogel

reservoir. These drugs have shown potential for use in conjunction with glioma treatment. Next, a new class of drug delivery reservoirs was formed by cross-linking peptide-functionalized hyaluronic acid with Q[8] for enhancing drug bioavailability in patient-derived xenograft models of glioblastoma [73].

Figure 36 in reference [72] illustrates a physical hydrogel that is cross-linked by the host-guest interaction of Q[8] and serves as an implantable drug delivery system for the brain. The hydrogel is composed of hyaluronic acid functionalized with phenylalanine-terminated peptides that bind in a 2:1 ratio with the Q[8] host. These interactions result in shear-responsive cross-links, allowing for injection of the hydrogel.

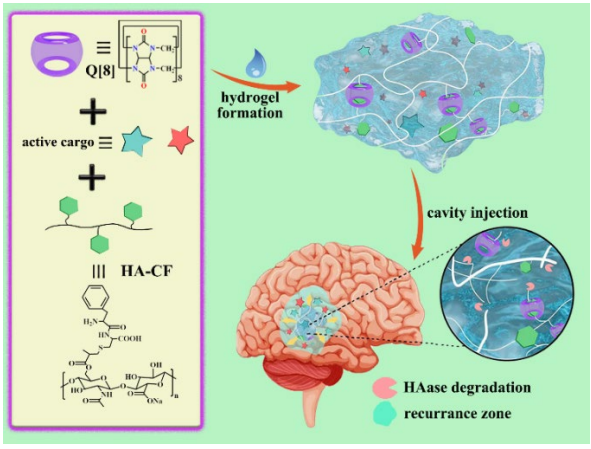

Figure 36. A syringe or needle may be used to implant the hydrogel inside a cavity used for the removal of a tumor.

Figure 37 depicts the subsequent investigation into the release properties of proteins, specifically examining the impact of protein molecular weight and polymer loading on the rate of protein release [101]. Supramolecular hydrogels with a polymer composition of only 1.5 wt% demonstrated an unprecedentedly sustained release of bovine serum albumin over a period of 160 days. This release significantly surpassed the current state-of-the-art in protein release from hydrogels, indicating the potential of these materials for sustained therapeutic applications.

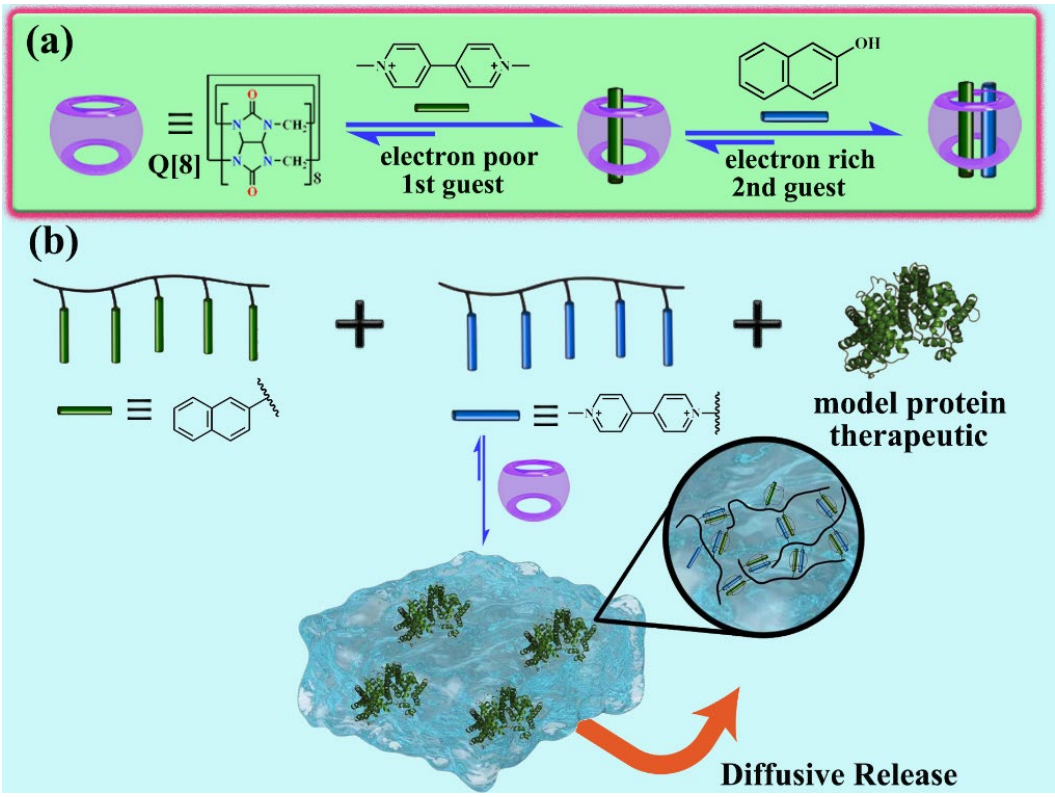

Figure 37. (a) Q[8] is bound to water in a two-step, three-component process; (b) the creation of hydrogels with a very high water content is shown schematically.

Biodegradable thermal gels from human calcitonin can be used for the long-term delivery of this drug [85]. *In vitro* studies of drug release from supramolecular gels containing 5-fluorouracil revealed their slow-release properties under acidic conditions. These findings indicate that Q[8]/EBCS gels have potential as carriers for pH-sensitive controlled release systems for drugs. [78].

An oral colon-targeted drug delivery hydrogel (OCDDH) was prepared as shown in Figure 38 [92]. The hydrogel possesses robust cross-linking mediated by host-guest complexation, which is reversible, allowing for easy adjustment of the degree of cross-linking and excellent self-healing ability. As a result, the hydrogel maintains exceptional stability in the gastric environment, making it a suitable candidate for orally administered colon-targeted formulations. In the colon, hydrogels

can undergo degradation by colon-specific enzymes, leading to the release of the loaded cargo in the local region.

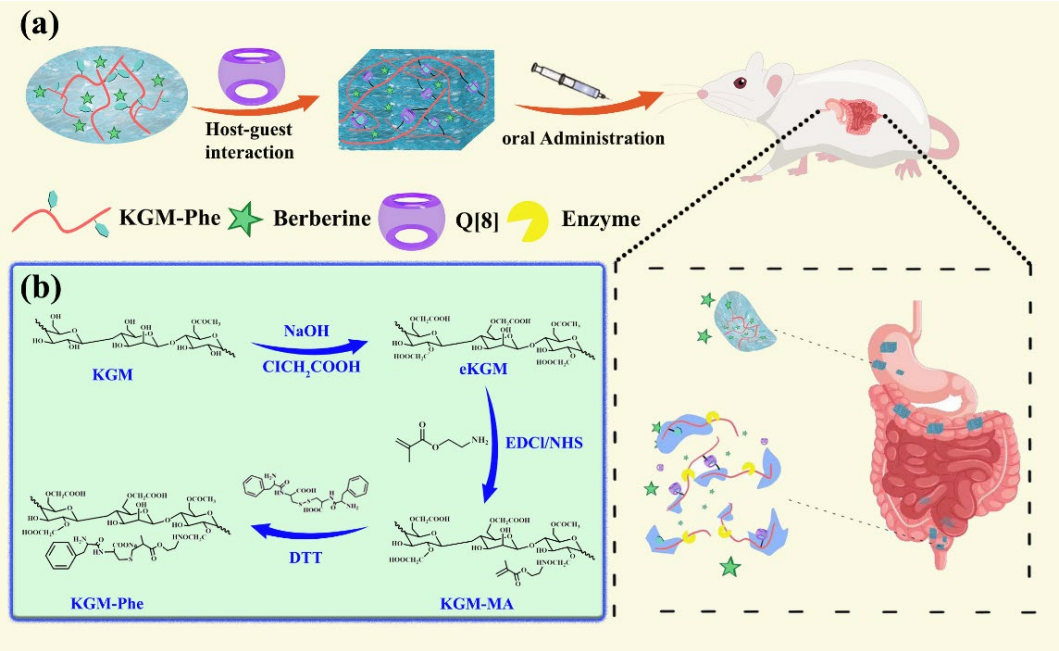

Figure 38. (a) Diagram showing the production of KGM hydrogels and their targeted drug release; (b) Synthetic pathway of phenylalanine-grafted KGM.

Supramolecular hydrogels based on virus-like particles (VLPs) can effectively load tetrasulfonated zinc phthalocyanine (ZnPc) with a loading efficiency of 99%. The protein cages in the hydrogel not only facilitate the quantitative loading of ZnPc but also improve its water solubility, preventing unwanted aggregation. Controlled release of VLPs and ZnPc cargo can be achieved without initial burst release. Cisplatin, an anticancer drug, was encapsulated in Q[7] and added to gelatin and 0-4% w/v polyvinyl alcohol (PVA)-based hydrogel for sustained drug release [57]. The *in vivo* effect of implanting 2% PVA hydrogels subcutaneously into A2780/CP70 xenograft nude mice showed that low-dose hydrogels containing cisplatin@Q[7] (30 μg equivalent drug) were as effective as high-dose intraperitoneal free cisplatin (150 μg) in inhibiting tumor growth. Webber and colleagues [52] proposed a different approach for targeting molecules to specific sites using a guest sag pattern shown in Figure 39. This approach relies on hydrogels containing a high density of Q[*n*] supramolecular hosts with a host-guest affinity (Keq=10^{12} M^{-1}).

Within a few hours of administration in mice, ~4% of model small molecules are spatially localized due to these high-intensity interactions.

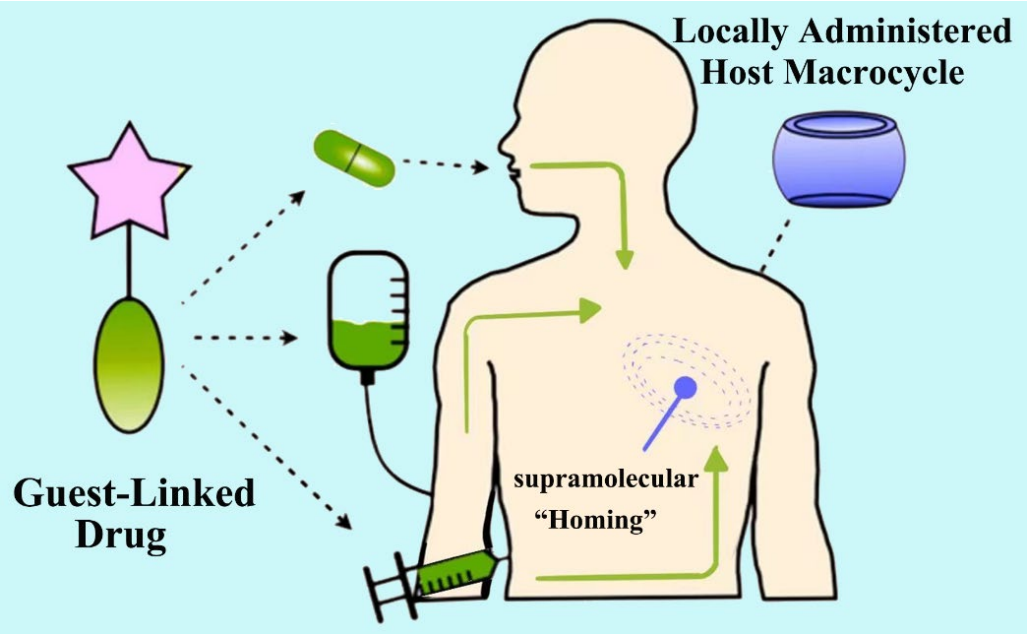

Figure 39. Schematic Diagram of Administration.

Usta *et al.* [80] described a "supramolecular hybrid hydrogel (SHH)" which forms a biocompatible dressing, is self-healing, dissolves on demand, is non-invasive to debride, and is prepared in a simple, rapid, and scalable way. Supramolecular hydrogels possess dynamic properties that allow them to dissolve when exposed to memantine, the latter being an FDA-approved drug. This property makes them highly suitable for use as wound dressings, as they can be easily removed from wounds. Such hydrogels hold immense promise for the development of a new generation of wound dressings.

The strong electrostatic interaction between Q[7] and γ-Fe_2O_3 nanoparticles was utilized to maintain the physical and chemical properties of the nanoparticles in a supramolecular manner [41]. The γ-Fe_2O_3 nanoparticles were able to generate heat and exhibit vibrational motion under an alternating magnetic field. This allowed for the formation of hybrid supramolecular hydrogels

with both thermal and chemotherapeutic modes, which were demonstrated *in vitro* and *in vivo* (Figure 40).

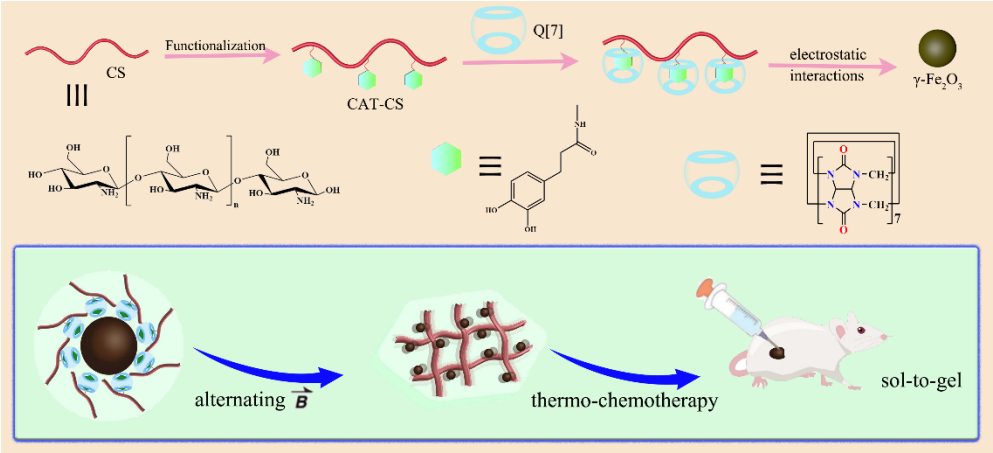

Figure 40. A graphical representation of the mediated hydrogel nanocomposites using Q[7].

4.2 Optical Applications

Ma *et al.* [58] demonstrated the first instance of pure organic room temperature phosphorescence excited by visible light in an aqueous solution using a supramolecular host-guest assembly strategy. Their unique Q[8]-mediated fourth-order stacked structure enabled tunable photoluminescence and visible light excitation, leading to the creation of multicolor hydrogels and cellular imaging. Liu *et al.* [63] synthesized an alkyl chain-modified oligo(*p*-styrene) (Py-OPV) derivative, which undergoes j-type dimerization when encapsulated in the cavity of Q[8], resulting in different emission properties depending on the monomer. By varying the concentration of Q[8], the fluorescence properties of the complexes could be easily altered. Luminescent supramolecular hydrogels were constructed based on acrylamide photopolymerization with Py-OPV and Q[8], allowing for the creation of hydrogels emitting various shades of blue light by confining them through embedding the components into the polymer. This novel method of preparing luminescent hydrogels provides a new reference method for creating specific luminescent materials. Kim *et al.* [46] used the inherent luminescent properties of hydrogels for cell tracing, while Zhang and colleagues [115] further explored the luminescent properties of the produced aqueous light-trapping system using a donor (supramolecular hydrogel) and acceptor (eosin Y disodium salt)

system. This process offers a fresh approach to the production of fluorescent and self-healing supramolecular hydrogels with numerous potential applications. Scherman *et al*. [69] synthesized fluorescent monomers by selecting pyridine groups with known fluorescent properties and then polymerizing them into fluorescent hydrogels. By integrating the dye and cross-link producing monomers into a single unit, this method reduces the amount of components needed to make luminous supramolecular hydrogels. *Trans-cis* photoisomerization of cyanostilbene units were used to construct fluorescence from multicomponent hydrogels that were sensitive to the rapid appearance of UV light irradiation for a short time and recovered during the cessation of light exposure [87]. Based on these characteristics, fluorescence-imprinted hydrogels were successfully made by combining supramolecular co-assembly. The fluorescent patterns imprinted utilizing the hydrogels are reversible and rewritable.

4.3 3D Printing

Recently, 3D printing has found use in a variety of industries and caught the interest of numerous researchers and indeed other communities. The use of 3D printing technology for hydrogels is a more cutting-edge direction. Tan's group [82] enabled the accumulation of hydrogels in the vertical direction by fusion molding, *i.e*., 3D printing of hydrogels. After 24 h, the hydrogel patterns were strong enough to be removed from the original substrate and transported. Even after several months of storage in water, the hydrogel patterns remained intact and they were still highly fluorescent. Zheng *et al.* [54-55] prepared 3D-engineered hydrogel scaffold microstructures using two-photon polymerization.

4.4 Catalytic applications

The Au/Q[8] hydrogel was used as both a catalyst and a reaction media in the reduction process of 4-nitrophenol (4-NP) with aqueous $NaBH_4$ solution [119]. These hydrogel composite catalyst systems have self-healing qualities and may be reused up to seven times. The activation parameters and reduction rate constants were computed for four distinct temperatures. Additionally, a dual-network phosphorescent light trapping (PLH) system, as depicted in Figure 41, was prepared and utilized in the cross-coupling reaction. The closed microenvironment and long-lasting photosensitizer exhibited a synergistic effect, resulting in enhanced activity, which offers a new strategy for the application of phosphorescent light energy transfer in photocatalysis [63].

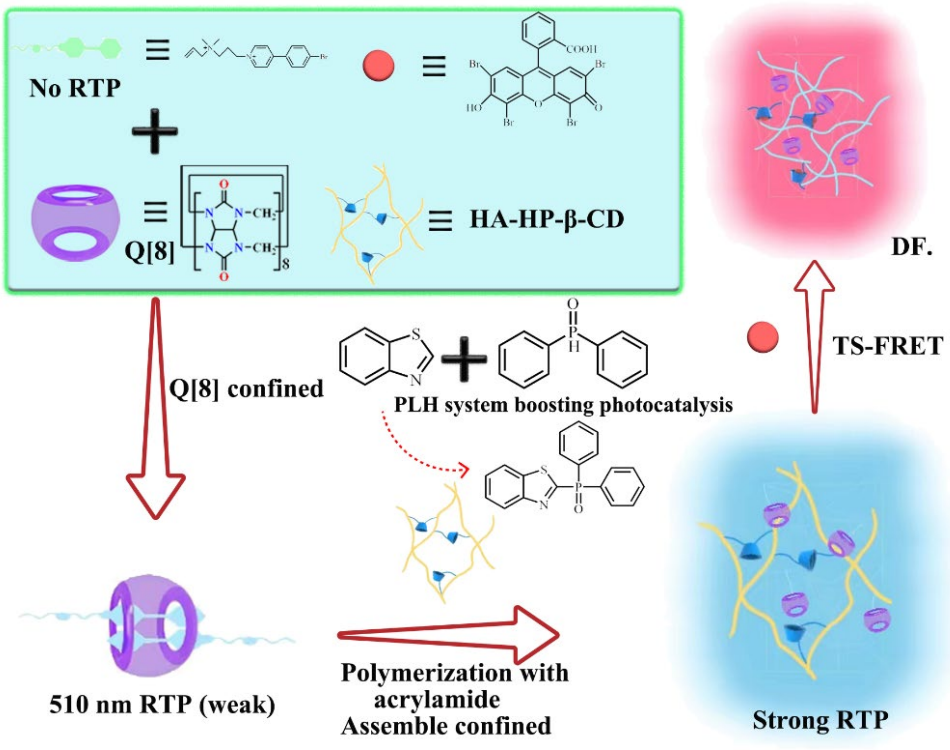

Figure 41. Diagram of photocatalytic effect (DF = delayed fluorescence).

4.5 Other applications

In addition to the above applications, supramolecular hydrogels have been used in many other areas, such as the use of supramolecular hydrogels for the detection of copper ions [39]. Dye adsorption was performed using TPE-4Q·Q[8] hydrogels as shown in Figure 42 [64]. In addition, supramolecular hydrogels can be used for sensing [84], control of cartilage formation in human mesenchymal stem cells (hMSCs) [47], molecular recognition [45], etc.

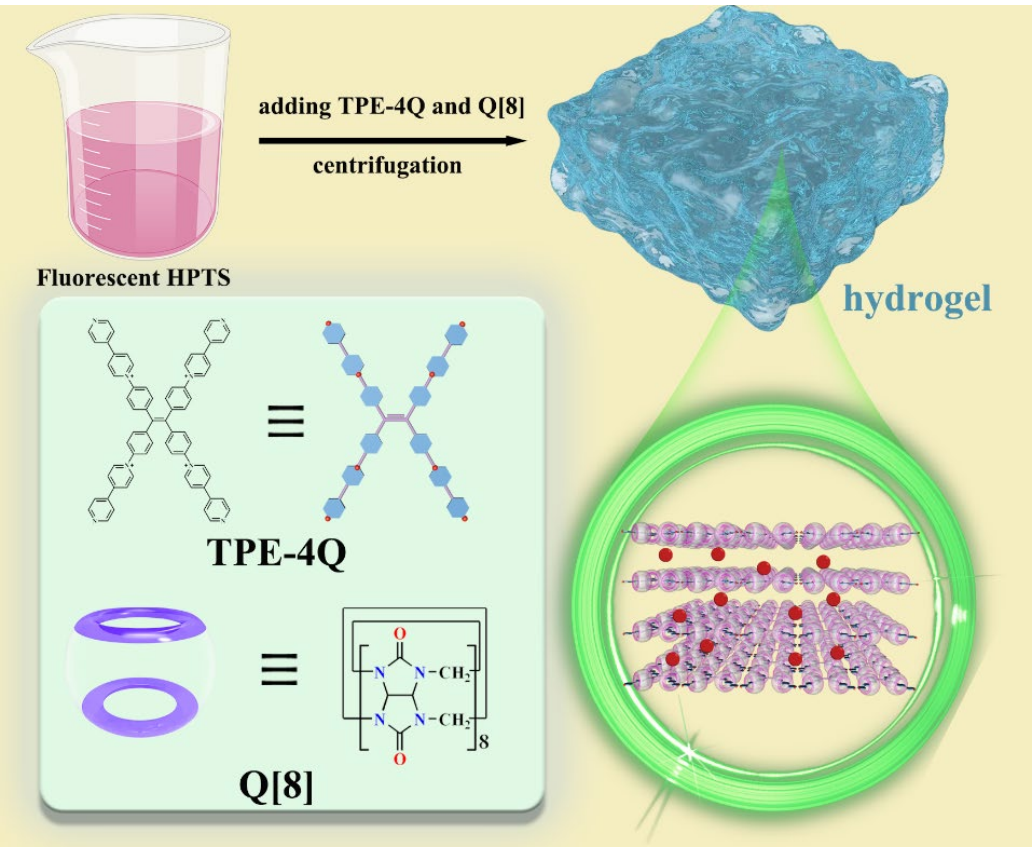

Figure 42. Schematic illustration of loading and removal of HPTS by the TPE-4Q·Q[8] hydrogel network.

5. Conclusion and outlook

This review provides an overview of the progress in research on Q[*n*]-based supramolecular hydrogels, a novel soft reactive material. By adjusting factors including the polymer backbone, strength and interaction dynamics, orientation, multi-reactivity, and adjustable degradability, the combination of polymer chains with supramolecular crosslinking offers an effective way in comparison to conventional covalent crosslinking techniques. Supramolecular crosslinking also provides dynamic behavior, which is essential in the production of high-performance materials, fault-tolerant goods, and components for sectors like coatings, electronics, transportation, and energy. Such dynamic behavior includes structural error correction, shear thinning, self-healing, elasticity, photosensitivity, biocompatibility, and plasticity.

Few studies have quantitatively described the link between the basic factors governing self-assembly and the macroscopic behavior of the resultant materials, despite the fact that research has concentrated on the synthesis of supramolecular hydrogels. Therefore, there is still a need for a systematic study of this complex relationship, as well as of the structure and dynamics of supramolecular hydrogels. Q[*n*]-based hydrogels, however, have demonstrated tremendous potential in biological applications such tissue engineering architecture, cell matrix culture, and drug delivery.

There are also a few supramolecular hydrogels constructed based on the main body of Q[*n*]s, especially those constructed based on the outer surface interactions of the Q[*n*] (OSIQ). The OSIQ have positive electrical properties and can form outer surface interactions with various guest molecules and polymer chains, cross-linking them to form supramolecular hydrogels while leaving the cavity of the Q[*n*] open. If suitable carriers can be loaded into the cavity, this will further expand the application of Q[*n*]s in the field of hydrogels, especially in drug delivery and sustained release.

Although many supramolecular hydrogels based on macrocyclic bodies have been constructed, many challenges still need to be addressed before these reports can be put into practical use. These challenges include further research into the dynamic formation mechanisms of hydrogels, gaining insight into the thermal and kinetic aspects of the process of forming hydrogels, and improving their properties. Additionally, experiments such as biocompatibility and cytotoxicity need further research to advance the application of hydrogels in biomedical and biomaterials. With the development of Q[*n*] chemistry, the development of novel Q[*n*]s and their derivatives and their application in the construction of supramolecular hydrogels is still challenging, but very promising. Furthermore, machine learning has the potential to analyze data and assist in decision-making in the medical field, and if applied to the construction and prediction of supramolecular hydrogel drug delivery systems, its value will be immeasurable. In conclusion, Q[*n*]-mediated hydrogels are still an emerging research area and will be accompanied by many opportunities and challenges, and more practical applications of supramolecular hydrogels constructed by opportunistic Q[*n*]s will be realized in the near future.

Acknowledgment

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Abbreviations

AA, Acrylic acid; ABP, 4-(4-Bromophenyl) pyridine-1-ium bromide; AD4VBDMA, *N*-Adamantyl-*N*-(4-vinyl benzyl)-*N*,*N*'-dimethyl ammonium chloride; AM, Acrylamide; AMP, *N*-Acryloyl morpholine; BAMB, Butylamine 4-methylbenzenesulfonate; BBR, Berberine; BPY^{+}, 4,4'-Bipyridine-1-ium chloride; CCMV, Cowpea chlorotic mottle virus; *α-CD, α*-Cyclodextrin; *β*-CD, *β*-Cyclodextrin; *γ*-CD, *γ*- Cyclodextrin; CMC, Carboxymethyl cellulose; CS-P(AM-G), Poly (acrylamide-co-1-benzyl-3-vinyl imidazolium bromide); DMA, *N*,*N*'-Dimethyl acrylamide; DMAEA, *N*,*N*'-Dimethylaminoethyl methacrylate; EBCS, *N*-(4-Diethylaminobenzyl) chitosan; HA, Hyaluronic acid; hcT, Human calcitonin; HEAm, Hydroxyethyl acrylamide; HEC, Hydroxyethylcellulose; HPC, Hydroxypropyl cellulose; KGM, Konjac Glucomannan; LMWG, Low molecular weight gel; MBA, *N*,*N*'-Methylene bisacrylamide; $Me_{10}Q[5]$, Decamethylcucurbit[5]uril; MH, Monomer hydrazine; MSC, Mesenchymal stem cell; MV, Methyl viologen; NIPAM, *N*-Isopropyl acrylamide; NS-Q[10], *Nor-Seco*-Cucurbit[10]uril; P4VBAM, Poly(*N*-(4-vinylbenzyl)-4,4'-bipyridinium dichloride-co-acrylamide); PA, Peptide amphiphile; PAAm, Polyacrylamide; *p*-PDA, *p*-Phenylenediamine; PEG, Polyethylene glycol; PEGDA, Polyethylene glycol diacrylate; PEGD, Polyethylene Glycol Dimethacrylate; PVA, Polyvinyl alcohol; Py-OPV, Alkyl chain-modified oligo(*p*-phenylenevinylene); Q[*n*], Cucurbit[*n*]uril; RTIPS, Reverse thermally induced phase separation; SA, Sodium alginate; SAM, Benzyl trimethyl ammonium chloride; SPCH, Supramolecular polymer–colloidal hydrogel; TPE, Tetrastyrene.

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BRIEFS

The table of contents contains the intention of the article and the key sections within it, including the construction methods, performance studies, catalytic applications, biological applications.