

Exploring Macrocycles in Functional Supramolecular Gels: From Stimuli Responsiveness to Systems Chemistry

Zhenhui Qi and Christoph A. Schalley*

Institut für Chemie und Biochemie, Freie Universität Berlin, Takustrasse 3, 14195 Berlin, Germany

CONSPECTUS: Supramolecular gels are ideal candidates for soft, stimuli-responsive materials, because they combine the elastic behavior of solids with the microviscous properties of fluids. The dynamic networks of fibers in supramolecular gels are reminiscent of the cytoskeleton of a cell and provide scaffolds to implement function. When gels are made responsive to stimuli, these mechanical properties can be controlled. Gel–sol transitions also open opportunities to immobilize molecules inside the gel’s cavities and to release them on demand. To establish selective responsiveness, suitable recognition sites are required influencing the properties of the fiber network depending on the presence of the stimulus. Supramolecular gels are expected to be stimuli-responsive *per se*, for example, to temperature, mechanical stress, or an environment that is competitive with the noncovalent interactions connecting the low-molecular weight gelators. Nevertheless, the opportunities for controlling the mechanical properties are rather limited, if one merely relies on interfering with these interactions. It would be much more promising to equip the gel with additional receptor sites that offer selectivity for a broader variety of chemical stimuli. Macrocycles often exhibit a distinct host–guest chemistry and thus are excellent candidates for this purpose. A broad variety of macrocycles differing with respect to structure, topology, solubility, or biocompatibility have been incorporated in gels and endow gels with responsiveness and function. Macrocycles can have different roles: They offer rather rigid scaffolds for the construction of structurally well-defined gelator molecules. Furthermore, their host–guest interactions can be integral to gel formation, if these interactions are required to build the gel fibers. Finally, macrocycles can also be functional groups with which gelators are equipped that would also form gels in the absence of the macrocycle. Here, the macrocycle can be used as a binding site to allow additional stimuli control. To combine different stimuli for triggering gel–sol transitions certainly expands the options for establishing stimuli responsiveness. If, for example, an agent trapped inside the gel is only liberated when two different stimuli are present simultaneously, its release can be controlled with much higher precision and selectivity compared with a gel that responds to one stimulus only.



In this Account, the recent progress in the construction of functional macrocycle-containing supramolecular gels is summarized. First, recent strategies to engineer responsiveness into macrocycle-containing gels are discussed. Next, different functions are presented including applications as responsive reaction media, for controlled drug-delivery or tissue engineering, and as self-healing materials. Finally, we highlight the recent progress in designing macrocycle-containing supramolecular gel materials exhibiting complex behavior. This field is part of systems chemistry and still in its infancy but appears to be one of the most promising routes to smart responsive materials.

■ INTRODUCTION

Combining the elastic behavior of solids with the microviscous properties of fluids makes gels a unique class of soft materials.^{1–3} Microscopically, gels consist of three-dimensional (3D) networks that span the volume of a liquid and entrap it through the surface-tension effect.⁴ These fibrous networks can be constructed either by covalent bonds (chemical or polymer gels) or by noncovalent interactions (physical or supramolecular gels). In supramolecular gels, low-molecular weight gelators form networks through noncovalent interactions such as hydrogen bonding, π – π interactions, metal coordination, or host–guest inclusion.⁵

Supramolecular gels, to which we restrict this Account, are particularly suited to implement stimuli responsiveness, because noncovalent interactions strongly depend on the environment. Consequently, temperature, mechanical stress, the choice of solvent, or the addition of molecules that compete with the

gel-forming interactions are stimuli that induce gel–sol transitions and have a significant effect on the gels’ mechanical properties. In particular, reversible changes in the gel network and the physical properties of these gels in response to a specific signal input are thus pivotal for the creation of responsive materials. The integration of selective molecular recognition units into the gelator molecules or their nanostructures is advantageous to create specific responses or develop multistimuli-responsive gels. The recognition process at these sites must of course affect the nanostructures of the gel in order to mediate a macroscopic property change.

Macrocycles often reversibly bind guest molecules with quite high selectivity and can be fine-tuned chemically. Many different

Special Issue: Responsive Host-Guest Systems

Received: May 19, 2014

Published: June 17, 2014

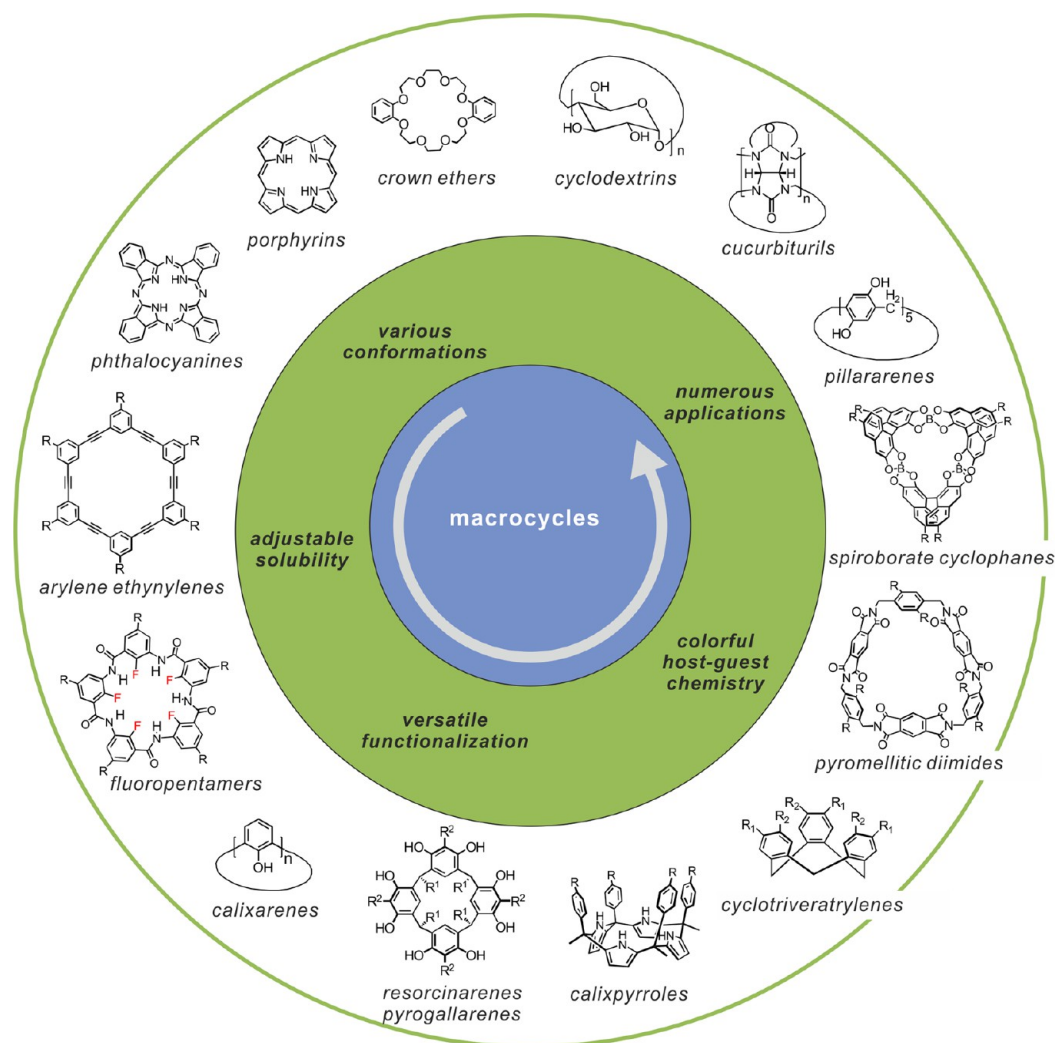
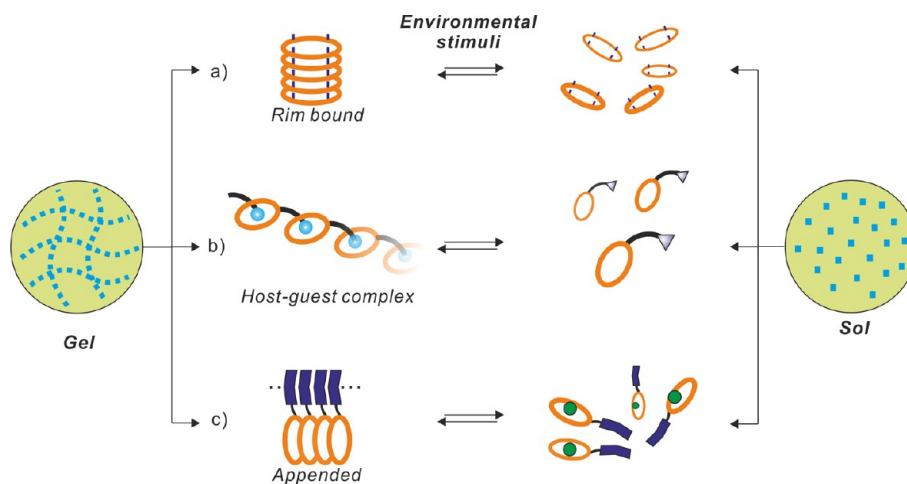


Figure 1. Macrocycles that were already utilized in supramolecular gels.

Scheme 1. Illustration of the Different Roles of Macrocycles in Supramolecular Gels: (a) Macrocycles as a Scaffold Only. (b) Macrocycles Involved Directly in Gel Formation. (c) Macrocycles Appended to a Gelator Molecule, but Not Directly Involved in Gelation



classes of macrocycles with different structure, solubility, and biocompatibility have been incorporated in gels (Figure 1).⁶ Because macrocycle–guest complexes are sensitive to environmental changes, external stimuli like temperature, pressure, light,

or competitive guests can control their formation or dissociation. These features were successfully utilized to construct sophisticated supramolecular architectures⁷ and molecular machines.⁸ Although the first reports on macrocycle-containing supramolecular

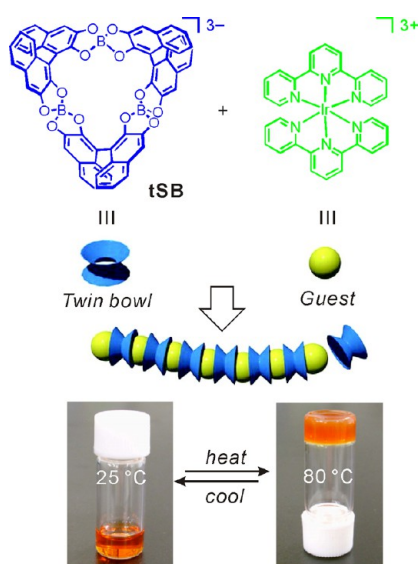


Figure 2. An example of gel formation that occurs only at elevated temperatures. Adapted from ref 26 with kind permission. Copyright 2009 American Chemical Society.

gels date back to the early 1990s,⁹ the utility of macrocycles and their host–guest chemistry for gel chemistry has been exploited more systematically only recently. The macrocycles in Figure 1 have either been part of the supramolecular gel network¹⁰ mediating the gel-forming noncovalent interactions or were appended to low-molecular-weight gelators (LMWGs) as functional groups that are not directly involved in these interactions.^{11,12} Some earlier reviews are available that focused on particular macrocycles for designing supramolecular gels.^{13–15} Very recently, Huang et al. published a survey of the recent progress in the area of macrocycle-based supramolecular polymers, a field closely related to supramolecular gels.¹⁶

In this Account, we summarize how to take advantage of the macrocycles' host–guest chemistry for fabricating functional gels. First, we discuss some recent achievements in engineering

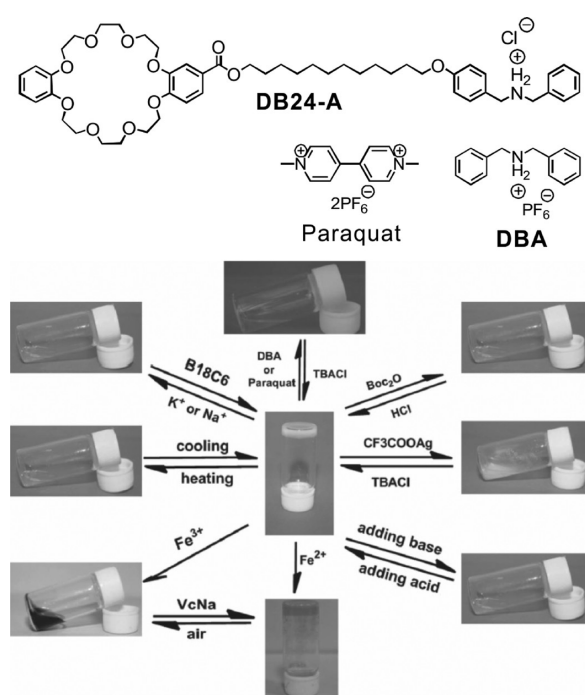


Figure 4. Chemical structure of the crown-ether-functionalized heteroditopic gelator DB24-A (top) and reversible gel–sol transitions of the supramolecular DB24-A gel in acetonitrile triggered by multiple stimuli. Adapted from ref 28 with kind permission from Wiley-VCH, copyright 2012.

responsiveness into macrocycle-containing gels. Based on this, diverse functions are presented in the second part. In the last section, we highlight recent developments of macrocycle-containing gels into materials with complex behavior.

■ RESPONSIVENESS: A PRIMER

Many macrocycle–guest pairs with binding strengths tunable, for example, by substitution with suitable functional groups exist. For example, azobenzene (Azo) and ferrocene (Fc) are

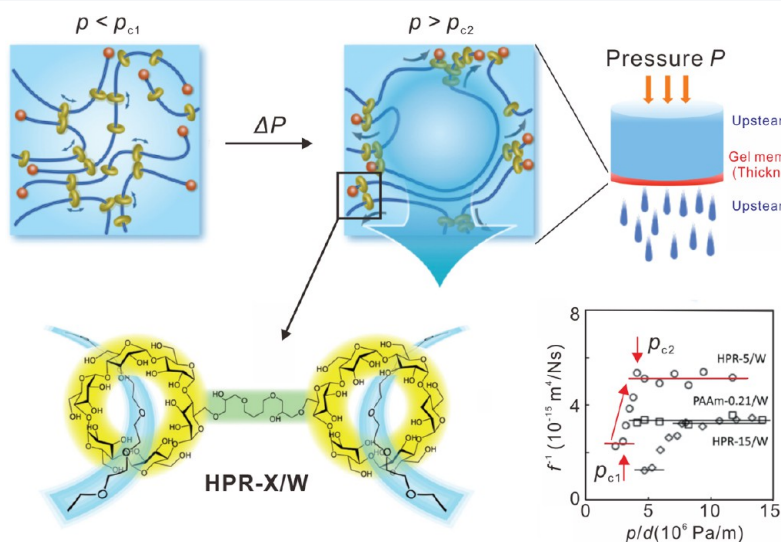


Figure 3. Schematic illustration of pressure-induced transitions of the network structure of supramolecular gels, which result in pressure-responsive fluid permeation through a gel membrane. Inset: Permeation rate-dependence on the pressure-to-membrane thickness quotient. HPR-X/W and PAAm-X/W, respectively, refer to SR gels and polyacrylamide hydrogels. Reprinted from ref 27 with kind permission from Wiley-VCH, copyright 2013.

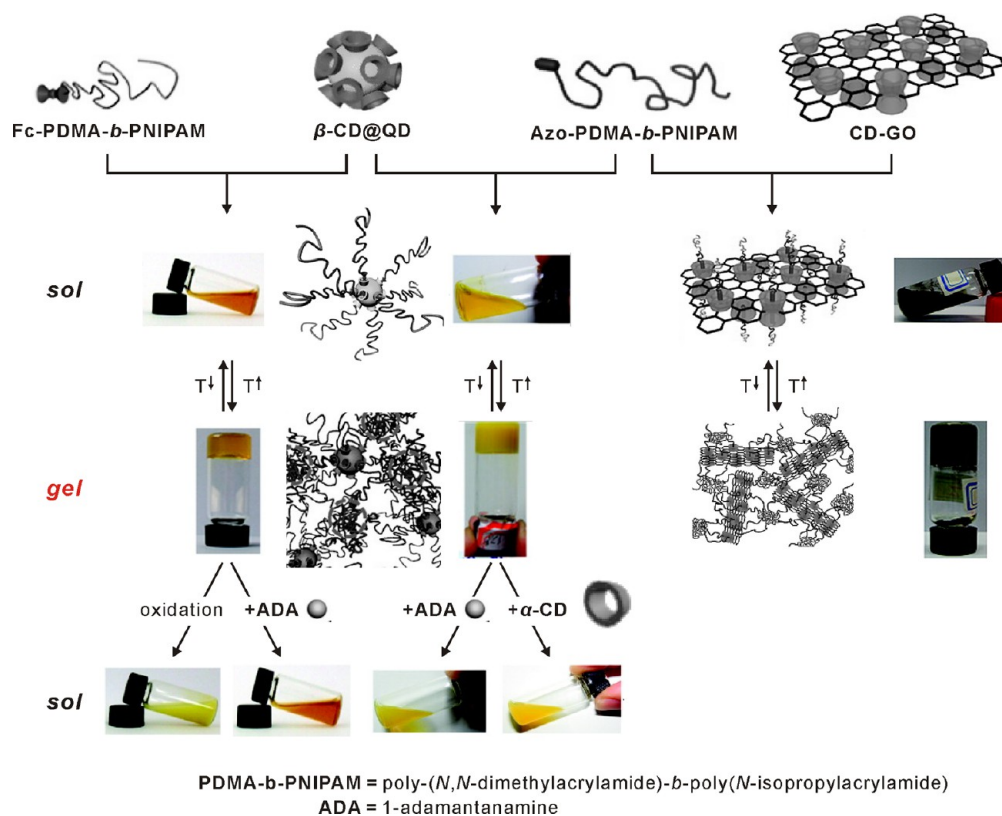


Figure 5. Jiang's hybrid cyclodextrin-containing supramolecular gel shows multiple gel–sol and sol–gel transitions triggered by different stimuli. Adapted from refs 30–32 with kind permission. Copyright 2010 and 2011 American Chemical Society.

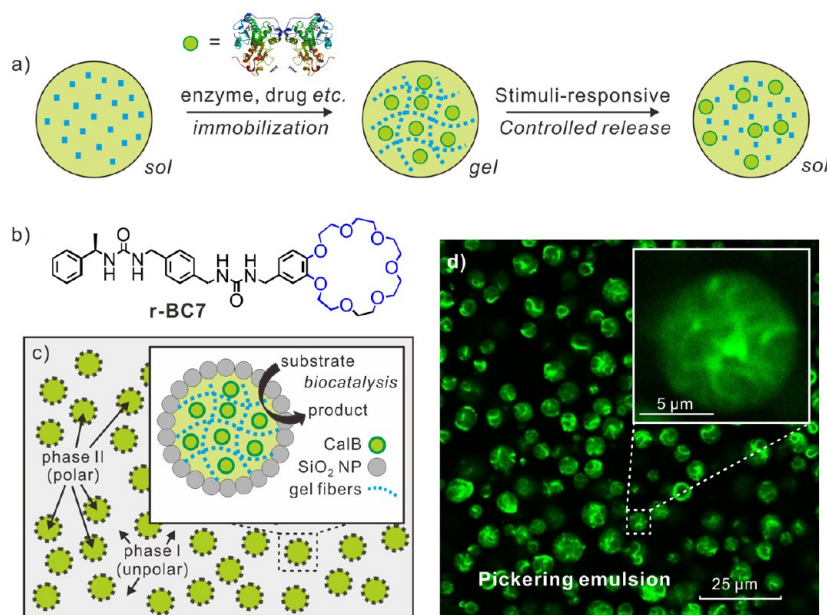


Figure 6. (a) Schematic illustration of responsive supramolecular gels for immobilization and controlled release. (b) The chemical structure of the chiral gelator r-BC7. (c) Its application as a new reaction medium. (d) After the formation of Pickering emulsions, enzyme catalyzed reactions can be performed in the polar phase inside the microparticles, while the surrounding medium is a nonpolar organic solvent. Adapted from ref 35 with kind permission from Wiley-VCH, copyright 2013.

popular guests for constructing photo- and redox-responsive macrocycle-containing gels.¹³ Crown ether/ammonium complexes can be addressed by acid/base addition.¹⁴ The macrocycles may have different roles in the gel. They can merely provide a suitable scaffold to direct the binding sites into

suitable positions for supramolecular polymerization (Scheme 1a). Macrocycles can also be directly involved in gel construction (Scheme 1b), when neighboring gelator molecules are held together in the supramolecular gel by noncovalent macrocycle–guest interactions. In this case, environmental changes and the

addition of stimuli such as competitive guests directly affect the gelator–gelator interaction and can trigger macroscopically detectable gel–sol transitions. They may finally be appended to a gelator molecule without directly participating in the gel formation event (Scheme 1c). Molecular recognition of a suitable guest can then indirectly affect gel formation. For example, charged guests may weaken the gel through charge repulsion; sterically demanding guest may lead to the destruction of the gel network through their bulkiness.

Chemical stimuli include the addition of acids/bases¹⁷ or ions,¹⁸ metal coordination,¹⁹ CO₂ absorption,²⁰ redox chemicals,²¹ chiral guest molecules,²² and biomolecules.²³ Combining such stimuli-responsive units with other stimuli such as temperature, pressure, light, or mechanical stress can be advantageous²⁴ since this opens a window toward controlling the gel properties with complex inputs that, for example, operate as logic gates.

But even thermoresponsiveness, which is a universal characteristic for supramolecular gels because supramolecular interactions are commonly temperature-dependent, can come with surprises. Normally, supramolecular gels show a gel–sol transition at temperatures above a critical gelation temperature. However, gel formation in some cases can also occur only at higher temperatures due to the particular binding properties of the macrocycles incorporated.²⁵ For example, Danjo et al. have reported a new class of supramolecular gels based on D₃-symmetric tris(spiroborate) cyclophanes that show gel formation only at elevated temperature.²⁶ Macrocycle tSB adopts a back-to-back twin-bowl shape and exhibits molecular recognition of cationic metal complexes through π – π and electrostatic interactions at both sides (Figure 2). Polymerization results in rapid gelation when a solution is heated above the lower critical solution temperature (LCST) of 78.5 °C. After cooling to ambient temperature, the gel returns into a clear solution within 15 min. Of course, such an unexpected temperature-dependence is best explained with entropically driven complex formation that originates from the liberation of several solvent molecules from the macrocycle cavity upon guest complexation.

Ito's pressure-responsive gel is another intriguing example for unusual responsiveness through macrocycle incorporation.²⁷ The design (Figure 3) is based on polyrotaxanes in which α -CD monomers are threaded onto a linear poly(ethylene glycol) (PEG) and cross-linked covalently to yield what was termed a slide-ring (SR) gel. Due to the "handcuff" α -CD dimers connecting two neighboring chains, the fluid permeation through SR gel membranes exhibits a nonlinear pressure dependence in marked contrast to conventional covalent polymer gels. The authors traced back this quasi-on–off control of fluid permeation rates to a pressure-induced transition within the network structure of SR gels. This transition is based on the high mobility of the α -CD rings along the PEG chains. The permeation rate is closely related to pore-size distribution. At low pressure, the SR gel is more or less homogeneous in the distribution of α -CD dimers resulting in smaller pore sizes and a low permeation rate. When the imposed pressure increased above a critical value, p_{c2} , the dimers locally stacked together. As a result, the SR gels have a heterogeneous network structure with significantly larger pores and a higher permeation rate.

MULTIPLE RESPONSIVENESS

A growing number of gels responsive to multiple stimuli have recently been reported, which are smart materials that predictably adapt to combinations of different external stimuli.

Huang's crown-ether-appended supergelator DB24-A is a fascinating example (Figure 4).²⁸ The crown-ether moiety on DB24-A can form a pseudorotaxane with the dibenzylamine incorporated in another DB24-A molecule forming supra-molecular polymers. The chloride counterion is pivotal to achieve low critical gelation concentrations (CGC). The CGC of DB24-A in acetonitrile is only 0.6 wt % with chloride but 4.6 wt % with PF₆[−] counterions.²⁹ Eight different stimuli exist that trigger gel–sol transitions: The crown ether binds competitive cations such as K⁺, Na⁺, dibenzylammonium (DBA), paraquat, and Fe³⁺, which destroy the supramolecular polymer fibers. Triethylamine as a base leads to dethrading of dibenzylamine. Protection of the secondary amine with di-*tert*-butyl dicarbonate (Boc₂O) covalently blocks the dibenzyl ammonium binding site. Both stimuli can be reversed by addition of acid. As mentioned above, changing the counter-anions, for example, by precipitation of AgCl with silver trifluoroacetate, also induces a gel–sol transition, when the gelator concentration is between the two CGCs mentioned above. This example nicely shows how the host–guest chemistry of macrocycles can enrich the stimuli responsiveness.

Jiang et al.^{30,31} synthesized β -CD-modified CdS quantum dots (β -CD@QD) and azobenzene- (Azo) and ferrocene-functionalized (Fc) block copolymers (Figure 5). Mixing β -CD@QD with either one of the block copolymers forms a

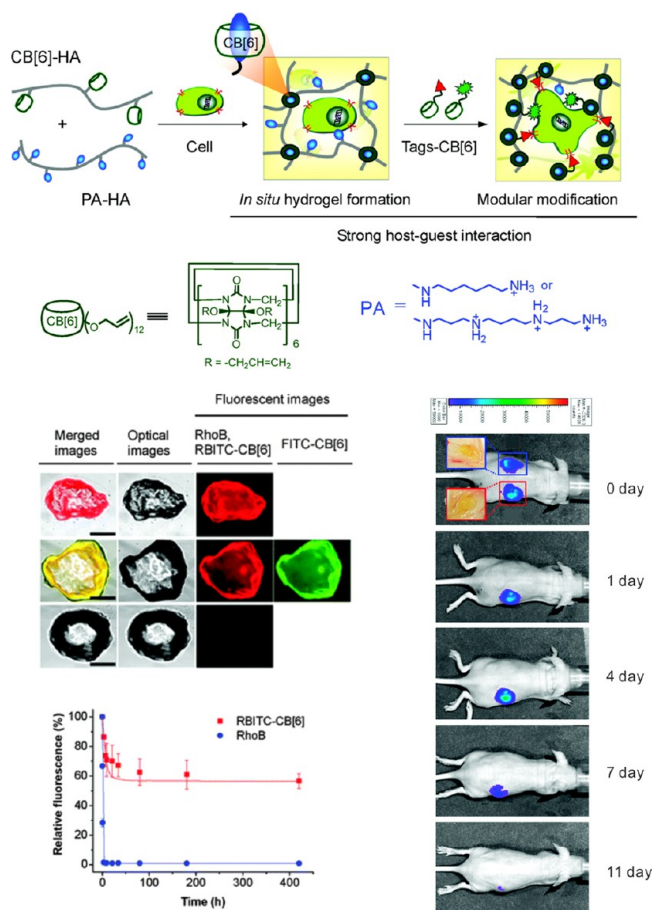


Figure 7. Schematic representation of the formation of supramolecular biocompatible hydrogel and its modular modification using highly selective and strong host–guest interactions of cucurbit[6]uril with polyamines. Adapted from ref 41 with kind permission. Copyright 2012 American Chemical Society.

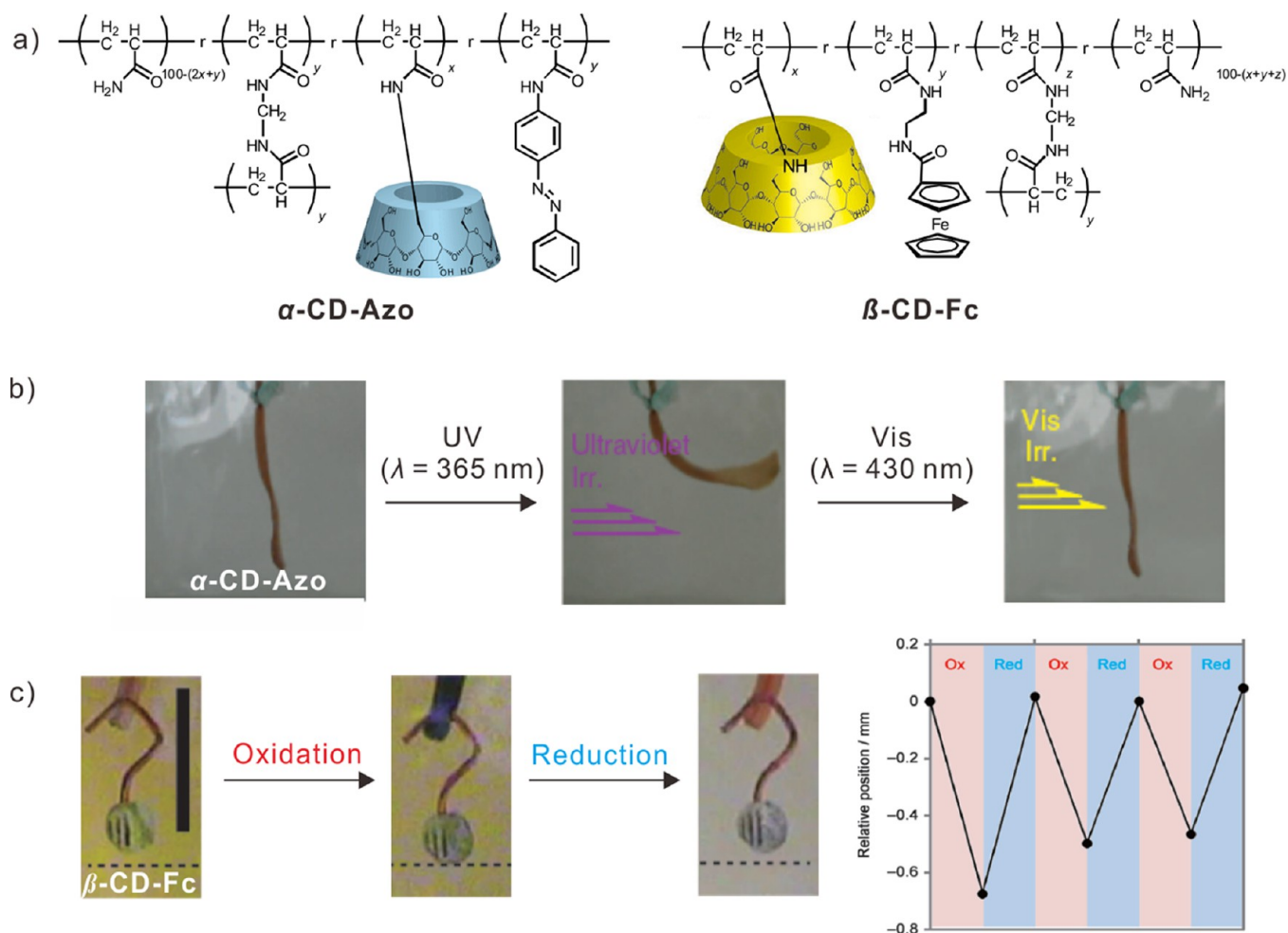


Figure 8. Artificial molecular actuators controllable by light and redox stimuli based on host–guest complexation of cyclodextrins with azobenzene and ferrocene. Adapted from ref 42 with kind permission from the Nature Publishing Group, copyright 2012, and from ref 43 with kind permission from Wiley-VCH, copyright 2013.

hybrid complex because of the inclusion of Azo or Fc in the cyclodextrin. The corresponding supramolecular gels exhibit thermo- and chemical responsiveness. In addition, the oxidation of the Fc moiety also stimulates the gel–sol transition. Following the same strategy, other materials like β -CD-functionalized graphene oxide sheets (CD-GO) form multi-stimuli-responsive gels.³²

■ RESPONSIVE REACTION MEDIA

Since chemical gels are interconnected by persistent non-reversible bonds, they are mechanically stable and can be considered permanent on most experiments' time scales. This feature is favorable for applications that require tough polymer materials, but it is unfavorable if these materials are to be further processed or recycled. In contrast, the tenability of the stability of supramolecular gels makes them promising candidates for responsive reaction media³³ and for immobilizing cargoes such as drugs or proteins that need to be released on demand.³ Shinkai's early crown-ether-substituted cholesterol gelators successfully served as removable templates for the fabrication of hollow silica nanotubes around the tubular gel fibers.³⁴

Recently, we proposed to utilize the selective responsiveness of a crown-ether-functionalized gelator for the immobilization and recycling of biocatalysts in Pickering emulsions (Figure 6).³⁵

The crown-ether-appended chiral gelator r-BC7 shows quite impressive gelation ability in a variety of solvents. Due to the crown ether, the resulting supramolecular gel is sensitive to multiple chemical stimuli, and the sol–gel phase transitions can be reversibly triggered by host–guest interactions. The 3D network in the gel is able to entrap the enzyme *Candida antarctica* lipase B and to release it upon the addition of potassium ions. Therefore, this gel system has been exploited as a novel matrix for enzyme-catalyzed reactions in organic chemistry. Pickering emulsions consist of microparticles that are stabilized by colloidal nanoparticles. Using a polar gelled phase inside these microparticles creates a suitable environment for the enzyme, which remains active, even though the medium surrounding the particles is a nonpolar organic solvent such as hexane. Nonpolar organic reactants nevertheless have access to the biocatalyst because of the large surface area of the microparticles. These particles are sufficiently stable to collect them after the reaction by centrifugation and reuse them in the next batch.

■ BIOMEDICAL APPLICATIONS

Cyclodextrins are macrocycles with excellent biocompatibility. They thus have attracted considerable attention as biomedically useful materials. Currently, cyclodextrins are the only family of macrocycles approved by the Food and Drug Administration to

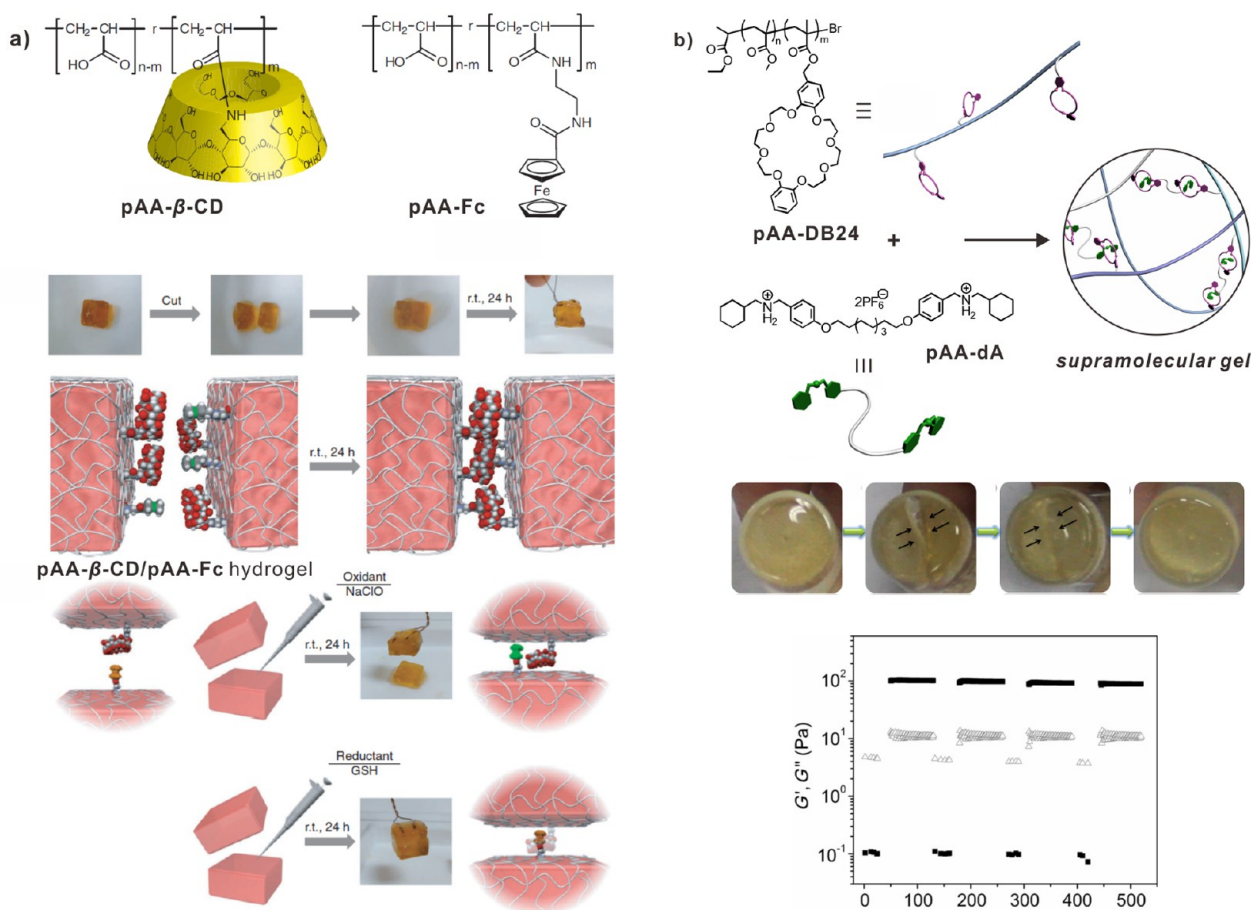


Figure 9. (a) Self-healable cyclodextrin-based supramolecular gels: The gel's healing ability is redox-responsive through the incorporated ferrocene side chains. Adapted from ref 44 with kind permission from the Nature Publishing Group, copyright 2011. (b) Self-healable crown-ether-based supramolecular gel based on crown ether/ammonium interactions. Adapted from ref 45 with kind permission from Wiley-VCH, copyright 2012.

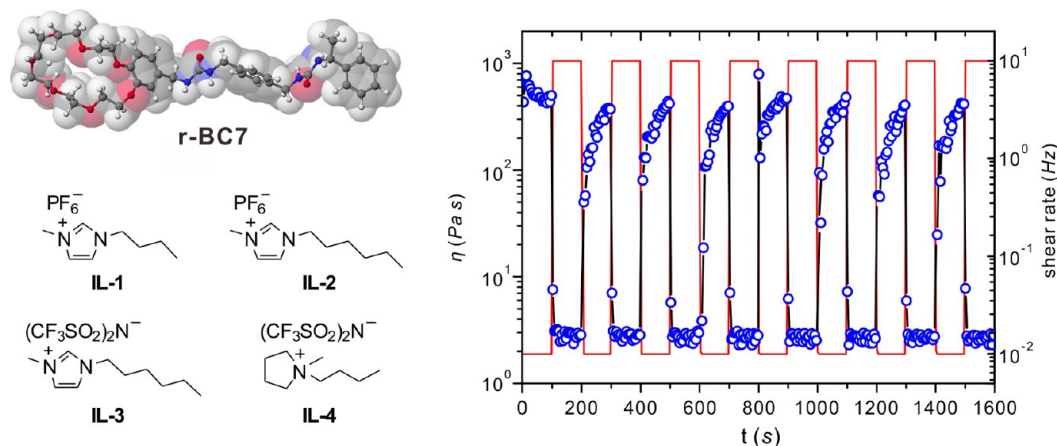


Figure 10. Self-recovering stimuli-responsive crown-ether-equipped supramolecular ionogels display fast recovery in step-rate time-sweep measurements. Adapted from ref 47 with kind permission of the Royal Society of Chemistry, copyright 2014.

be used in food and medical applications. In 1994, Li et al. reported the first necklace-like CD-polypseudorotaxane based on linear water-soluble polymers.⁹ The resulting polypseudorotaxane is biocompatible and shows thixotropic properties and shear-thinning and has been used as an injectable hydrogel drug-delivery system. Later, CD-based supramolecular hydrogels based on block copolymer poly(pseudo)rotaxanes flourished.³⁶ For example, Kros and co-workers recently developed a series of cyclodextrin-based photoresponsive hydrogels as injectable protein

carriers that release their load in a stimulus-controlled way.³⁷ In 2010, two research groups reported also cucurbiturils (CB[n]) to be generally nontoxic so that they can also be used in biomedical applications.^{38,39} Scherman's group designed CB[8]-based hydrogels and found that they can be employed for sustained therapeutic applications.⁴⁰

More recently, Kim's lab further extended the application of CB[6]-containing supramolecular gels toward cellular engineering. They reported an easy-to-prepare hydrogel using CB[6]- and

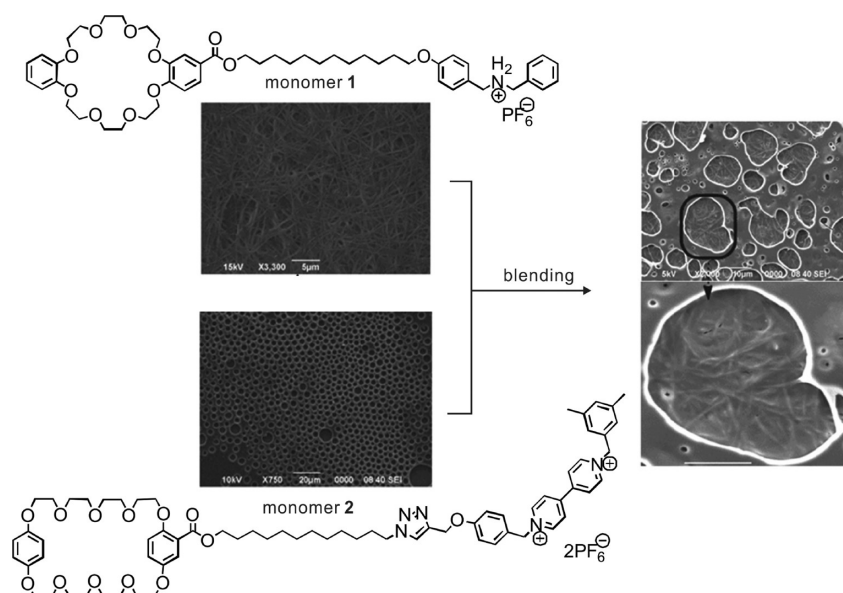


Figure 11. Microscopic self-sorting organization observed when two types of crown-ether monomers were blended. Adapted from ref 55 with kind permission from Wiley-VCH, copyright 2012.

polyamine-conjugated hyaluronic acids (CB[6]-HA and PA-HA; Figure 7).⁴¹ The strong host–guest interaction was used as a driving force for the cross-linking of biopolymer chains. After mixing of CB[6]-HA, PA-HA, and NIH3T3 cells, the gel, entrapping cells, formed *in situ* after 2 min. Cytocompatibility studies showed the resulting gels to possess high cell viability, enzymatic degradability, and negligible cytotoxicity, which are essential characteristics for their application to three-dimensional cellular engineering. Intriguingly, some uncomplexed 1,6-diaminohexane (DAH) moieties in the CB[6]/DAH-HA hydrogels provide additional groups for dynamic modular modification of the obtained hydrogels through the addition of CB[6] tagged with fluorescein isothiocyanate (FITC), rhodamine B derivatives, or RGD-based adhesion peptides. The authors demonstrated that treatment of the CB[6]/DAH-HA hydrogel with c(RGDyK)-CB[6] (c(RGDyK) is a promoter for cell adhesion) was able to postmodify the hydrogel as a stable RGD environment for efficiently proliferating the entrapped NHDF human fibroblast cells.

MECHANICAL MOTION

Macroscopic shape changes of gels induced by environmental stimuli are of particular interest for the creation of actuators and artificial muscles. Among the increasing number of successful muscle mimics, Harada's group developed a versatile scaffold of macrocycle-functionalized supramolecular actuators (Figure 8).⁴² The α -CD-Azo gel exhibits reversible deformation resulting in changes of both size and shape under UV–vis irradiation. Amazingly, the deformation of this supramolecular hydrogel depends on the direction of the incident light. Similarly, replacing the α -CD/Azo pair by β -CD and Fc units leads to a redox-responsive expansion and contraction of the resulting β -CD-Fc gel.⁴³

SELF-HEALING MATERIALS

Self-healing is crucial to the survival of living species. Aiming to extend lifetimes and ensure sustainability, supramolecular gels with self-healing properties are an interesting research topic. Two pieces of research from Harada's and Huang's groups used

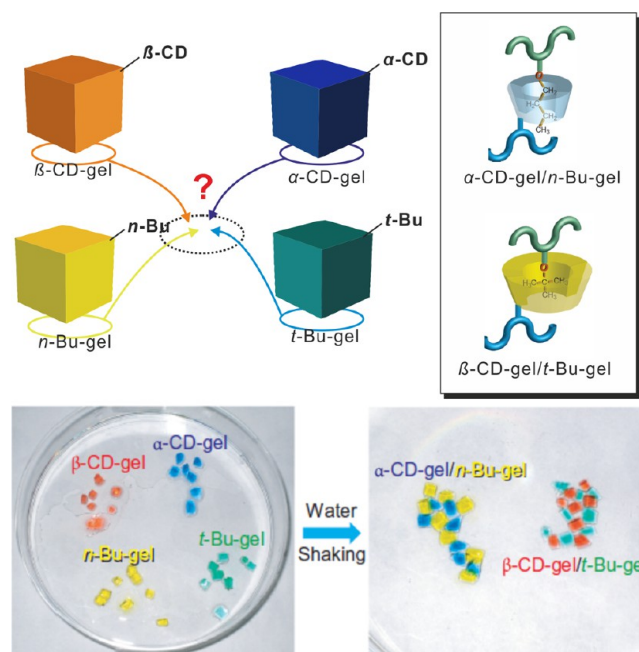


Figure 12. Self-sorting on a macroscopic level in “the party of gels”: The molecular recognition preferences at the microscopic level determine the binding preferences at the macroscopic level. Only those gel blocks that have matching recognition units interact with each other. Reprinted from ref 56 with kind permission from the Nature Publishing Group, copyright 2011.

host–guest complexes of macrocycles to develop self-healing supramolecular gels.^{44,45} As shown in Figure 9, both self-healing gels are based on poly(acrylic acid) backbones with different side chains. Harada et al. utilized cyclodextrins and ferrocenes as the recognition units, while Huang employed the crown-ether/secondary ammonium binding motif. Both groups demonstrated host–guest inclusion to be the key factor driving the healing process. Since the formation of the inclusion complex between Fc and β -CD is redox sensitive, self-healing of the pAA- β -CD/pAA-Fc hydrogel can be controlled by redox

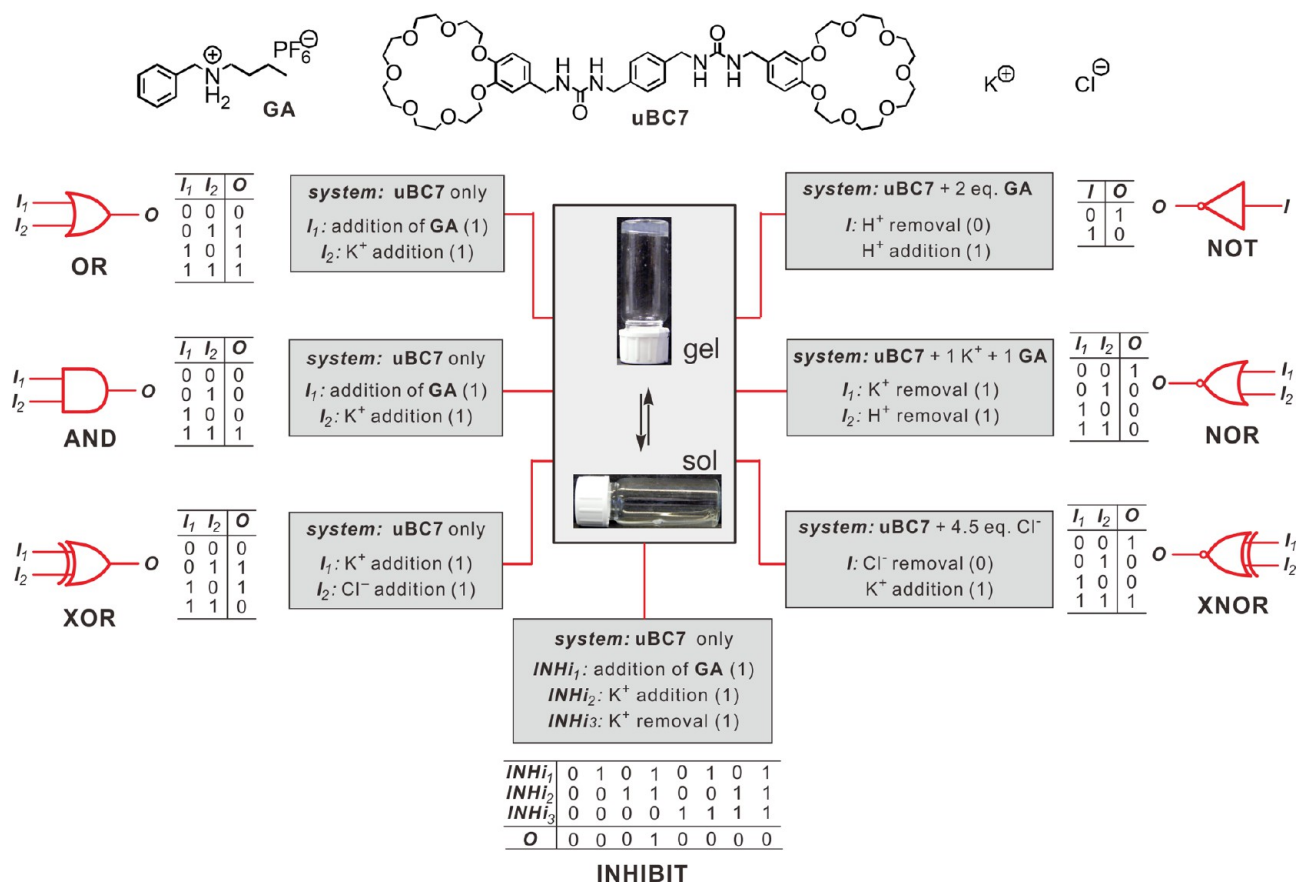


Figure 13. Seven logic gates constructed on the basis of multistimuli-responsive bis-urea gelator uBC7 and different combinations of chemical stimuli.

stimuli. Huang et al. extended the self-healing gels to supramolecular gels based on low molecular-weight gelators: A crown-ether based supramolecular gel was generated through orthogonal self-assembly of two homoditopic monomers and a transition metal cross-linker.⁴⁶

Self-healing was also observed recently for a supramolecular ionogel (Figure 10).⁴⁷ We serendipitously discovered that gelator r-BC7 forms gels not only in a number of organic solvents but also in ionic liquids. The mechanical strength of the resulting ionogels is significantly higher than that of the organogels. The storage moduli, G' , increased to levels in the range of 10^5 Pa, which is even comparable to that of cross-linked protein fibers. Moreover, the change of solvent causes the gel to exhibit unusually rapid self-recovering properties (Figure 10). Shear rate changes are quickly reflected in the mechanical properties. At low shear rates, the gels' viscosities are more than 2 orders of magnitude higher compared with those at high shear rates. When the shear rate is reduced again, the initial mechanical properties of the gel recover within ca. 100 s. Even though the ionic liquid is itself a guest for the crown ether, pseudorotaxane formation with secondary alkyl ammonium ions still induce gel-sol transitions. Consequently, the ionogels can be controlled through an external chemical stimulus. These gels are the first macrocycle-equipped supramolecular gels in pure ionic liquid that show self-healing.

■ FROM SUPRAMOLECULAR GELS TOWARD SYSTEMS CHEMISTRY

Stimuli-responsiveness is only the beginning, if one thinks about chemical systems exhibiting complex behavior. Quite

recently, the term systems chemistry⁴⁸ was coined for complex mixtures of molecules that are interconnected in a reactivity network and exhibit emergent properties. Self-organization phenomena can occur, if they operate far from thermodynamic equilibrium. Developing gels in this direction, creating, for example, spatiotemporal patterns depending on the sequence, amounts and types of stimuli added, remains challenging.⁴⁹ Yoshida's intriguing examples for the integration of oscillating Belousov-Zhabotinsky reactions into polymer gels represent one approach to construct unique gel materials.⁵⁰ The autocatalytic step causing the oscillations between two states of a redox catalyst, for example, causes viscosity oscillations of gels⁵¹ and achieves directional transport of macroscopic particles on the surface of gels.⁵² Similarly intriguing examples on the basis of supramolecular gels are not yet available, but a number of groups are working to implement systems chemistry in supramolecular gels. This field is thus still in its infancy, but several steps in this direction have been made.

Besides stimuli responsiveness, self-sorting phenomena are another central aspect for the realization of chemical systems.⁵³ As mentioned previously, dynamic fibrous gel architectures possess some similarity to the cell skeleton. Therefore, the self-sorted arrangement of other components across the fibrous skeleton is certainly important. The orthogonal self-assembly of supramolecular gels with surfactants reported by van Esch et al. can be seen as a method to construct cell architecture mimics.⁵⁴ Recent attempts by Huang et al. examined two different supramolecular polymers and their mixtures with respect to self-sorting phenomena and observed the formation of very

different superstructures for both pure polymers and a third one differing from both for the mixture (Figure 11).⁵⁵ Monomer 1 forms a supramolecular gel in which fibrous networks exist, while monomer 2 self-assembles into supramolecular polymers with honeycomb-like structures. Upon blending of these two monomers, a distinguished self-sorting organization of two types of microstructures was observed.

Self-sorting is not only achievable on the microscopic level of molecules in solution. Self-discriminating recognition on the microscopic scale can also be utilized to direct the assembly of macroscopic objects into larger aggregated structures. Harada's group⁵⁶ used two acrylamide gels equipped with two cyclodextrins of different sizes. They served as the host gels (α -CD-gel and β -CD-gel, respectively). *n*-Butyl (*n*-Bu) and *t*-butyl (*t*-Bu) groups were selected as the corresponding guests, which were also attached to polyacrylamide polymers (*n*-Bu-gel and *t*-Bu-gel, respectively). In solution, *t*-Bu groups bind strongly to β -CD, while the *n*-Bu group prefers α -CD. When differently colored gel pieces, each one containing one of the four side chains, were mixed and shaken in water (Figure 12), self-sorting was observed. Pieces of α -CD-gel selectively connect to *n*-Bu-gel blocks and β -CD-gel cubes exclusively bind to *t*-Bu-gel pieces producing perfectly self-sorted "gel islands". Such a macroscopic self-sorting molecular recognition can be further by controlled by other factors such as light.⁵⁷

Complex behavior can also be achieved in multistimuli-responsive gels, when different inputs cooperate as logic gates. Recently, we reported gelator uBC7 (Figure 13), which responds to different inputs.⁵⁸ The complexation of K^+ , the formation of pseudorotaxanes with secondary ammonium ions, or the disruption of hydrogen bonds by chloride addition are stimuli, whose effects can be reversed by addition of a cryptand, deprotonation and subsequent dethreading of the ammonium ion, and the precipitation of the chloride ions by Ag^+ or K^+ , respectively. With this gelator, seven different logic gates including the three-input INHIBIT gate can be constructed, depending on the choice of inputs as well as the additional components of the chemical system added to the gelator initially. With respect to complex behavior, it is interesting to note that the OR and the AND gate operate on the basis of the same two inputs. They differ by the amount of signal present. If only one equivalent of GA and K^+ are used, the resulting gate is an AND gate. When two equivalents of these two inputs are added, the result is an OR gate.

The last example to be discussed here combines almost all aspects of self-organization of complex systems. It is based on a very simple dynamic combinatorial library containing only one peptide-substituted 1,3-dithiobenzene monomer, PSH (Figure 14).⁵⁹ Under conditions that allow reversible disulfide formation, macrocycles of different sizes can form and equilibrate with each other. Through peptide-peptide β -sheet interactions, these macrocycles can stack and form fibers. Most interestingly, the library composition depends to a large extent on the particular way in which mechanical energy is provided: Without any agitation, three- and four-membered rings are most prominent, with shaking, hexamers prevail, and heptamers are most prominent when the solution is stirred. Upon irradiation with light of the appropriate wavelength, the disulfides can be cleaved and cross-connected between different layers in the stack resulting in photoinduced gelation as shown in Figure 14.⁶⁰

The surprisingly complex mechanosensitivity of these systems can be explained when one invokes the following three points: (a) The more peptides a macrocycle incorporates,

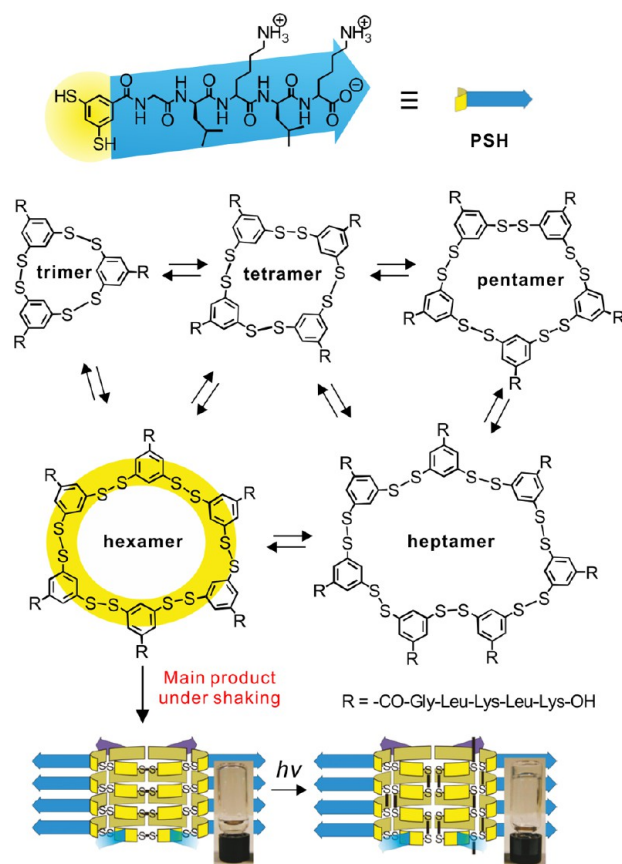


Figure 14. Schematic representation of Otto's hydrogel formed upon photoinduced covalent capture of macrocycle stacks from dynamic combinatorial libraries. The agitation condition plays a significant role in exclusively producing hexameric macrocycles. Reprinted from ref 60 with kind permission from Wiley-VCH, copyright 2011.

the more stable the stacks become. (b) A macrocycle already present in solution can act as a template for the formation of another one with the same number of PSH monomers incorporated. (c) Agitation leads to an autocatalytic growth when fibers are cut into pieces. Each cut doubles the number of templating fiber ends at which new macrocycles can attach. Different ways to apply mechanical force exert different strength of mechanical stress. Those fibers that bind with the appropriate strength are then amplified. Too loosely bound monomers will not template efficiently because the templating interactions are too weak. Too strongly bound fibers will survive, and autocatalytic growth is not initiated. Finally, the dynamic combinatorial library shifts toward one of the macrocycles as the main product depending on the type of agitation. This example is intriguing also for the following aspect: Usually, dynamic combinatorial libraries are considered to move into thermodynamic equilibrium. Otto's system clearly shows that the application of a constant energy flow through the system by agitation can clearly shift the system away from the equilibrium.

CONCLUSIONS

The marriage of macrocycles and supramolecular gels brings numerous opportunities for designing novel responsive functional gels. We have highlighted recent advances in the fabrication and application of functional gel materials based on the incorporation of macrocycles and their dynamic host-guest chemistry. However, there is still much room to expand

this area. Possible future directions may include the following aspects: (1) The utility of newly developed macrocycles; most research focuses on the “classical” macrocyclic work horses well-known in supramolecular chemistry. (2) There is still large space for exploring functions of gel materials. Many naturally existing gel objects are hard to mimic by artificial analogues. One intriguing example, for example, is the shark’s skin, which is covered by a gel layer to provide an antifouling effect. (3) The integration of many existing or new gels into complex chemical systems is a largely unexplored area, from which effects will emerge that are beyond our imagination now. Although many stimuli-responsive gels are already known, the systems chemistry aspect appears to be one of most promising routes to smart responsive materials.

AUTHOR INFORMATION

Corresponding Author

*E-mail: c.schalley@fu-berlin.de.

Notes

The authors declare no competing financial interest.

Biographies

Zhenhui Qi received his M.Sc. under the supervision of Prof. Junqiu Liu and Prof. Jiacong Shen from Jinlin University, China in 2009. Then, he obtained his Ph.D. degree at Freie Universität Berlin, Germany, in the group of Prof. Dr. Christoph A. Schalley. His research interests focus on responsive materials, functional surfaces, and the mass spectrometric characterization of noncovalent complexes.

Christoph A. Schalley received his Ph.D. with Prof. Helmut Schwarz at Technical University Berlin followed by a postdoctoral position with Professor Julius Rebek, Jr. at the Scripps Research Institute in La Jolla. His research interest lies in supramolecular chemistry and mass spectrometry. He authored more than 180 publications and edited 7 books. For his work in mass spectrometry and gas-phase chemistry of noncovalent complexes, he was awarded the Matlack-Herzog Prize from the German Society for Mass Spectrometry in 2006.

REFERENCES

- (1) de Jong, J. J. D.; Feringa, B. L.; van Esch, J. Responsive Molecular Gels. In *Molecular Gels. Materials with Self-Assembled Fibrillar Networks*; Weiss, R. G., Terech, P., Eds.; Springer: Dordrecht, the Netherlands, 2006; pp 895–927.
- (2) George, M.; Weiss, R. G. Molecular Organogels. *Soft Matter Composed of Low-Molecular-Mass Organic Gelators and Organic Liquids?* *Acc. Chem. Res.* **2006**, *39*, 489–497.
- (3) Hirst, A. R.; Escuder, B.; Miravet, J. F.; Smith, D. K. High-Tech Applications of Self-Assembling Supramolecular Nanostructured Gel-Phase Materials: From Regenerative Medicine to Electronic Devices. *Angew. Chem., Int. Ed.* **2008**, *47*, 8002–8018.
- (4) Sangeetha, N. M.; Maitra, U. Supramolecular Gels: Functions and Uses. *Chem. Soc. Rev.* **2005**, *34*, 821–836.
- (5) Buerkle, L. E.; Rowan, S. J. Supramolecular Gels Formed from Multi-component Low Molecular Weight Species. *Chem. Soc. Rev.* **2012**, *41*, 6089–6102.
- (6) Steed, J. W.; Atwood, J. L.: *Supramolecular Chemistry*; Wiley: New York, 2000.
- (7) Jiang, W.; Schalley, C. A. Integrative Self-Sorting is a Programming Language for High Level Self-Assembly. *Proc. Natl. Acad. Sci. U.S.A.* **2009**, *106*, 10425–10429.
- (8) Schalley, C. A.; Beizai, K.; Vögtle, F. On the Way to Rotaxane-Based Molecular Motors: Studies in Molecular Mobility and Topological Chirality. *Acc. Chem. Res.* **2001**, *34*, 465–476.
- (9) Li, J.; Harada, A.; Kamachi, M. Sol–Gel Transition during Inclusion Complex Formation between α -Cyclodextrin and High

Molecular Weight Poly(ethylene glycol)s in Aqueous Solution. *Polym. J.* **1994**, *26*, 1019–1026.

- (10) Liu, K. L.; Zhang, Z. X.; Li, J. Supramolecular Hydrogels Based on Cyclodextrin-Polymer Polypseudorotaxanes: Materials Design and Hydrogel Properties. *Soft Matter* **2011**, *7*, 11290–11297.
- (11) Foster, J. A.; Steed, J. W. Exploiting Cavities in Supramolecular Gels. *Angew. Chem., Int. Ed.* **2010**, *49*, 6718–6724.
- (12) Suzuki, Y.; Taira, T.; Osakada, K. Physical Gels Based on Supramolecular Gelators, Including Host-Guest Complexes and Pseudorotaxanes. *J. Mater. Chem.* **2011**, *21*, 930–938.
- (13) Chen, G.; Jiang, M. Cyclodextrin-Based Inclusion Complexation Bridging Supramolecular Chemistry and Macromolecular Self-Assembly. *Chem. Soc. Rev.* **2011**, *40*, 2254–2266.
- (14) Zheng, B.; Wang, F.; Dong, S.; Huang, F. Supramolecular Polymers Constructed by Crown Ether-Based Molecular Recognition. *Chem. Soc. Rev.* **2012**, *41*, 1621–1636.
- (15) Guo, D.-S.; Liu, Y. Calixarene-Based Supramolecular Polymerization in Solution. *Chem. Soc. Rev.* **2012**, *41*, 5907–5921.
- (16) Dong, S.; Zheng, B.; Wang, F.; Huang, F. Supramolecular Polymers Constructed from Macrocyclic-Based Host-Guest Molecular Recognition Motifs. *Acc. Chem. Res.* **2014**, DOI: 10.1021/ar5000456.
- (17) Hsueh, S.-Y.; Kuo, C.-T.; Lu, T.-W.; Lai, C.-C.; Liu, Y.-H.; Hsu, H.-F.; Peng, S.-M.; Chen, C.-h.; Chiu, S.-H. Acid/Base- and Anion-Controllable Organogels Formed From a Urea-Based Molecular Switch. *Angew. Chem., Int. Ed.* **2010**, *49*, 9170–9173.
- (18) Verdejo, B.; Rodriguez-Llansola, F.; Escuder, B.; Miravet, J. F.; Ballester, P. Sodium and pH Responsive Hydrogel Formation by the Supramolecular System Calix[4]pyrrole Derivative/Tetramethylammonium Cation. *Chem. Commun.* **2011**, *47*, 2017–2019.
- (19) Yan, X.; Xu, D.; Chi, X.; Chen, J.; Dong, S.; Ding, X.; Yu, Y.; Huang, F. A Multiresponsive, Shape-Persistent, and Elastic Supramolecular Polymer Network Gel Constructed by Orthogonal Self-Assembly. *Adv. Mater.* **2012**, *24*, 362–369.
- (20) Xu, H.; Rudkevich, D. M. Reversible Chemistry of CO₂ in the Preparation of Fluorescent Supramolecular Polymers. *J. Org. Chem.* **2004**, *69*, 8609–8617.
- (21) Gasnier, A. I.; Royal, G.; Terech, P. Metallo-Supramolecular Gels Based on a Multitopic Cyclam Bis-Terpyridine Platform. *Langmuir* **2009**, *25*, 8751–8762.
- (22) Maeda, K.; Mochizuki, H.; Osato, K.; Yashima, E. Stimuli-Responsive Helical Poly(phenylacetylene)s Bearing Cyclodextrin Pendants that Exhibit Enantioselective Gelation in Response to Chirality of a Chiral Amine and Hierarchical Super-Structured Helix Formation. *Macromolecules* **2011**, *44*, 3217–3226.
- (23) Hu, J.; Zhang, G.; Liu, S. Enzyme-Responsive Polymeric Assemblies, Nanoparticles and Hydrogels. *Chem. Soc. Rev.* **2012**, *41*, 5933–5949.
- (24) Segarra-Maset, M. D.; Nebot, V. J.; Miravet, J. F.; Escuder, B. Control of Molecular Gelation by Chemical Stimuli. *Chem. Soc. Rev.* **2013**, *42*, 7086–7098.
- (25) Zhou, J.-L.; Chen, X.-J.; Zheng, Y.-S. Heat-Set Gels and Egg-Like Vesicles Using Two Component Gel System Based on Chiral Calix[4]arenes. *Chem. Commun.* **2007**, 5200–5202.
- (26) Danjo, H.; Hirata, K.; Yoshigai, S.; Azumaya, I.; Yamaguchi, K. Back to Back Twin Bowls of D₃-Symmetric Tris(spiroborate)s for Supramolecular Chain Structures. *J. Am. Chem. Soc.* **2009**, *131*, 1638–1639.
- (27) Katsuno, C.; Konda, A.; Urayama, K.; Takigawa, T.; Kidowaki, M.; Ito, K. Pressure-Responsive Polymer Membranes of Slide-Ring Gels with Movable Cross-Links. *Adv. Mater.* **2013**, *25*, 4636–4640.
- (28) Dong, S.; Zheng, B.; Xu, D.; Yan, X.; Zhang, M.; Huang, F. A Crown Ether Appended Super Gelator with Multiple Stimulus Responsiveness. *Adv. Mater.* **2012**, *24*, 3191–3195.
- (29) Dong, S.; Luo, Y.; Yan, X.; Zheng, B.; Ding, X.; Yu, Y.; Ma, Z.; Zhao, Q.; Huang, F. A Dual-Responsive Supramolecular Polymer Gel Formed by Crown Ether Based Molecular Recognition. *Angew. Chem., Int. Ed.* **2011**, *50*, 1905–1909.

- (30) Liu, J.; Chen, G.; Guo, M.; Jiang, M. Dual Stimuli-Responsive Supramolecular Hydrogel Based on Hybrid Inclusion Complex (HIC). *Macromolecules* **2010**, *43*, 8086–8093.
- (31) Du, P.; Liu, J.; Chen, G.; Jiang, M. Dual Responsive Supramolecular Hydrogel with Electrochemical Activity. *Langmuir* **2011**, *27*, 9602–9608.
- (32) Liu, J.; Chen, G.; Jiang, M. Supramolecular Hybrid Hydrogels from Noncovalently Functionalized Graphene with Block Copolymers. *Macromolecules* **2011**, *44*, 7682–7691.
- (33) Díaz Díaz, D.; Kuhbeck, D.; Koopmans, R. J. Stimuli-Responsive Gels As Reaction Vessels and Reusable Catalysts. *Chem. Soc. Rev.* **2011**, *40*, 427–448.
- (34) Jung, J. H.; Ono, Y.; Hanabusa, K.; Shinkai, S. Creation of Both Right-Handed and Left-Handed Silica Structures by Sol–Gel Transcription of Organogel Fibers Composed of Chiral Diaminocyclohexane Derivatives. *J. Am. Chem. Soc.* **2000**, *122*, 5008–5009.
- (35) Qi, Z.; Wu, C.; Malo de Molina, P.; Sun, H.; Schulz, A.; Griesinger, C.; Gradzielski, M.; Haag, R.; Ansorge-Schumacher, M. B.; Schalley, C. A. Fibrous Networks with Incorporated Macrocycles: A Chiral Stimuli-Responsive Supramolecular Supergelator and Its Application to Biocatalysis in Organic Media. *Chem.—Eur. J.* **2013**, *19*, 10150–10159.
- (36) Li, J. Self-Assembled Supramolecular Hydrogels Based on Polymer - Cyclodextrin Inclusion Complexes for Drug Delivery. *NPG Asia Mater.* **2010**, *2*, 112–118.
- (37) Peng, K.; Tomatsu, I.; Kros, A. Light Controlled Protein Release from a Supramolecular Hydrogel. *Chem. Commun.* **2010**, *46*, 4094–4096.
- (38) Hettiarachchi, G.; Nguyen, D.; Wu, J.; Lucas, D.; Ma, D.; Isaacs, L.; Briken, V. Toxicology and Drug Delivery by Cucurbit[n]uril Type Molecular Containers. *PLoS One* **2010**, *5*, No. e10514.
- (39) Uzunova, V. D.; Cullinane, C.; Brix, K.; Nau, W. M.; Day, A. I. Toxicity of Cucurbit[7]uril and Cucurbit[8]uril: An Exploratory in Vitro and in Vivo Study. *Org. Biomol. Chem.* **2010**, *8*, 2037–2042.
- (40) Appel, E. A.; Loh, X. J.; Jones, S. T.; Dreiss, C. A.; Scherman, O. A. Sustained Release of Proteins from High Water Content Supramolecular Polymer Hydrogels. *Biomaterials* **2012**, *33*, 4646–4652.
- (41) Park, K. M.; Yang, J.-A.; Jung, H.; Yeom, J.; Park, J. S.; Park, K.-H.; Hoffman, A. S.; Hahn, S. K.; Kim, K. In Situ Supramolecular Assembly and Modular Modification of Hyaluronic Acid Hydrogels for 3D Cellular Engineering. *ACS Nano* **2012**, *6*, 2960–2968.
- (42) Takashima, Y.; Hatanaka, S.; Otsubo, M.; Nakahata, M.; Kakuta, T.; Hashidzume, A.; Yamaguchi, H.; Harada, A. Expansion–Contraction of Photoresponsive Artificial Muscle Regulated by Host–Guest Interactions. *Nat. Commun.* **2012**, *3*, No. 1270.
- (43) Nakahata, M.; Takashima, Y.; Hashidzume, A.; Harada, A. Redox-Generated Mechanical Motion of a Supramolecular Polymeric Actuator Based on Host–Guest Interactions. *Angew. Chem., Int. Ed.* **2013**, *52*, 5731–5735.
- (44) Nakahata, M.; Takashima, Y.; Yamaguchi, H.; Harada, A. Redox-Responsive Self-Healing Materials Formed from Host–Guest Polymers. *Nat. Commun.* **2011**, *2*, No. 511.
- (45) Zhang, M.; Xu, D.; Yan, X.; Chen, J.; Dong, S.; Zheng, B.; Huang, F. Self-Healing Supramolecular Gels Formed by Crown Ether Based Host–Guest Interactions. *Angew. Chem., Int. Ed.* **2012**, *51*, 7011–7015.
- (46) Yan, X.; Xu, D.; Chen, J.; Zhang, M.; Hu, B.; Yu, Y.; Huang, F. A Self-Healing Supramolecular Polymer Gel with Stimuli-Responsiveness Constructed by Crown Ether Based Molecular Recognition. *Polym. Chem.* **2013**, *4*, 3312–3322.
- (47) Qi, Z.; Traulsen, N. L.; Malo de Molina, P.; Schlaich, C.; Gradzielski, M.; Schalley, C. A. Self-Recovering Stimuli-Responsive Macrocyclic-Equipped Supramolecular Ionogels with Unusual Mechanical Properties. *Org. Biomol. Chem.* **2014**, *12*, 503–510.
- (48) von Kiedrowski, G.; Otto, S.; Herdewijn, P. Welcome Home, Systems Chemists! *J. Syst. Chem.* **2010**, *1*, 1–6.
- (49) Giuseppone, N. Toward Self-Constructing Materials: A Systems Chemistry Approach. *Acc. Chem. Res.* **2012**, *45*, 2178–2188.
- (50) Yoshida, R. Self-Oscillating Gels Driven by the Belousov-Zhabotinsky Reaction as Novel Smart Materials. *Adv. Mater.* **2010**, *22*, 3463–3483.
- (51) Yoshida, R.; Takahashi, T.; Yamaguchi, T.; Ichijo, H. Self-Oscillating Gel. *J. Am. Chem. Soc.* **1996**, *118*, 5134–5135.
- (52) Murase, Y.; Maeda, S.; Hashimoto, S.; Yoshida, R. Design of a Mass Transport Surface Utilizing Peristaltic Motion of a Self-Oscillating Gel. *Langmuir* **2009**, *25*, 483–489.
- (53) Safont-Sempere, M. M.; Fernández, G.; Würthner, F. Self-Sorting Phenomena in Complex Supramolecular Systems. *Chem. Rev.* **2011**, *111*, 5784–5814.
- (54) Brizard, A.; Stuart, M.; van Bommel, K.; Friggeri, A.; de Jong, M.; van Esch, J. Preparation of Nanostructures by Orthogonal Self-Assembly of Hydrogelators and Surfactants. *Angew. Chem., Int. Ed.* **2008**, *47*, 2063–2066.
- (55) Dong, S.; Yan, X.; Zheng, B.; Chen, J.; Ding, X.; Yu, Y.; Xu, D.; Zhang, M.; Huang, F. A Supramolecular Polymer Blend Containing Two Different Supramolecular Polymers through Self-Sorting Organization of Two Heteroditopic Monomers. *Chem.—Eur. J.* **2012**, *18*, 4195–4199.
- (56) Harada, A.; Kobayashi, R.; Takashima, Y.; Hashidzume, A.; Yamaguchi, H. Macroscopic Self-Assembly through Molecular Recognition. *Nat. Chem.* **2011**, *3*, 34–37.
- (57) Yamaguchi, H.; Kobayashi, Y.; Kobayashi, R.; Takashima, Y.; Hashidzume, A.; Harada, A. Photoswitchable Gel Assembly Based on Molecular Recognition. *Nat. Commun.* **2012**, *3*, 603.
- (58) Qi, Z.; Malo de Molina, P.; Jiang, W.; Wang, Q.; Nowosinski, K.; Schulz, A.; Gradzielski, M.; Schalley, C. A. Systems Chemistry: Logic Gates Based on the Stimuli-Responsive Gel-Sol Transition of a Crown Ether-Functionalized Bis(urea) Gelator. *Chem. Sci.* **2012**, *3*, 2073–2082.
- (59) Carnall, J. M.; Waudby, C. A.; Belenguer, A. M.; Stuart, M. C.; Peyralans, J. J.; Otto, S. Mechanosensitive Self-Replication Driven by Self-Organization. *Science* **2010**, *327*, 1502–1506.
- (60) Li, J.; Carnall, J. M. A.; Stuart, M. C. A.; Otto, S. Hydrogel Formation upon Photoinduced Covalent Capture of Macrocyclic Stacks from Dynamic Combinatorial Libraries. *Angew. Chem., Int. Ed.* **2011**, *50*, 8384–8386.