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Hydrogels *locked* by molecular recognition aiming at responsiveness and functionality

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The principle of molecular recognition originating from the concept of lock-and-key has been one of the foundation stones for modern chemistry and biology. Molecular recognition in either biomolecules or synthetic molecules leads to non-covalent linkages, which are featured by responsiveness, reversibility and competition, differing from the covalent bonds. Therefore, recently, this concept has been introduced to and employed in the field of functional materials with great success. In this review, these materials will be examined from the molecular recognition point of view, without considering the origins of the binding pairs involved. First, the structural characters of hydrogels *locked* by molecular recognition are discussed in detail with emphasis on the chemical structure and architectures of the interaction pairs and the corresponding polymers. As the new hydrogel materials inherit the reversible advantages from non-covalent interactions as well as the specificities of the host–guest or ligand–acceptor pairs, their corresponding responses to various stimuli are discussed in the second part of this review. Compared to the smart materials made of responsive polymers, the hydrogels *locked* by molecular recognition are featured by the precise control of the responsiveness to various environmental stimuli *via* sophisticated design of the interaction sites by changing their chemical structures, density location and linking chemistry to the polymer backbones *etc.* Finally, representative applications of these hydrogels are briefly described.

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1 Introduction

Molecular recognition, initiated by Fischer, is a concept in chemistry with about 100 years of history. He proposed that there was a lock-and-key principle for enzyme specificity to sugars,[1] which was greatly related to the fit of the geometric

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Guosong Chen got her BA in the Chemistry Department, Nankai University, China. She stayed in the same department and got her PhD in 2006, working on cyclodextrin-based supramolecular chemistry. Then she did her postdoctoral work on carbohydrate chemistry in the Chemistry Department, Iowa State University, US. In 2009, she joined Prof. Ming Jiang's group as a lecturer in the Department of Macromolecular Science at Fudan University. She was promoted to associate professor in Oct. 2011. Sharing with Prof. M. Jiang, she got the "Feng Xinde Polymer Price" in 2012, which was sponsored by Elsevier. Currently, she is working on macromolecular self-assembly inspired by supramolecular chemistry and glycoscience.

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shape and chirality between the sugar molecules and the binding sites of enzymes.[2] In fact the "lock-and-key" interactions are transient even in their equilibrium state, although the word "*locked*" is used to represent the binding state of the interaction species in this paper. Promoted by the achievements of modern biology, many delicate binding pairs of acceptors or substrates (*e.g.* proteins) with their ligands have been revealed, especially since the end of the last century.[3] Now this principle is more than well-known and crucial for many biological processes, including signal transportation, gene transcription and regulation *etc.*

Chemists are good at learning from nature and synthesizing new compounds to mimic the merits of the natural ones. Many synthetic or semi-synthetic acceptors have been explored after the synthesis of crown ethers by Peterson, including the families of cyclodextrins,[4–6] calixarenes,[7] cucurbiturils[8] *etc.*, with emphasis on their molecular recognition abilities for various molecules and ions, which have promoted the growth of supramolecular chemistry.[9] In parallel to acceptors and ligands in biochemistry, here the interacting counterparts are denoted as hosts and guests by supramolecular chemists, where the 'host' molecules possessing convergent binding sites are capable of enclosing the 'guest' molecules with divergent binding sites *via* non-covalent interactions.[10] Selective binding ability remains as the most important character of host–guest pairs, which is greatly influenced by van der Waals and hydrophobic interactions, size/shape fitness and electron density of the two molecules.[11] Since then, the lock-and-key concept has in fact stepped over synthetic and biological compounds.

Standing on the shoulders of giants, scientists right now are more focusing on functional materials based on the principles at molecular/supramolecular levels. One of the most attractive such materials is hydrogel.[12] It is a kind of soft material containing a rather low percentage of solid components with a large amount of water,[13] which can be easily identified by the simple "inversion test".[14] Recently, hydrogels with responses to environmental stimuli became an even more fascinating research area because of their theoretical values and promising applications.[15] Hydrogels are traditionally made of polymeric networks, but now a variety of new building blocks and structures for hydrogels bloom in the new century. Generally, responsive polymeric hydrogels can be divided into two categories: first, the environmental responses to temperature, pH, and light irradiation *etc.* are caused by the inherent characters of the polymeric backbone or the major component. This has been the major part of the responsive polymeric hydrogels and has already been reviewed by a few research groups.[16–19] In the second type of hydrogels, the inter-polymer linkage, which is always the minor moiety of the hydrogel, plays a key role in the responsiveness.[20,21] In this category, the hydrogel formation is due to the inter-polymer chains being *locked* by the linkage of molecular recognition and the gel-to-sol transition or swelling state may be realized by *unlocking* the linkage under environmental stimuli. In our opinion, this second type of hydrogel is more promising, attractive and challenging, because the responsiveness can be tuned by the specific changes of the localized linkages, which may provide more room for us to design multi-functional materials, irrespective of the inherent responsiveness of polymer chains. In this review, we summarize the structure features, responsiveness, applications of hydrogels controlled by molecular recognition, *i.e.* hosts and guests, or acceptors and ligands. In our discussion, we try to cross the boundary of interactions between the ligand and acceptor in biological systems and the host and guest in synthetic compounds, as in our opinion, the common features of the interactions existing respectively in the biological and synthetic systems will help us develop new bio-related materials in further inter-disciplinary studies. In addition, we are following the general "convergent–divergent" scope of molecular recognition (*i.e.* in short, host includes guest, acceptor recognizes ligand), thus other interesting reversible interactions *e.g.* dynamic covalent bond,[22–24] multiple hydrogen bond and metal–ligand interactions have been ignored. From this viewpoint, hydrogels with only recognition sites covalently bound to polymer chains cannot be discussed, although some of them also have attractive responsive properties from molecular recognition. It is worth mentioning that, although most of the hydrogels in this review are made of polymers, some examples, *i.e.* supramolecular hydrogels of small molecules, are included, since they have shown comparable properties to those from polymers and are growing rapidly as a newly emerging research branch in materials science.[25–28]

Ming Jiang graduated from the Chemistry Department at Fudan University, China in 1960. Since then he has served within the Chemistry, Materials and Macromolecular Science Department at Fudan University as assistant, lecturer and then as associate professor. He was promoted to professor in 1988. He was also visiting scientist at the University of Liverpool, UK from 1979 to 1981. Professor Jiang was elected Member of the Chinese Academy of Sciences in 2005 and Fellow of Royal Society of Chemistry in 2009. His research is mainly in physical chemistry of polymers and supramolecular chemistry with emphasis on macromolecular self-assembly.

2 Molecular recognition pairs

Various "lock" and "key" molecules used in constructing the hydrogels *locked* by molecular recognition discussed in this review are shown in Fig. 1. The synthetic host molecules include crown ethers,[29,30] cyclodextrins (CDs)[31–33] and cucurbit[8]urils (CB[8]s).[34,35] All of them have ring structures, which can accommodate guest molecules, *via* inclusion complexation. Among the three families of hosts, CDs are emphasized in this review because of their satisfactory binding ability and hydrophilicity. Although calixarenes are widely used as hosts,[36] generally they form organogels[37] due to their hydrophobicity,

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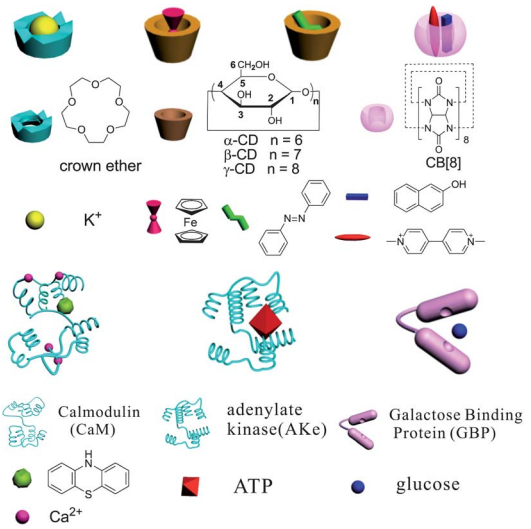

Fig. 1 Cartoons of structures of various lock-and-key molecules discussed in this review (the cartoon symbols for each of the interaction units here are used in all the figures below).

which is beyond the scope of this review. This also explains the rather limited contributions from CBs and crown ethers compared to those from CDs. For the biological acceptors, different proteins, including calmodulin (CaM),[38] adenylate kinase (AKe),[39] and glucose binding protein (GBP),[40] will be discussed together with their corresponding ligands (Fig. 1).

The common strategies to achieve the reversibility of hydrogels *via* responsiveness of host–guest pairs are shown in Fig. 2. α-CD can accommodate *trans*-azobenzene (*trans*-Azo) much more strongly than its *cis* isomer, and the *trans–cis* isomerization can be easily achieved by UV-vis light irradiation (Fig. 2A).[41,42] Similarly, β-CDs bind to the neutral compound ferrocene (Fc) much more strongly than to its oxidized state, ferrocenium ion (Fc^+) (Fig. 2B).[43,44] For CB[8], one host cavity can include two different guest molecules, typically a viologen and a 2-naphthol with 1 : 1 : 1 (host : guest1 : guest2) ratio, and the association and dissociation of this triplex can be tuned by the redox state of viologen (Fig. 2C).[35] Furthermore, for a given host–guest complex, its dissociation could be generally realized by supramolecular means, *i.e.* by addition of a competitive host or guest, which may form a stronger new pair than the original one (Fig. 2D).[45] Sometimes it is called the chemical response of the complexation in addition to the well-known optical and electrical responses. Similarly, binding to a ligand may induce the conformational change of the protein, which also contributes greatly to responsive hydrogels (Fig. 2E).[38] Regarding the soft materials with proteins as one component, this review will focus more on the hydrogels that have proteins covalently attached to the backbone, in order to compare to their synthetic counterparts. In this case, more synthetic difficulties are encountered, which limits the amount of reports. In addition, the hydrogels made by molecular imprinting are not included in this review.

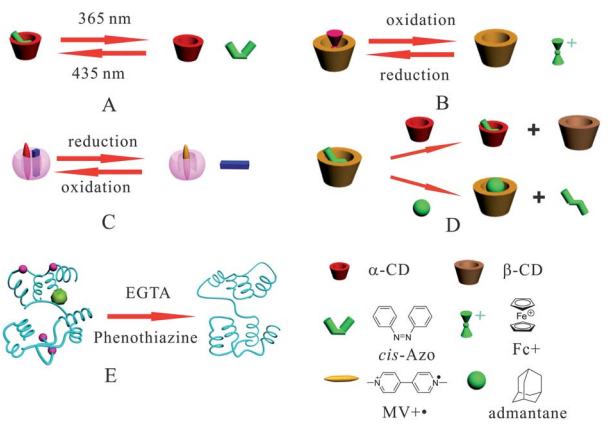

Fig. 2 Typical responsive host–guest pairs (the cartoon symbols for each of the interaction units here are used in all the figures below).

3 Structural features of interacting components

Generally, polymeric hydrogels are composed of a 3D network of polymers, while supramolecular hydrogels[46,47] are more commonly constructed by fibers and tubes made of supramolecular polymers. In both structures, in order to incorporate appropriate responsiveness, a dedicated design of the chemical structure with proper density and location of the molecular recognition sites is an important premise. In this section, we try to sort the varieties of hydrogels driven by molecular recognitions reported in the literature into six categories according to the structural features of the interacting components, *i.e.* polymers, proteins and small molecules, and we also address some important issues that should be noted when preparing responsive hydrogels. In each category, we will take several examples to demonstrate the structural features. For clarity, the words "host" and "guest" will be always employed for not only the synthetic pairs, but also the biologically active pairs, unless otherwise stated.

3.1 Hosts or guests on the short side chains of polymers

As shown in Fig. 3, the hosts on side chains of polymer A can interact with the guests on the side chains of polymer B, resulting in the formation of a hydrogel. There are typically two methods to prepare the responsive materials with this type of structure: (1) polymer A with hosts and polymer B with guests are prepared separately followed by mixing them together in solution leading to hydrogel formation (Fig. 3a); (2) polymer A

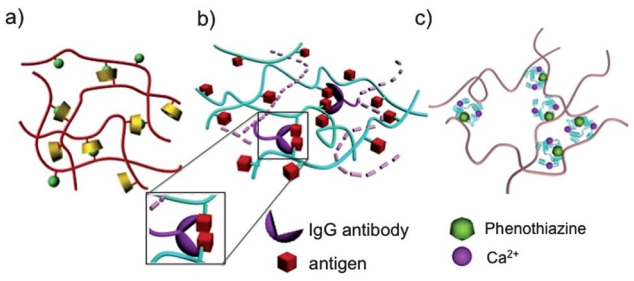

Fig. 3 Schemes for different methods to prepare responsive hydrogels from polymers with hosts–guests on side chains.[38,48]

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containing hosts is mixed with monomers with and without guest moieties and chemical crosslinker to form a semi-interpenetrating network (semi-IPN) hydrogel (Fig. 3b) *via* copolymerization. Such semi-IPN hydrogel incorporated with antigen–antibody interaction was first prepared by Miyata *et al.*,[48] which was a milestone in responsive hydrogels based on biological molecular recognition. In this case, antibodies (*i.e.* rabbit immunoglobulin G, rabbit IgG) were successfully attached to acrylamide, followed by copolymerization with native acrylamide monomer in the presence of an antigen-containing polymer. Later on, proteins modified with monomers have been used to prepare hydrogels, especially by the same research group.[49,50] (3) Hosts and guests modified with only one acrylamide copolymerized with non-functionalized monomers and chemical crosslinkers can be included in this category as the third class. A representative example came from the hydrogel incorporated the molecular recognition in CaM and phenothiazine (Fig. 3c).[38]

The hydrogel shown in Fig. 3a is composed of two polymer chains with respective host and guest moieties. However, as reported recently, hydrogels can be simply produced from the polymers with identical backbone carrying respective host and guest moieties attached by post-polymerization modifications. Here, either natural polymers (*e.g.* polysaccharides dextran or curdlan) or synthetic ones (*e.g.* poly(acrylic acid) (PAA)) are applicable.[51–53] The post-polymerization method for introducing interaction sites is required to be mild and efficient, in order to retain the structure of the polymers and to avoid unexpected side reactions. Thus "click" chemistry is widely employed.[54] For example, Kros[51] reported a light responsive hydrogel system composed of dextrans functionalized by Azo and β-CD respectively, using the efficient reaction between thiol and maleimide.

In this category, the host or guest moieties are often located at the ends of the side chain. Naturally one may ask whether the side spacer, usually a hydrocarbon chain, affects the inter-polymer interactions and then the hydrogel formation or not, as the hydrocarbon chain is a weak guest for cyclodextrin.[32,55–57] Lincoln *et al.* studied the host–guest interaction between a polymer containing CD and the counterpart polymer containing Ada, not only at a molecular level but also from the macroscopic view of polymeric networks.[58–60] In order to investigate the length effect of the side chain, the host–guest molecules were tethered to the polymer main chain through hydrocarbon spacers with different lengths. It was found that when the spacers on one of the polymers were very short, after the formation of the first host–guest complexation with its counterpart polymer, significant steric hindrance from the counterpart polymer chain would retard the further inter-polymer complexation. However, if the length of side chain is very long, the side chain themselves can enter the cavities of CDs either on the same polymer chain or on another polymer chain, which of course would compete with the desired association between CD and Ada, retarding the preferred complexation.[58] Therefore, only an appropriate length of the spacer could ensure strong inter-polymer binding, which was proved by the zero-sheer viscosities of the polymer mixture.

3.2 Guest/host polymers connected by low-molecular-weight hosts/guests

In this category, one of the polymer chains constructing the network can be replaced by a low-molecular-weight compound, *i.e.* hosts of synthetic pairs or ligands of the natural ones. Briefly, there are five typical classes in this category. Firstly, CD dimers/oligomers induced gelation or viscosity increase of polymers containing guest moieties (Fig. 4a). A CD dimer was proved to be able to crosslink linear random copolymers of NIPAM (*N*-isopropylacrylamide) and Ada-containing units, leading to the formation of a hydrogel.[55] Auzély-Velty *et al.* prepared a CD tetraplex (cyclic tetramer of CDs) and found that it crosslinked Ada-modified polysaccharide chitosan and induced viscosity increase of the solution. They further proved that this tetraplex[61] was more efficient as a crosslinker than a dimer of CDs.

It is known that, besides 1 : 1 binding ratio, host–guest pairs can form 1 : 2 binding complex, *i.e.* one host cavity binds two guest molecules simultaneously with a satisfactory binding constant, leading to the second class of hydrogels. The two guest polymers may be the same or not, determined by the host cavity and properties of the guests. With a larger cavity than α-CD and β-CD, γ-CD can include two linear LPEIs (poly(ethylene imine)s) (Fig. 4b). When γ-CD was mixed with polysaccharides with grafts of block copolymer PEG-*b*-LPEI (polyethylene glycol-*b*-LPEI), a network structure formed, induced by the double strand complex of γ-CD and LPEI grafts at pH 10. This network structure was further proved by the obvious viscosity decrease caused by the dissociation of this double strand complex at pH 4, when LPEI was protonated.[62] Similarly, a β-CD tube formed by crosslinking reaction of free CDs with epichlorohydrin,[63] can accommodate two long alkyl chains from both ends of the tube serving as a crosslinker, which also induced the formation of polymeric network, and then hydrogel (Fig. 4c).[64] Besides, as we mentioned earlier, host molecule CB[8] was recently proved to be able to bind naphthalene and viologen stepwise and effectively.[34,35,65] Compared to the 1 : 2 binding mode of CDs with guests as a binary system, this 1 : 1 : 1 binding mode as a ternary system of CB[8] brought more structural and functional variations (Fig. 4d). Recently, Scherman *et al.*[35] reported the

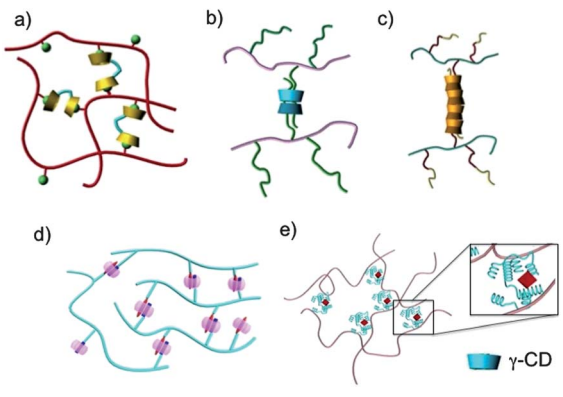

Fig. 4 Guest–host-containing polymers connected by low-molecular-weight hosts–guests.[35,39,55,62,63]

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preparation of two copolymers containing pendant methyl viologen as the first guest and naphthoxy derivative as the second guest, respectively, by free radical polymerization. After the addition of host CB[8] to the mixture of the two guest copolymers, hydrogels formed. In the preparation of the copolymers, various comonomers with different ionic nature were used, in order to identify the electronic effects of the parent polymer on the properties of supramolecular hydrogels. By mixing with the neutral copolymer of naphthoxy derivatives and host CB[8], it was found that the copolymers composed of cationic viologen comonomers with positively-charged comonomers formed hydrogels much more easily than those with neutral or negative comonomers. This phenomena was explained by the more rigid chain made by the strong electronic repulsion on one copolymer resulting in more exposure of guests for binding.

Some protein-containing hydrogels can be regarded as the third class in this category. Proteins were firstly modified with two or more acrylic esters. After polymerization of the protein derivatives with additional acrylic monomers and chemical crosslinkers, a hydrogel formed directly (Fig. 4e). When ligands bind to the proteins, the induced conformation change of the protein and the related conformation change of the network can further tune the gelation state of the soft material. Hydrogels containing the molecular recognition pairs of GBP and glucose,[40] adenylate kinase and ATP (adenosine-5′-triphosphate),[39] are all in this class.

3.3 Hosts/guests along the polymer main chain

Supramolecular hydrogels in this category are rare compared to the others. To introduce synthetic host–guest molecules into polymer main chains, divalent modification is necessary instead of the monovalent modification for the pendent position, which brings some difficulties in synthesis. For example, controlled modification of both of the primary and secondary faces of CD is much more difficult than the mono-modification of its primary face. However, the chemical functionalities of the two ends of peptide (amine and carboxylic acid) or DNA/RNA (hydroxyl and phosphodiester), provide advantages to achieve this type of structure. As shown in Fig. 5, hydrogels formed by mixing two different polymers, each of which contained complementary polypeptide sequences respectively (Fig. 5).[66] The driving force of the hydrogel formation is the molecular recognition between the two complementary peptide domains. The peptide sequences were designed to be short in order to integrate multiple domains on one polymer chain easily. Meanwhile, in these backbones, the linking polymer segments between the specific peptide domain sequences should be long enough to ensure the flexibility and efficiency of inter-polymer recognition. It was also proved that the hydrogels formed with the domains with different association abilities gave different elastic and viscous moduli for the resultant soft materials. The modulus of the hydrogel formed by a stronger binding pair is five times higher than that formed by a weaker pair at room temperature within the linear viscoelastic range.

The sliding hydrogel initiated by Okumura as a special example can be placed in this category. When an α-CD dimer was mixed with PEG chains, the two cavities in one dimer had a great chance of being threaded by different PEG chains, thus the dimer served as a crosslinking point. The free sliding character of α-CD on PEG chain was consistent with the "host/guest on polymer main chain" feature, resulting its responsiveness to tensile deformation.[67] Those α-CDs were blocked onto the PEG chain by modification of bulky groups at the chain end, which brought about hydrogel stability as well as flexibility.

3.4 Recognition moieties at polymer ends

Simply introducing recognition moieties to the chain end of linear polymers are often not strong enough to form hydrogels, because of shortage of binding sites. Thus examples in this category are highlighted by the introduction of star-shape polymers[68] instead of the linear ones. Hennink *et al.* reported a novel hydrogel system, based on cholesterol-ended 8-arm PEG with either free β-CD,[69] or β-CD-ended 8-arm PEG.[68] The elastic modulus of the hydrogel composed of the 8-arm β-CD-ended PEG as the host and 8-arm cholesterol-ended PEG as the guest was much higher than that of the same host and *linear* cholesterol-ended PEG, at the same weight content. This result clearly showed the strong gelation ability of the 8-arm structures.

3.5 Hybrid inclusion complex (HIC)

Jiang and Chen proposed a new strategy *via* using a hybrid inclusion complex (HIC, Fig. 6a) as a precursor to fabricate supramolecular hydrogels.[70–72] The HIC is composed of an

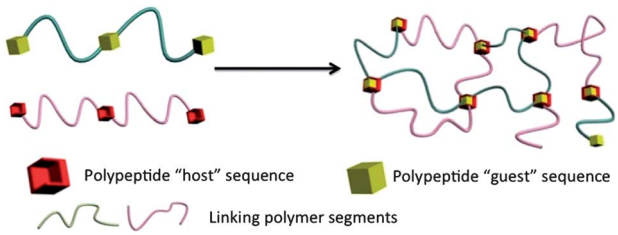

Fig. 5 Supramolecular hydrogel prepared by mixing polymers with hosts–guests on the main chain.[66]

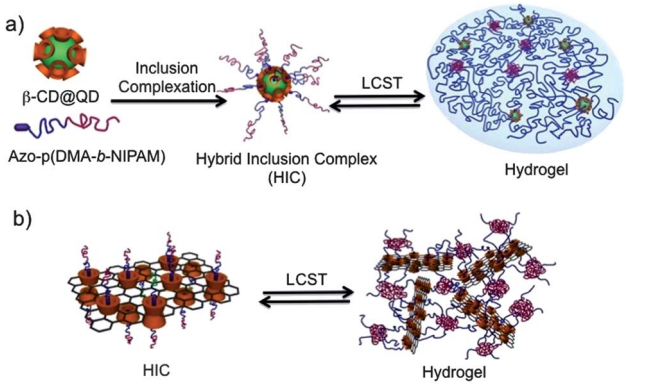

Fig. 6 Hydrogels based on hybrid inclusion complex (HIC) with quantum dots (QD) (a)[70,71] and graphene sheets (b).[72]

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inorganic core and an organic polymeric shell, where the core and shell are connected by inclusion complexation (Fig. 6a). For a long time, supramolecular hydrogels have suffered from rather poor mechanical strength, compared to their chemically crosslinked counterparts. Introduction of inorganic species, *e.g.* clay, has been proved to significantly increase the mechanical properties of the chemically crosslinked hydrogels.[73] It initiated interest in introducing inorganic nanoparticles or nanosheets into supramolecular hydrogels, to improve the mechanical properties, and more importantly, to render new functionalities. Targeting at such hybrid supramolecular hydrogels, after mixing QDs (quantum dots) of CdS covered by β-CDs, with block copolymers with an azo moiety at one of their ends, *i.e.* azo-p(DMA-*b*-NIPAM) (poly(*N*,*N*′-dimethylacrylamide)-*b*-poly-(*N*-isopropylacrylamide)), a supramolecular structure HIC formed *via* molecular recognition. In this HIC, the second block pNIPAM formed the outer layer of the shell. After heating to the LCST of pNIPAM, the pNIPAM block began to aggregate and finally led to hydrogels formed by the HIC. Thus the hydrogel had two distinctive crosslinks, the hydrophobic domains of pNIPAM and the multivalent nanoparticles (Fig. 6a).

Inorganic CD-modified nanoparticles of silica,[74] gold nanoparticles,[75] and functionalized polymers with Ada, azo and Fc were successfully used in constructing HICs and then the hydrogels, aiming at different functionalities. Aggregation of HICs can also be induced by the PPR (polypseudorotaxane) structure of PEG and α-CD.[74] In this case, HIC firstly formed between the silica particle coated with β-CDs and Ada-ended PEG. Then the free end of PEG threaded into the α-CDs, resulting in inter-HIC aggregation, and finally a hydrogel.

Not only zero dimensional nanoparticles, 2D nanosheets, *e.g.* reduced graphene oxide and clay, were employed too. Jiang and Chen found that clay enhanced both of the elastic modulus and viscous modulus of hybrid supramolecular hydrogel by one order of magnitude compared to the native one.[76] It was interesting to notice that by using the same block copolymer (Azo-PDMA-*b*-PNIPAM) with the same molecular weight and at the same solid content, formation of hydrogel from HIC with graphene nanosheets was much easier than that with QDs.[72] As shown in Fig. 7, for HIC of graphene, gelation took place around 32 °C within one to two minutes, while for HIC of QDs, the process covered a range of temperature from 35–45 °C within 10 min. This difference could be attributed to the high thermoconductivity of graphene sheets.

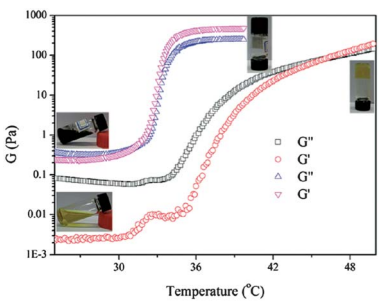

Fig. 7 Rheology properties of HIC hydrogel of QD (yellow sample) and HIC hydrogel of graphene (black sample),[72] heating rate 1 °C min^{-1}. (Reprinted with permission from J. H. Liu, G. S. Chen and M. Jiang, *Macromolecules*, 2011, **44**, 7682. Copyright (2011) American Chemical Society.)

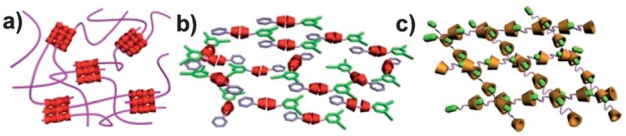

Fig. 8 Miscellaneous types of supramolecular hydrogels formed by (a) threading PEG chain into α-CDs;[77] (b) threading linear small molecule into α-CDs[57] and (c) formation of supramolecular polymers, then fibers and finally hydrogels.[45]

3.6 Miscellaneous types

As shown in Fig. 8, there are other noteworthy types of hydrogels to mention, but which are hard to include in the previous categories. Some of them were based on the PPR hydrogel of α-CD and PEG (Fig. 8a), where the latter threaded into the cavities of the former.[77] Strong hydrogen bonding between the adjacent CDs threaded by PEG led to inter-polymer microcrystalline domains, which acted as physical crosslinks to prompt the hydrogel formation. The progress of such PPR hydrogels in the last two decades has been summarized in several reviews.[78,79] Until now, among all host families, CDs are the only hosts exhibiting this property, *i.e.* being threaded and the resultant PPR forming hydrogels. This can be attributed to the multiple hydrogen bonds between the CDs as well as their restricted movement and regular packing, after being threaded by polymeric guest chains.

This threading feature could induce hydrogel formation even without using guest polymers as reported by Osakada and his coworkers.[57] Here the gel formation was realized by threading a linear small molecule, which was a short alkyl chain with two stoppers at both ends into the cavities of α-CDs. The length of the alkyl chain was long enough to hold two α-CDs, while the stopper significantly retarded the de-threading process of α-CDs. The authors demonstrated that the hydrogel formed only when the alkyl spacer was longer than ten carbon atoms, suitable to form [3]pseudorotaxane, *i.e.* two α-CDs on the same chain, and the stoppers *e.g.* 3,5-dimethoxyphenyl and pyridyl moieties formed inter-rotaxane hydrogen bonds (Fig. 8b). Another new route to hydrogels developed recently was based on host/guest supramolecular polymers, which formed from a single building block possessing both host and guest units, or after mixing divalent hosts and guests (Fig. 8c). Special design of such building blocks was required to avoid molecular recognition at intramolecular level or oligomer level. For cinnamoyl amino trinitrobenzene (TNB)-modified β-CD, the intermolecular host/guest interaction between CD and TNB linked the building blocks into supramolecular polymers, which then self-assembled into fibrils, and eventually a hydrogel.[45] Different in approach but equally satisfactory in result, by employing a multifunctional monomer, which contained two viologen moieties as electron acceptors and two anthracene moieties as electron donors, a supramolecular polymer was obtained after CB[8] was added.[34] When the concentrations of

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monomer and CB[8] were increased, hydrogels formed. Besides, supramolecular hydrogel was also achieved by using modified β-CD and a guest with two Fc moieties.[80]

4 Responsive features of hydrogels achieved with molecular recognition

The non-covalent characters incorporated in supramolecular hydrogels have great potential to tune the responses of the soft material. In the literature, the hydrogels made of "smart" polymers are commonly sensitive to temperature and/or pH, which, somehow cannot be tuned precisely as the sensitivity comes from the inherent behaviour of the whole polymeric backbone to environmental stimuli. Molecular recognition is probably helpful to solve this problem as more factors can be adjusted and controlled during synthesis, which include the density and location of the binding sites *etc.* More importantly, as the kinetics and thermodynamics of molecular recognition pairs can often be precisely measured by various measurements,[81,82] the responses of the resultant hydrogel driven by such molecular interactions to environmental changes, such as mechanical stress, temperature, or chemical reagent, becomes understandable and controllable. In this section, we will briefly review some of the interesting published results according to the types of the responses, such as temperature, light, redox and chemicals.

4.1 Temperature

Temperature is one of the extensively studied environmental triggers, which is crucial to physiological applications of hydrogel. There has been a large amount of research work on chemical hydrogels responsive to temperature based on temperature-sensitive polymers, particularly pNIPAM.[83] Here we focus on the hydrogels with similar responsive properties, but only achieved by molecular recognition pairs. Generally the dynamic nature makes the complexation between host and guest molecules thermo-sensitive, so does the hydrogel. For example, upon heating, in the PPR hydrogel of α-CD and PEG, the α-CD rings will slide off, leading to the dissociation of PPR hydrogel. Based on this principle, a significant amount of work on the temperature responses of PPR hydrogels has been reported with various polymers such as block copolymer,[84] brush polymer,[85] super-branched polymer *etc*.[86]

Besides PPR hydrogels, some of the other host–guest hydrogels with very different structures share the similar responsiveness to temperature. The hydrogels made of an 8-arm star polymer crosslinked by the association of β-CD and Ada[68,69] exhibited satisfactory thermoreversibility upon heating and cooling steps, although the pair has a high binding constant. In the dynamic rheology measurement, as temperature increased from 4 °C to 37 °C, a dramatic decrease of G' and G'' was observed. Below 17 °C, G' was larger than G'', showing the solid character of soft material. 17 °C was the temperature at which the curves of G' and G'' intercepted each other, indicating the gel-to-sol transition. The heating–cooling cycles were repeated several times without an apparent modulus loss. Similar results were observed in molecular recognition hydrogels with different

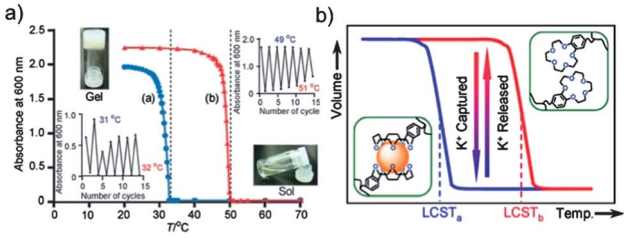

Fig. 9 Thermal responsibility of hydrogel (a) formed by [3]pseudorotaxane (blue and red lines for the guest of 12-carbon chain and 10-carbon chain, respectively)[87] (Reproduced from ref. 87 with permission from The Royal Society of Chemistry) and (b) the tunable LCST by complexation between crown ether and K^+ ions[30] (Reprinted from ref. 30 with permission from Elsevier).

polymeric backbone and even higher binding ability.[35] These results demonstrated that the inherited thermoreversible nature of hydrogels made of molecular recognition is the basic character of this type of materials.

Furthermore, the temperature of the sol–gel transition can be tuned by changes of the interaction units at a molecular level. For example, hydrogels formed by [3]pseudorotaxane of CDs with a 10-carbon chain and a 12-carbon chain, exhibited distinct gel-to-sol transitions at 49 °C and 32 °C, respectively (Fig. 9a).[87] Here effective tuning of molecular recognition in hydrogel was well demonstrated as the difference of 2 carbons in the guests made a change in the gelation temperature as large as 17 °C. Moreover, Chu *et al.* prepared a stimuli-responsive hydrogel of chemically crosslinked pNIPAM that had pendant crown ethers.[30] The crown ethers bound to K^+ ions to form a stable 2 : 1 host–guest complexation, which provided an additional crosslinking factor to the system. Thus as shown in Fig. 9b, without K^+ ions, the transition temperature for hydrogel shrinking ($LCST_b$) was much higher than that with K^+ ions ($LCST_a$), showing the tuneable nature of the hydrogels with molecular recognition.

4.2 UV and visible light irradiations

Light responsive systems have attracted growing interest since it is a clean trigger source and can be tuned remotely. In such studies, guest molecules of azo and its derivatives have played a

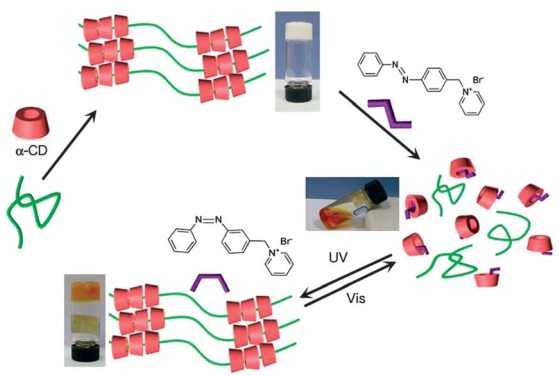

Fig. 10 A schematic summary of the photo responsive PPR hydrogels.[89]

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major role as their *cis* and *trans* forms possess very different abilities in complexation with CD hosts, and the *trans–cis* isomerization can be realized by UV light irradiation. Linear polymers modified with azo groups on their side chains were used more often to achieve the light responsiveness.[51,88] Harada and his coworkers reported several photo-responsive hydrogels, most of their sol–gel transitions were controlled by the reversible binding between CD and azo.[41] For example, by mixing a CD-functionalized curdlan with azo-modified poly(acrylic acid),[52] the CD-azo binding served as crosslinker, thus *trans*-azo induced gel state which was converted to sol under UV irradiation.

For PPR hydrogels composed of PEG and α-CDs, although both components are not active for light irradiation, photo-induced reversible gel-to-sol transitions was realized by pure 'supramolecular routes' in Jiang's group.[42] As shown in Fig. 10,[89] addition of a water-soluble azo compound to PPR hydrogel of PEG and α-CD in water removed the α-CD rings from the PEG chains resulting in a transparent solution, due to the stronger complexation of *trans*-azo/α-CD than that of PEG/α-CD. Subsequent irradiation with UV light drove the α-CD cavities to move back to the PEG chains since UV light induced isomerization of *trans*-azo to its *cis* form, and consequently lost the ability to form a acomplex with α-CD, resulting in a hydrogel again. Further irradiation with visible light can make a gel-to-sol transition occur and start another cycle (Fig. 10). Based on the competitive host–guest interactions, this reversible sol–gel process was observed repeatedly by alternation of UV and visible light irradiation. The same principle was also successfully employed in HIC hydrogels, where the mechanical strength was greatly enhanced by clay.[76]

4.3 Electrical and redox stimuli

Redox-responsive systems may be applied to benign electro-functional systems, such as electrically switchable materials.[90,91] Inclusion complexation between CD and Fc is well-known and has been extensively studied because of their reversible association controlled by the redox state of Fc, which can be tuned either electrochemically or chemically, *i.e.* with redox reagents. A redox-responsible hydrogel system was achieved by a combination of β-CD, PAA with dodecyl chains attached randomly, and a redox-responsive guest, ferrocenecarboxylic acid (Fc-A).[92] The initial hydrogel of the PAA formed due to the hydrophobic interactions of the dodecyl chains. But the hydrogel was dissociated by addition of β-CD which formed inclusion complex with the alkyl chains. The subsequent addition of guest Fc-A led to the transfer of β-CD from alkyl chains to Fc-A, thus the ternary mixture exhibited the gel behaviour again due to the recovered hydrophobic interactions of dodecyl chains. When Fc-A was tuned to its oxidized state, it lost its ability to form a complex, β-CD formed a complex with dodecyl chains again and consequently the mixture became a sol. The HIC hydrogels containing Fc-ended block copolymer mentioned earlier (Fc–HIC) can also achieve similar responses,[70] *i.e.* the gel-to-sol transition took place after addition of an oxidizing agent, *e.g.* $K_3Fe(CN)_6$ to the hydrogel (Fig. 11). In addition, it was found that Fc retained its electrochemical activity inside the gel as

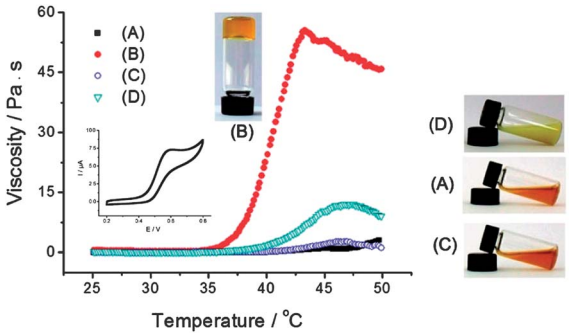

Fig. 11 Steady-state rheology measurements and photos of (A) copolymer itself for Fc–HIC hydrogel, (B) Fc–HIC supramolecular hydrogel, (C) sol of the hydrogel after supramolecular competition, (D) sol of the hydrogel after $K_3Fe(CN)_6$ oxidization; (Inset) electrochemical sensitivity of Fc–HIC hydrogel[70] (Reprinted with permission from (P. Du, J. H. Liu, G. S. Chen and M. Jiang, *Langmuir*, 2011, **27**, 9602). Copyright (2011) American Chemical Society.).

detected by cyclic voltammetry (inset in Fig. 11). The supramolecular hydrogel consisting of modified β-CD and Fc-containing guest reported by Fang *et al.* also showed responsiveness to different type of chemical oxidants.[80]

4.4 Chemical responsive

The chemical responsiveness of the hydrogels is mostly based on the dynamic and competitive nature of molecular recognition.[93] For example, the hydrogel composed of trinitrobenzene (TNB) modified β-CD as discussed earlier, can first form a supramolecular polymer, then hydrogels at certain concentrations.[45,94] The hydrogel turned into sol by addition of either Ada-containing molecules as a competitive guest or urea as a denaturing reagent, which could break the hydrogen bonds between CDs. Meanwhile, the hydrogel was induced to sol by an excess of native β-CD as a competitive host. In addition, the gel-to-sol transition also occurred upon addition of methyl orange (MO) as a competitive guest, followed by sol-to-gel transition upon addition of α-CD, which was a stronger host for MO. This reversible gel-to-sol transition was performed several times upon the alternative additions of MO and α-CD. This perfect chemical reversibility can be performed due to the ultra low solid content of hydrogels made of the supramolecular polymer. Similarly, the hydrogel made of [3]pseudorotaxane is also sensitive to NaCl, urea or phloroglucinol.[57,87] Furthermore, the hydrogels triggered by thermo,[57] photo[54] and redox[70] stimuli may also be responsive to addition of competitive guest molecules.

In the above examples, the transitions are realized by solely adding chemicals, *i.e.* competitive host or guest into the hydrogels. However, in more common cases, perfect reversible sol–gel transitions were realized by adding a competitive host–guest in combination with photo or redox stimuli. As in the example discussed above (Fig. 10),[89] the PPR hydrogel was dissociated by addition of the azo compound. But the following sol-to-gel and gel-to-sol transitions were achieved by light irradiations, which induced the isomerization of the azo compound. Essentially, the reversible transitions are based on

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the interaction strength sequence of *trans*-azo/α-CD > PEG/α-CD > *cis*-azo/α-CD. Similarly, the sequence for redox-reversible hydrogel with competitive guest Fc-A was Fc-A/β-CD > C_{12}/β-CD > Fc^+-A/β-CD.[92]

We now focus more on protein-containing hydrogels. Compared to their synthetic counterparts, this type of hydrogels does not prevalently have multiple responsive properties. And the protein-containing hydrogel, as reported so far, always has reversible swelling–deswelling properties instead of sol–gel transition triggered by molecular recognition. This is because such protein-containing hydrogels were prepared *via* copolymerization of acrylate-modified protein with hydrophilic monomer and chemical crosslinker. The additional crosslinker was necessary for two reasons: the molecular recognition between ligand and protein was not normally strong enough to efficiently crosslink the polymer chain, and the relatively large size of protein reduced the crosslinking efficiency as well.

Despite the structural complexities and modification difficulties, protein-containing hydrogels, to some extent, are probably even more promising in further applications than their synthetic counterparts, due to their biocompatibility and specificity of responsiveness. In the semi-IPN hydrogel incorporated with antigen–antibody interactions,[48] an addition of free antigen induced dissociation of the original antigen–antibody complex, leading to the antigen-responsive swelling of the hydrogel. This mechanism resembled that of gel-to-sol transition induced by supramolecular competitions in the synthetic category. Moreover, this hydrogel also showed responsive shape-memory behaviour, *i.e.* stepwise changes in antigen concentration induced reversible swelling changes of the hydrogel.

Another type of chemically responsive hydrogel containing proteins accomplished the "swelling–deswelling" process not only by competition between the binding pairs, but also by the related conformational changes of the protein itself. It is known that certain proteins perform a substantial conformational change in response to a given stimulus. This conformational change can manifest in different manners and result in an actuation,[95] *i.e.* catalytic or signalling event, movement, interaction with other proteins and so on. In all cases, the sensing–actuation process of proteins is initiated by a recognition event that can be translated into a mechanical action. Thus this type of protein is an ideal component for designing new nanomaterials with responses related to molecular recognition. In this field, representative proteins include Ca^{2+} binding protein (CaM), a mutant of adenylate kinase (AKtm, ligand: ATP)[39] and glucose-binding protein (GBP, ligand: glucose).[40] Daunert *et al.* reported a hydrogel containing a genetically engineered protein, which was capable of producing a ligand-responsive action (Fig. 12).[38] The hydrogel was prepared from allylamine mono-modified CaM, polymerizable guest phenothiazine, co-monomer acrylamide and chemical crosslinking reagent. Hydrogels formed with the protein and its guest covalently attached to the polymer main chain as pendant groups. Firstly, saturation with Ca^{2+} made CaM ready to bind phenothiazine, which not only induced the protein to a more restrictive conformation, but also crosslinked the hydrogel. Subsequent removal of Ca^{2+} from the hydrogel with a solution containing chelator EGTA (ethylene glycol tetraacetic acid), made the hydrogel swell, due to the release of the immobilized phenothiazine, and then conformational change of CaM from constrictive conformation to a much looser one as well.[96] A competitive ligand chlorpromazine, which bound CaM stronger than phenothiazine, also relaxed the protein conformation and further deswelled the hydrogel as EGTA did. Furthermore, the swelling–deswelling process of the hydrogel was fully monitored by controlling the concentration of the competitive ligand.[97]

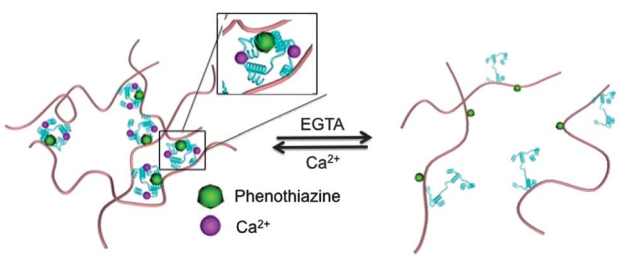

Fig. 12 Schematic illustration of ligand-responsive hydrogel containing allylamine modified CaM.[38]

5 Functionality and applications

Besides responsive sol–gel transition and swelling–deswelling properties, hydrogels with molecular recognition also feature in various applications.[98] This section cannot cover all possible functionalities. Instead, we plan to discuss a couple of representative applications, which are related to molecular recognition and the corresponding responsiveness. For each of the application, only one or two examples will be demonstrated in detail. We would like to mention that, although in this section some of the hydrogels were not *locked* by the molecular recognition, their functions and applications are fully based on such interactions.

5.1 Self-healing

People are fascinated by living nature's faculty to spontaneously repair damage. One striking example in human body can be found in skin—minor cuts and bruises are healed completely, whereas more severe injuries lead to scars. In either case the

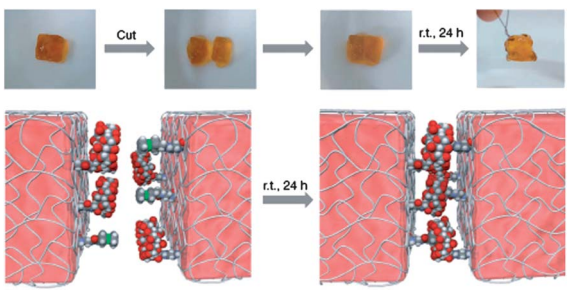

Fig. 13 Self-healing process of hydrogel formed by inclusion complexation between β-CD and Fc (From ref. 53, Harada *et al*. Copyright Nature Publishing Group).

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operational capability of the system is largely restored. Of course, imparting self-healing properties to non-living systems is enormously attractive, simply considering the reduction in costs and risks in some specific circumstances.[99] Recently, Harada *et al.* reported good examples of realizing such self-healing behaviour of supramolecular hydrogels on macroscopic scale.[53,100] As shown in Fig. 13, the two cut pieces could be rejoined and the crack was sufficiently healed to form one gel. For the case of Fc being oxidized to Fc^+ by NaClO on the cut surface, this re-adhesion was not observed. But the self-healing took place again after the reduction of oxidized Fc^+ by glutathione. Therefore, the whole process gave strong evidence that the molecular recognition did play a crucial role in this self-healing process.

Bones can be restored to their original shape, structure and mechanical strength after breaking.[101] A full recovery of hydrogel microstructure (Fig. 5) was investigated to mimic this bone feature. After the hydrogel formed by peptide recognition pairs on polymer main chain was injected onto a macroscopic slide through a syringe, changes in its viscoelastic properties were monitored by a microrheometer, in which the Brownian motion trajectories of micrometer-sized fluorospheres embedded within the hydrogel were tracked over time. As shown in Fig. 14,[66] viscoelasticity of the material exhibited continuous recovery, indicated as the mean-squared displacement (MSD) of fluorospheres. Comparing the results in Fig. 14A and B concluded that the stronger binding pairs brought the material much faster recovery ability (5 min after injection, red curves) than the weaker ones (30 min after injection, blue curves), which gave another quantitative relationship between the molecular structure and the macroscopic properties.

5.2 Sensors

Hydrogels can be used as sensors for ion detection by incorporating crown ethers[102–105] into the network. Alternatively, complexation of a guest with various cations changed its ability to bind with γ-CD, leading to high sensitivity to metal ions of the hydrogel.[106]

Furthermore, supramolecular hydrogel can be used as a matrix of a specific sensor.[107–111] Hamachi reported a fluorescent lectin (*i.e.* a protein which binds to sugars specifically) array in a supramolecular hydrogel matrix for saccharide detection

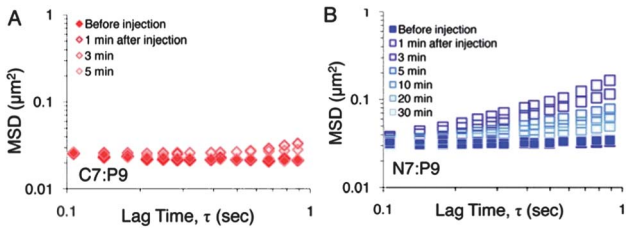

Fig. 14 Microrheology behavior of hydrogel showing the self-healing properties.[66] Stronger molecular recognition (A, curves in red) leads much quicker recovery of mean-squared displacement (MSD) of the fluorospheres inside the gel than that of weaker pairs (B, curves in blue). Lag time: time scale of the experiment (Reprinted with permission from Proc.Nat.Acad.Sci., USA) .

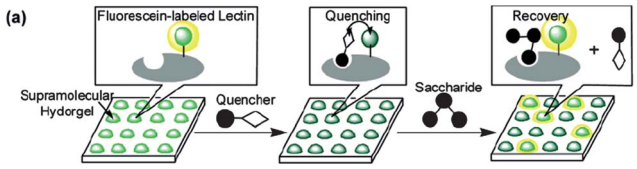

Fig. 15 Schematic illustration of supramolecular hydrogel used for saccharide detection.[112]

(Fig. 15).[112] In this assay, the hydrogel first formed an array on a plate, followed by incubation with fluorescent lectins, which rendered fluorescence to the hydrogel. The fluorescent intensity was first decreased by a quencher, which bound to the lectin. After an analyte, *i.e.* saccharide, was dropped onto the hydrogel, if it bound to the lectin, this competitive binding would remove the quencher from the lectin and recover the fluorescence of the hydrogel. Multiple saccharides can be detected at the same time by one array system. From this example, two facts should be emphasized: (1) the rather low solid content and versatility of hydrogels made of supramolecular polymers brings the soft material great promise for simple analytical methods with high sensitivity and low cost. (2) The dynamic nature of molecular recognition can be employed to detect the desired analytes.

5.3 Delivery

Hydrogels have wide applications in delivery.[113–115] Many studies showed that CD-containing hydrogels could lead to delivery of drug molecules in a longer and more linear sustained manner.[116] In principle, as the swelling state of hydrogels can be tuned by molecular recognition, the transport rate of the drug inside the gel is adjustable. If a ligand served as the hydrogel backbone, cleavage of this ligand induced by molecular recognition may dissociate the soft material and promote the release of the preloaded sample, which was reported by Ulijn[117] *et al.* and other research groups. Moreover, Akiyoshi and coworkers

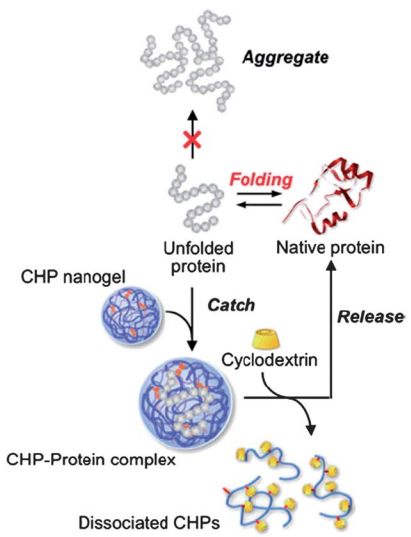

Fig. 16 Schematic representation of the artificial nanogel chaperone system.[118]

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came up with a new nanogel containing cholesterol-bearing pullulan,[118–121] which performed controlled release in a different manner. This nanogel prevented the denaturation of horseradish peroxidase (HRP) by forming complex with the protein. When CD was introduced, the cholesterol groups on pullulan preferred to form inclusion complex with CD, leading to dissociation of the nanogel, which consequently released native HRP in a controllable manner (Fig. 16).[118] Thus this function of the hydrogel was labelled as "artificial nanogel chaperone" as the protein can be protected and released.

6 Outlook

In this review, we present a general view of functional hydrogels, which have their responsiveness and applications stemming from molecular recognition, *i.e.* "lock-and-key" character. Due to the tremendous contributions from biologists, chemists and material scientists, this lock-and-key concept, which was born 110 years ago, is still vivid and productive and is spreading over different disciplines. Apparently we cannot cover all of the brilliant related examples, *e.g.* hydrogels with the function of cell culture material,[122,123] but we do want to demonstrate that we can actually look at this concept and focus on its common features almost neglecting the boundaries between the host–guest interaction in supramolecular chemistry and the ligand–acceptor interaction in biology, which right now keep blurring all the time.[124] This idea may help us to look at biological problems by using chemical tools, as well as to look at chemical or material problems by using biological tools. Based on more precise and intensive understanding of molecular recognition, we will be able to fabricate more sophisticated systems by harmoniously incorporating both factors originated from living world and synthetic world, thus we may come up with more general principles to understand nature and make more valuable functional biomaterials, aiming at attractive multiple functionalities.

Acknowledgements

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