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Macroscopic Supramolecular Assembly and Its Applications

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Abstract Macroscopic supramolecular assembly (MSA) has been a recent progress in supramolecular chemistry. MSA mainly focuses on studies of the building blocks with a size beyond ten micrometers and the non-covalent interactions between these interactive building blocks to form ordered structures. MSA is essential to realize the concept of "self-assembly at all scales" by bridging most supramolecular researches at molecular level and at macroscopic scale. This review summaries the development of MSA, the basic design principle and related strategies to achieve MSA and potential applications. Correspondingly, we try to elucidate the correlations and differences between "macroscopic assembly" and MSA based on intermolecular interactions; the design principle and the underlying assembly mechanism of MSA are proposed to understand the reported MSA behaviors; to demonstrate further applications of MSA, we introduce some methods to improve the ordered degree of the assembled structures from the point of precise assembly and thus envision some possible fields for the use of MSA.

Keywords Macroscopic supramolecular assembly; Multivalency; Supramolecular materials; 3D ordered structures; Precise assembly

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INTRODUCTION

In 1987, Donald J. Cram, Jean-Marie Lehn and Charles J. Pedersen were awarded jointly with the Nobel Prize in Chemistry "for their development and use of molecules with structure-specific interactions of high selectivity". The concept of supramolecular chemistry was later proposed in Lehn's presentation lecture. Different from classical molecular chemistry based on covalent bonding between atoms, supramolecular chemistry is dedicated to the functional molecular aggregates formed by non-covalent intermolecular interactions between molecules[1–3]. For decades, the research field of supramolecular chemistry has arisen as a booming interdiscipline to promote the fusion of chemistry, physics, biology, material, life science *etc.*, and becomes sophisticated with complex self-assembled structures with fascinating functions. Very recently in 2016, the Nobel Prize in Chemistry was again awarded jointly to three supramolecular chemists, Jean-Pierre Sauvage, Sir J. Fraser Stoddart and Bernard L. Feringa "for the design and synthesis of molecular machines".

Rather than chemical synthesis in covalent chemistry to obtain new species, supramolecular chemistry uses the manner of self-assembly to produce new molecular aggregates[4]. Two major factors in self-assembly, *i.e.* building blocks (or basic units) and the corresponding supramolecular interactions, act as "bricks" and "glue", respectively, to build supramolecular architectures (assemblies)[5–8]. The structure and performance of these assemblies or materials are largely dependent on the intrinsic properties of building blocks and the categories of the used non-covalent interactions. Therefore, much efforts have been made to develop both building blocks and interactions to obtain complex or hierarchical structures such as molecular machines, micelles, vesicles *etc.* The developed building blocks have covered a wide range from small molecules to molecular aggregates, polymers, biomolecules, nanoparticles/nanotubes/nanosheets *etc.*; correspondingly, commonly used supramolecular interactions include molecular recognition, hydrogen bonding, coordinate bonding, electrostatic interactions, van der Waals force and so on[9–16]. Until now, most reports regarding supramolecular assembly mainly start with the building blocks of molecules or objects at nanoscale. For these cases, the number of the interacting events between two building blocks is not large because normally the effective contact area is quite limited at this scale. However, the study on the building blocks with a size larger than 10 μm (macroscopic scale) is still lacking, which means that the important connection between microscale and macroscopic supramolecular chemistry is missing to realize the concept and manufacture envision of "self-assembly at all scale". The emergence of macroscopic supramolecular assembly (MSA, supramolecular assembly of large building blocks with a size larger than 10 μm) is intended to establish the necessary connection. To the best of our current understanding, we distinguish MSA from conventional self-assembly based on the capability of self-propulsion. Normally, building blocks

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exceeding the size of 10 μm can hardly be driven by Brownian motion while molecular building blocks have no problems in colliding each other through thermal motions. Therefore, we defined the bottom boundary of the building block size for MSA as 10 μm. For the upper limit of the building block size, most methods can handle spontaneous self-propulsion for random collision of objects below 1 cm. With a larger size, electromechanical driving forces will be necessary, thus reducing the spontaneity and randomness of motions and collisions. For these reasons, we limit the size of building blocks in MSA to the range from 1 μm to 1 cm. In this range, the spontaneous and random features both in thermodynamics and kinetics can be well maintained, thus contributing to connections with molecular assembly and bulk supramolecular materials.

For conventional molecular assembly, the number of interactive groups is quite limited. In most cases, the occurrence of an assembly event only requires two interactive groups involved. For example, one host molecule and one guest molecule are enough for a supramolecular assembly event. However, for MSA, the number of interactive groups is huge, the distribution of these groups on a large surface is complex, and the interactive process in random collisions of large surfaces further increases kinetic possibility of the assembly process. Thus the assembly mechanism of MSA is a much more complex surface-surface multivalent process rather than simple supramolecular recognition between one or some interactive pairs. To start with, we need to answer fundamental questions regarding MSA, such as "whether weak non-covalent intermolecular interactions could render macroscopic building blocks to form stable assemblies spontaneously?", "is it possible to fabricate supramolecular bulk materials through direct self-assembly of large building blocks?" Demonstration and elucidation of MSA are significant to establish a new methodology of manufacture or materials processing because MSA can eliminate the uncertainty and the difficulty in control across a wide length range in the traditional fabrication mode of supramolecular materials by hierarchical assembly from molecules or nanoscale building blocks.

The implementation of MSA is mainly determined by the binding strength of two interactive macroscopic surfaces. To handle the challenge of assembling large building blocks, early study mainly used the strategy of "the force range of the used supramolecular interactions matches the size of the building blocks", *i.e.* using long ranged forces such as capillary forces, electric field forces, magnetic forces to enable millimeter or centimeter-sized objects to interact when they are relatively distant from each other and finally to form ordered structures based on the basic principle of "minimizing the system energy"[17, 18]. Because these reports did not involve any molecular interactions between building blocks in the assembly process, they are not regarded as MSA although the idea of "macroscopic assembly" is presented in these works. Therefore, the strict MSA will require numerous surface molecules to simultaneously reach a short interactive distance, normally nanoscale for most intermolecular interactions, to form sufficient binding strength. This is challenging because most macroscopic objects have high surface roughness due to the limitation in material fabrication, leading to problems like inhomogeneous distribution of surface molecules, difficulty in reaching nanoscale distance for sufficient surface contacting of two interactive building blocks *etc.* These intrinsic problems normally cause observable failure of assembly events (Fig. 1)[19, 20]. Currently two strategies have been demonstrated to achieve MSA of soft and rigid building blocks, respectively: (1) using polymeric gels as the building blocks and meanwhile inducing supramolecular interactive groups in the gel fabrication, such as host or guest molecules, donor or acceptor of hydrogen bonding *etc.*[21]; (2) pre-coating a "flexible spacing coating", a highly flowable and self-healable polyelectrolyte multilayer[20] beneath the supramolecular groups on rigid non-gel building blocks. Both strategies take advantage of high flowability to promote molecular recognition of numerous groups between two macroscopic surfaces and thus MSA: on one aspect, the flowable surface contributes to lowered surface roughness for sufficient contacting of two surfaces and molecules reaching interactive distance; on the other aspect, the outmost supramolecular groups have high freedom to realize supramolecular recognition through multivalent effect[22–24], thus enhancing the apparent binding constant of the macroscopic building blocks.

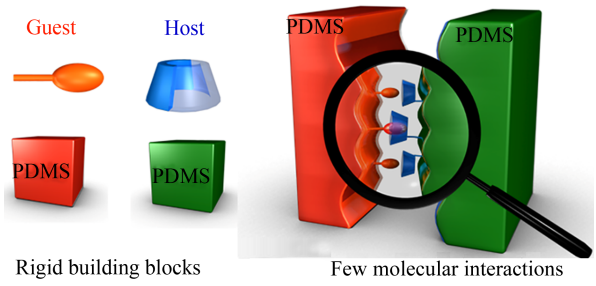

Fig. 1 Schematic illustration of the MSA of two rigid polydimethylsiloxane (PDMS) building blocks

Based on these two strategies, MSA can provide a novel solution to the fabrication of supramolecular materials towards applications as biomaterials, *i.e.* directly using large building blocks to assemble through weak intermolecular interactions to obtain bulk materials. Centering on the topic of MSA, this review tries to present the recent progress of the area of MSA from the point of "how to realize MSA and use it for the fabrication of biomaterials and aspects". Mechanism regarding the principle of MSA and promising applicable areas of MSA will be discussed to further interpret the opportunities and challenges of this research field.

MACROSCOPIC ASSEMBLY DRIVEN BY LONG RANGED FORCES

The modern industry has stepped into a new era of mechanical automatization or artificial robotics. Then why should we still care about self-assembly of macroscopic objects? Whitesides *et al.* tried to answer this question in their perspective paper entitled "self-assembly at all scales"[25]. The concept of self-assembly is applicable to all sizes from

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molecular to plenary scale and the insight into the assembly process is essential for better understanding of the complex biological world. Besides, self-assembly may provide new routes to microfabrication or nanofabrication and extend microelectronics from 2D to 3D systems[26, 27]. At that time, there were few works on the assembly behaviors of the building blocks with a size above micrometer scale. Some groups tried to tackle the problem of micrometer or millimeter-scaled building blocks having a size much larger than the interactive distance of intermolecular interactions based on the idea of "the interactive distance of the applied forces matches the size of the building blocks". They mainly used long ranged forces such as capillary forces, magnetic forces, electric field forces or took advantage of paramagnetic properties of most objects for alignment.

On the aspect of assembly driven by capillary forces, Whitesides *et al.* have prepared polygonal building blocks with anisotropic wettability of different surfaces and demonstrated assembly at the interface of immiscible liquid phases (*e.g.* perfluorodecalin/water) (Fig. 2)[18]: the menisci formed by the hydrophobic surfaces of the building blocks are opposite to those formed by the hydrophilic surfaces; when two building blocks approach and two similar mensci reach the interactive distance of capillary force, these two surfaces will coalesce to minimize the interfacial free energy of the system, leading to the result of macroscopic assembly. To further exploit the functions of these macroscopic assemblies, they applied the principle of macroscopic assembly driven by capillary forces and realized the assembly of electronic devices[28]: millimeter polymer building blocks with a shape of truncated octahedron (6 cubic faces and 8 hexagonal faces) are fabricated with a template method; each cubic face is patterned with metal circuit for the connection of LED; they make the building blocks rotate in liquid tin solder, which only selectively wet the metal surfaces rather than the polymer faces; based on the anisotropic surface wettability, they realize precise assembly of these building blocks driven by capillary forces and obtain stable ordered structures after cooling down for solidification; the as-prepared assembly can light all LED after connecting to power.

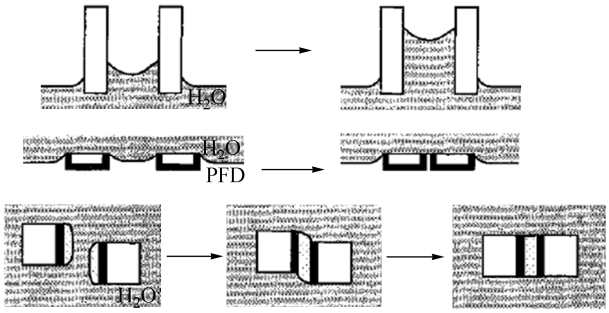

Fig. 2 Mechanism of macroscopic assembly driven by capillary forces (The black sides and white sides are hydrophobic and hydrophilic, respectively.) (Reprinted with permission from Ref. [18]; Copyright (2001) American Chemical Society)

Recently, by applying the above principle, a few groups have achieved macroscopic assembly by using capillary forces as the driving forces. For example, Stebe *et al.* prepared building blocks of SU8 photoresist with a size of tens of micrometer and an anisotropic shape[29]. They investigated the influences of shape parameters such as length/width ratio on the geometry of the assembled structures (Fig. 3a). Vermant's group obtained micrometer ellipsoid building blocks by mechanical stretching round polymer balls and realized assembly of these building blocks in a side-by-side manner at interfaces (Fig. 3b)[30]. de Simone *et al.* prepared hundreds of micrometer-scaled polymer rods with segments of different surface wettability and obtained macroscopic assemblies at water/oil interface based on capillary force (Fig. 3c)[31]. Besides, Liu *et al.* fabricated substrates with patterned surface wettability and prepared silicon building blocks with wetting properties matching the

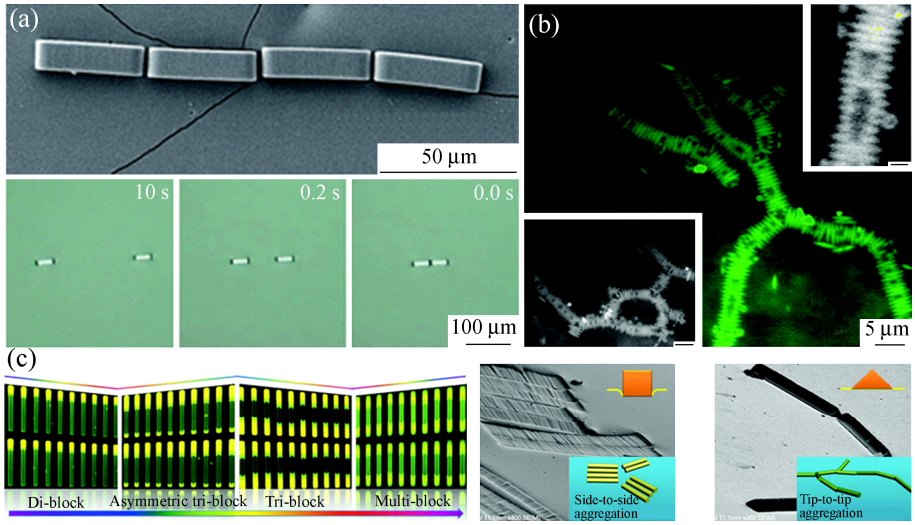

Fig. 3 Examples of macroscopic assembly driven by capillary forces: (a) particles of SU8 photoresist (Reprinted with permission from Ref. [29]; Copyright (2009) The Royal Society of Chemisry); (b) polymer ellipsoid (Reprinted with permission from Ref. [30]; Copyright (2011) American Chemical Society); (c) polymer rods (Reprinted with permission from Ref. [31]; Copyright (2012) American Chemical Society)

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patterned area on the substrates, thus having realized a large scale of assembly of the building blocks on the substrates through the mechanism based on both shape matching and capillary interactions[32]. Although the above works demonstrated assembly induced by capillary forces, the limitation lies in the dependence on the formation of interface: the macroscopic building blocks should form menisci at two immiscible phases; without post-solidification methods, the formed ordered structures cannot maintain after leaving the interface. For example, a pair of hydrophobic building blocks can be associated through capillary forces at the air/water interface; if lifting one of the building block out of the interface, the formed assembly will disassociate due to the disappearance of the menisci dependent on the interface.

On the aspect of macroscopic assembly driven by magnetic forces, Zrínyi *et al.* used magnetic responsive hydrogel building blocks by loading magnetic nanoparticles in the hydrogel fabrication[33]; they obtained aggregated assemblies in the center under gradient magnetic field and regular chain-like assemblies under uniform magnetic field. Similarly Xu's group tailored the geometry of the magnetic responsive hydrogel assemblies by using templates of designed shapes and further chemically crosslinked the structures to stabilize these assemblies, which were used as 3D biological scaffold for cell growth (Fig. 4a)[34]. Whitesides *et al.* directly combined ferromagnetic nickel nanorod and other non-magnetic materials to form sub-micro building blocks, which self-assembled into closely-packed hexagonal aggregates of rods under magnetic field[35]. They interpreted the mechanism with the principle of minimizing the interfacial free energy (Fig. 4c). Besides incorporating ferromagnetic and paramagnetic species, Demirci *et al.* took advantage of diamagnetic properties of most materials to control the motions of non-magnetic hydrogel building blocks[36]; with guided localization, they aligned the hydrogels into ordered structures (Fig. 4b).

For macroscopic assembly driven by electric field, de Simone's group applied alternate electric field to microscale polymer building blocks of different shapes to produce polarization effects on these building blocks due to the dielectricity[37]. The charges separate and move towards two ends of the building blocks, thus creating attraction forces between oppositely charged ends of the building blocks to form chain structures (Fig. 4d). Whitesides *et al.*[38] reported electrostatic assembly of macroscopic polymer spheres of the same dimension but with opposite charges generated by contact electrification when agitated on flat metallic surfaces; these spheres assembled to highly ordered, closely-packed arrays (Fig. 4e) because of the balance between repulsive interactions of like-charged spheres and attractive forces of unlike-charged ones. The above driving forces of macroscopic assembly, *i.e.* magnetic force, electronic force and capillary force share several characteristics in common: (1) the force range is long enough and the force strength is sufficient to enable assembly of macroscopic building blocks; (2) surface modification of building blocks is not necessary to form assemblies; (3) the interactions between the building blocks and the environment (*e.g.* interfaces, electric field,

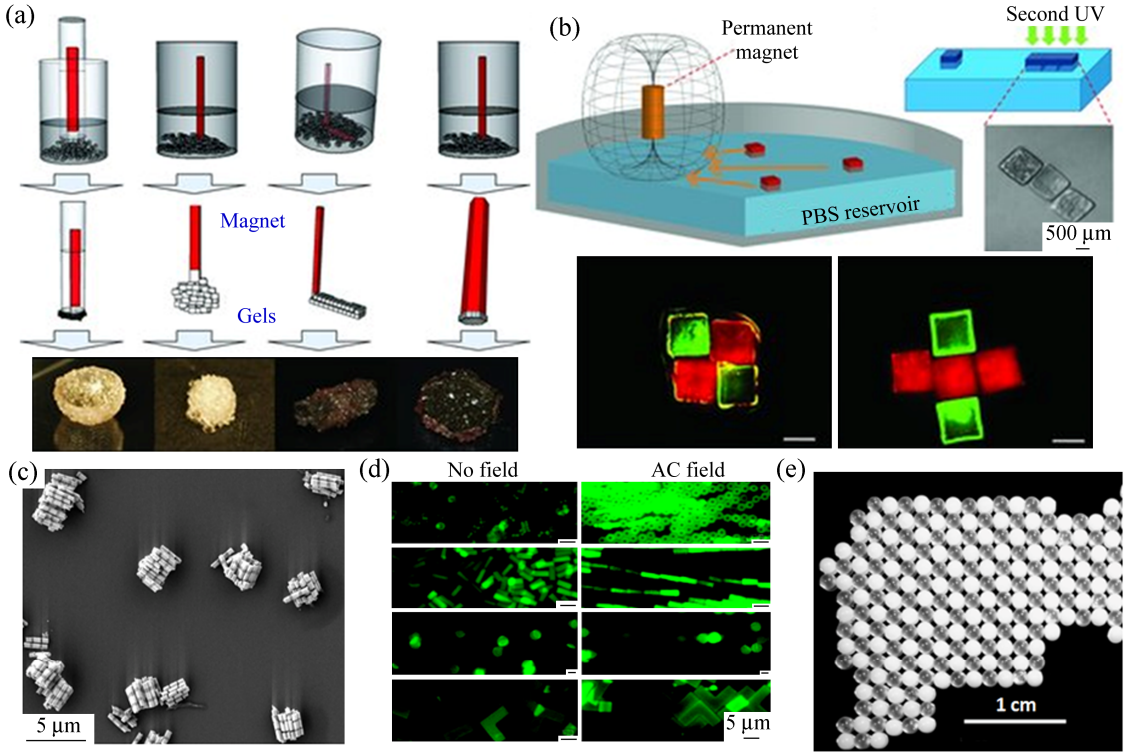

Fig. 4 Magnetic-field-driven assembly of (a, b) hydrogels (Reprinted with permission from Refs. [34, 36]; Copyright (2011, 2013) WILEY-VCH Verlag GmbH & Co. KgaA, Weinheim) and (c) metal nanorods (Reprinted with permission from Ref. [35]; Copyright (2003) American Chemical Society); (d, e) Assembly of polymer particles driven by electronic field (Reprinted with permission from Ref. [37]; Copyright (2008) American Chemical Society) (Reprinted with permission from Ref. [38]; Copyright (2003) Nature Publishing Group)

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magnetic field) determine the assembled patterns based on the principle of minimizing the systematic free energy. However, these kinds of macroscopic assemblies obtained in the presence of interfaces or external field are highly dependent on the environment. Without post-crosslinking to solidify the assembled structures, the assemblies cannot be maintained, which is also a bottleneck problem limiting the applications of self-assembled structures. Therefore, whether directly using chemical interactions such as intermolecular interactions can realize the assembly and simultaneously the stabilization of the assemblies remains a challenge as well as a fundamental question to be answered.

MACROSCOPIC SUPRAMOLECULAR ASSEMBLY

Unlike the above long-ranged forces, classical supramolecular chemistry uses intermolecular interactions such as electrostatic interactions, hydrogen bonding, charge transfer, coordination bonding *etc.*, which always have short interactive distance at nanoscale or even lower scale[39, 40]. The most important difference between macroscopic assembly and MSA lies in the fact whether the assembly result is caused by molecular interactions, *i.e.* the overlapping or influences between the electron clouds between chemical groups. In contrast, macroscopic assembly is mainly caused by physical interactions such as capillary forces. For the building blocks of molecular or nanoscaled level, the size range of interactive distance is comparable with that of the building blocks. Therefore, by modifying supramolecularly interactive groups onto these building blocks or further anisotropic modification, self-assembly or even programmable assembly is possible to obtain ordered structures[41, 42]. However, for macroscopic building blocks, the supramolecular interactions have much shorter force range than the size of the building blocks. To tackle the problem of interactive distance far from matching building block size, two issues are necessary to enable MSA: (1) the interactive molecules (*e.g.* host/guest groups) on the surface of the building blocks should reach the corresponding interactive distance, *i.e.* the two interactive macroscopic surfaces should have enough close contact within nanometer range; (2) numerous binding events (*e.g.* molecular recognition between host/guest groups) between macroscopic surfaces should occur effectively to provide sufficient association strength. Simply modifying the macroscopic surfaces with supramolecular groups is not enough to meet the above two requirements because the surface roughness is not ignorant for macroscopic surfaces: when two surfaces approach, the roughness normally higher than nanometer or even hundreds of nanometers may probably hinder close contact of the surfaces or molecular interactions. With a low percentage of effective molecular interactions between two macroscopic surfaces, the association strength is not sufficient enough to realize MSA under shaking process.

The effect of increasing building block size hindering molecular interactions has been demonstrated by de Cola *et al.* with the assembly of micrometer zeolite through reversible and dynamic nitroxide exchange process[19]. They prepared alkoxyamine-functionalized and nitroxide-terminated zeolites (length: 1 μm), respectively, and loaded green or red dyes in the cavity of zeolites to distinguish the surface molecules. For alkoxyamine-functionalized zeolites, extra spacer of tetraethylene glycol (TEG) was added between the alkoxyamine moiety and the zeolite channel. They found it difficult to obtain long chain assemblies without the TEG spacer while an ordered chain structure (Fig. 5) was possible under identical experimental conditions if a TEG spacer of a certain length is introduced. This result indicated that increasing the building block size to 1 micrometer already confronts the challenge of realizing assembly by simply modifying interactive molecules onto the building block surfaces. What if the building block size is further increased? Whether is supramolecular assembly still possible? We have checked the assembly behaviors of cubic PDMS building blocks with a side length of 3 mm and modified with polyelectrolyte multilayers bearing host/guest moiety. Under sufficient shaking process in water, we did not observe any assembly behaviors. The reason for the failure of assembly in this case is that the surface supramolecular groups on rigid macroscopic building blocks have very limited mobility and the possibility to reach molecular interactive distance by either contacting or self-adaption in collisions under shaking process is quite low, leading to week binding strength. To handle the problem of low binding strength in MSA, several systems or methods have been proposed to realize MSA, including: (1) material selection such as using the highly flowable system of hydrogels to lower the surface roughness and improve the mobility of the surface molecules; (2) introducing soft spacing between rigid non-hydrogel building blocks and supramolecular groups to realize similar effects of hydrogel systems; (3) applying mechanical pressure to force the contact of surfaces and increase chances of molecular interactions.

MSA of Hydrogels

Harada *et al.* used the first strategy of selecting highly flowable hydrogel systems to demonstrate MSA driven by various supramolecular interactions[21, 43–45]. Taking host/guest molecular recognition as an example, they copolymerized normal hydrogel monomer with monomer bearing host or guest groups in the fabrication of hydrogels to introduce supramolecular surfaces onto hydrogel building blocks. These hydrogels were cut into a millimeter-scaled size and shaken in water; the hydrogels bearing host groups selectively assembled with those guest groups, leading to aggregates or chain-like assemblies (Fig. 6). The reason for the successful MSA of hydrogels is mainly the flowable property of hydrogels. On one aspect, the "self-flattening" effect of flowable system can reduce the surface roughness and promote tight contacting of two macroscopic surfaces; on the other aspect, compared with rigid surfaces, the hydrogel surfaces provide high mobility of the surface molecules with low limitations caused by solid substrate. Thus the interactive molecules have a high chance for effective binding. With the specific hydrogel materials, many classical supramolecular interactions can be used for MSA. Harada's group reported MSA based on other intermolecular interactions such as metal-ligand interaction[46], electrostatic attraction[47], base-pairing of DNA strands[48] *etc*. (Fig. 7). Moreover,

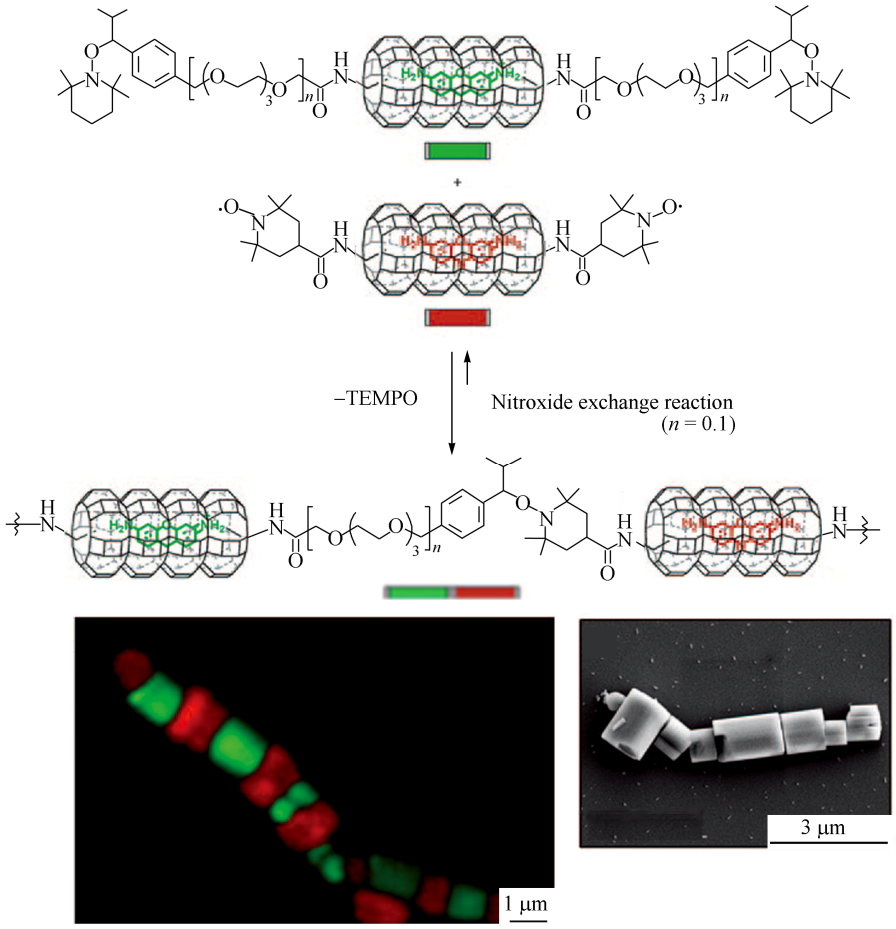

Fig. 5 Assembly of microscale zeolites through dynamic nitroxide exchange process (Reprinted with permission from Ref. [19]; Copyright (2010) WILEY-VCH Verlag GmbH & Co. KgaA, Weinheim)

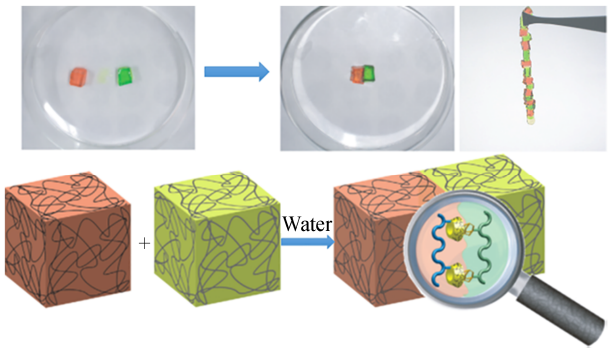

Fig. 6 MSA of hydrogels (Reprinted with permission from Ref. [21]; Copyright (2010) Nature Publishing Group)

stimuli-responsive properties of the applied supramolecular interactions were demonstrated for the control of dynamic MSA behaviors through adjusting of photo[49], pH values[50], temperature[51], solvent[52], pH/glucose[53], redox properties[47] and so on. These works have proven that the supramolecular assembly behaviors observed for building blocks of molecular level or nanoscale can similarly be observed for macroscopic hydrogel systems.

Based on hydrogel systems, some progress has been made to tailor the geometry of the assembled in MSA. Yin *et al.* used rolling circle amplification to attach giant DNA onto hydrogel building blocks and realized prescribed assembly through hybridization of complementary DNA strands (Fig. 8a)[54]. The edge lengths of the used hydrogel cubes range from 30 μm to 1 mm, all of which can achieve MSA. Besides, assisted by photolithography method, anisotropic building blocks were obtained with DNA strands on one specific face and thus led to assemblies associated with designated geometry. Xie's group tried to control the assembled patterns through a supramolecular Lego way[55]: they prepared hydrogels with both host/guest groups and stimulus-responsive groups such as carboxylic acid groups were pre-deformed mechanically; reversible molecular recognition was used as supramolecular interlock between building blocks. Theoretically interactive hydrogels can be assembled into arbitrary geometries and disassembled if necessary just like Lego assembly. Moreover, the responsive functional groups can induce 3D shape change of the assemblies, thus increasing the complexity of the assembled systems as shown in Fig. 8(b). Dynamic assembly/disassembly is also possible for organic gels as reported by Tang *et al*[56]. They introduced quadruple hydrogen bond unit of UPy in the fabrication of organic gels and realized MSA in a polar solvent of dimethylsulfoxide. When changing the solvent to an apolar solvent toluene, the structures are disassembled due to the shielding of protons. Through adjustment of solvent, the macroscopic organic gels can be

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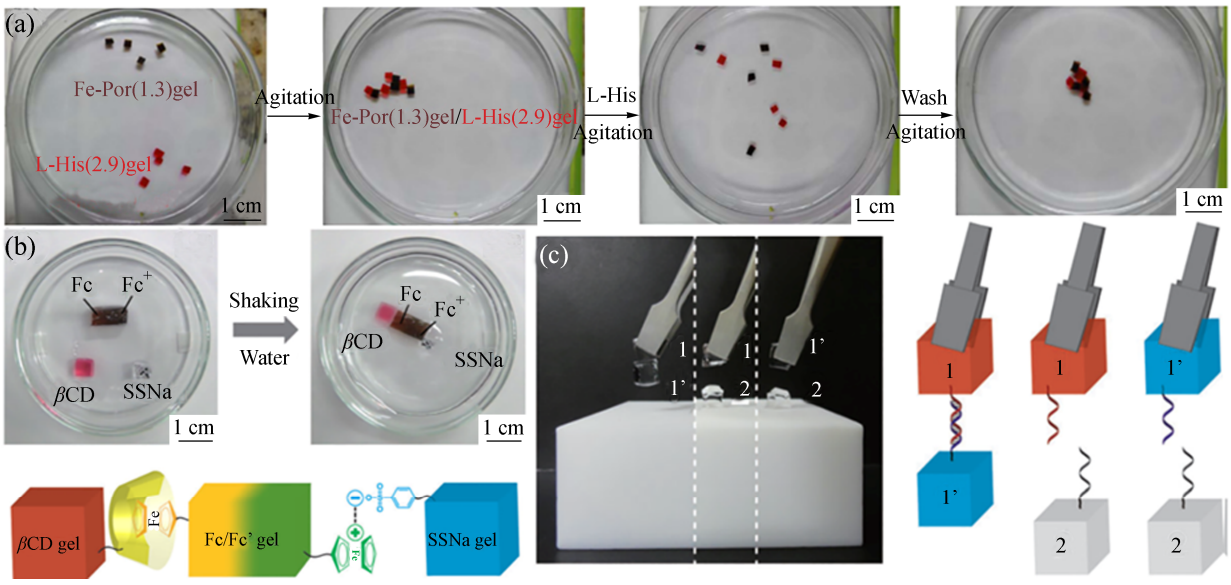

Fig. 7 MSA of hydrogels driven by (a) metal-ligand interaction (Reprinted with permission from Ref. [46]; Copyright (2013) Nature Publishing Group), (b) electrostatic interaction (Reprinted with permission from Ref. [47]; Copyright (2014) WILEY-VCH Verlag GmbH & Co. KgaA, Weinheim) and (c) base pairing (Reprinted with permission from Ref. [48]; Copyright (2015) WILEY-VCH Verlag GmbH & Co. KgaA, Weinheim)

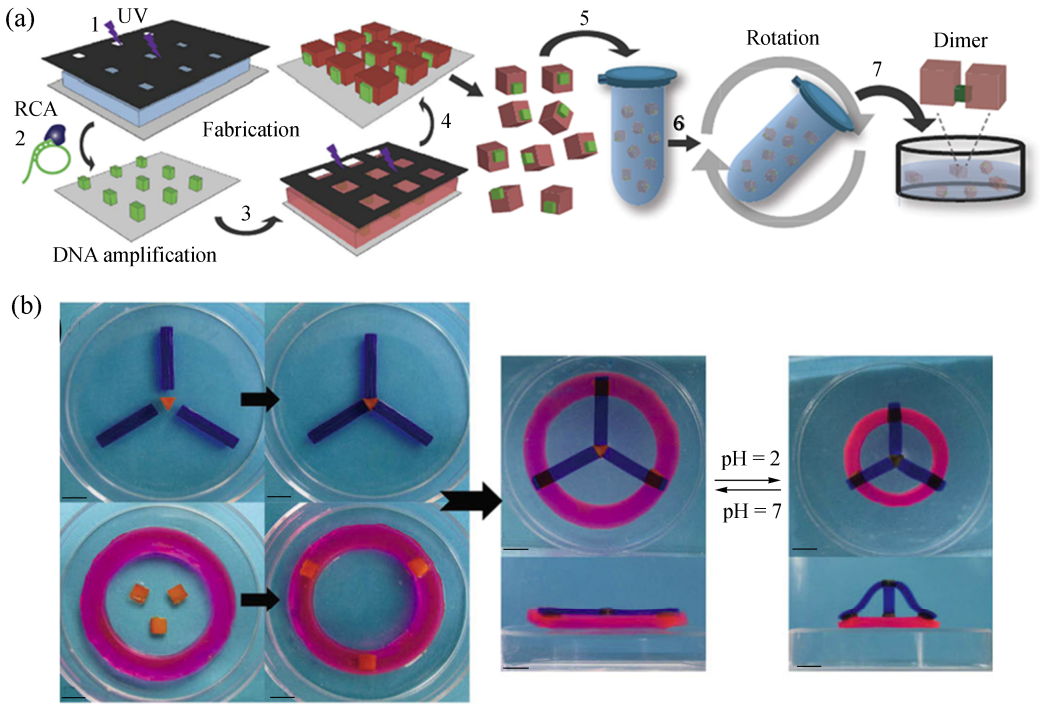

Fig. 8 (a) MSA of hydrogels driven by DNA hybridization (Reprinted with permission from Ref. [54]; Copyright (2013) Nature Publishing Group); (b) Stimulus-responsive MSA (Reprinted with permission from Ref. [55]; Copyright (2014) WILEY-VCH Verlag GmbH & Co. KgaA, Weinheim)

controlled to assemble or disassemble.

Until now, gel systems as the building block materials enable sufficient intermolecular interactions between two macroscopic surface under shaking process to achieve MSA due to the intrinsic property of high flowability. Even though, how to break the limit of MSA on materials and how to establish versatile design principle of MSA still remain important fundamental problems.

MSA of Non-hydrogel Building Blocks

Inspired by the flowability of hydrogel systems to increase the mobility of the surface molecules, we considered introducing highly flowable coating onto rigid non-hydrogel building blocks before modification of supramolecularly interactive groups[20]. As shown in Fig. 9, millimeter scaled PDMS cubes and molecular recognition of β-cyclodextrin (CD)/azobenzene (Azo) are used as model building blocks

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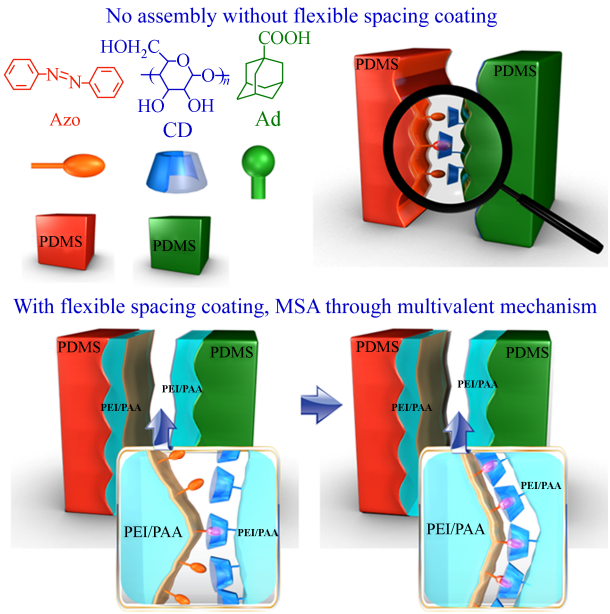

Fig. 9 Illustration of MSA through the presence of the flexible spacing coating (Reprinted with permission from Ref. [20]; Copyright (2014) WILEY-VCH Verlag GmbH & Co. KgaA, Weinheim)

and supramolecular interaction for MSA of rigid materials. When the CD or Azo groups are directly modified onto the PDMS surfaces and shaking them in water, MSA is not possible because most CD/Azo groups can hardly reach nanoscale interactive distance and thus the binding strength is not strong enough to form any assemblies. If we pre-coat the building blocks with a "flexible spacing coating" with high flowablity, two issues can be tackled: (1) the rough surface can be smoothed to some degree when this coating is deposited because the flowable system tends to fill valleys; (2) the surface rigidity is lowered and extra molecules modified onto this flexible spacing coating should have higher mobility than those on bare surfaces. With the flexible spacing coating, the CD/Azo groups on the surface are not highly restricted and thus can adjust their conformation, orientation, location *etc.* to adapt to the binding events when two interactive surfaces approach. Numerous interactive groups with soft and flexible links are easier to follow multivalent mechanism, which can enhance the apparent binding constant and realize MSA.

In an attempt to establish a design principle of MSA based on "flexible spacing coating promoting MSA", we used millimeter cubic PDMS as model building blocks and modified the surfaces through layer-by-layer assembled technique with composite polyelectrolyte multilayers: the bottom layer is the poly(ethyleneimine) (PEI)/poly(acrylic acid) (PAA) multilayer working as the flexible spacing coating with thick[57, 58], flowable[59], sticky, and self-healing[60] properties; the second layer is the poly(diallyldimethylammonium chloride) (PDDA)/poly-(sodium-*p*-styrenesulfonate) (PSS) film to decrease the stickiness of PEI/PAA; the outmost layer is the PDDA/PAA-CD (PAA grafted with cyclodextrin groups) or PDDA/PAA-Azo (azobenzene-functionalized PAA) as the supramolecular interactive layer. With the above combination, the surface roughness is reduced due to the sufficient thickness and flowability of the flexible spacing coating and meanwhile the supramolecular interactive groups are highly mobile. The presence of the anti-adhesion layer of PDDA/PSS handles the side effect of stickiness caused by the thick PEI/PAA layer[61]. As a result, identical building blocks with the same host groups or guest groups could not associate with each other but the interactive host or guest building blocks could selectively form assemblies. The strategy or idea of introducing spacing layer works well to associate large building blocks not only in this case but also in De Cola's work[19] in promoting the assembly chance of 1-μm zeolite with a TEG polymer spacer. However, further fundamental questions such as "whether flexible spacing coating is necessary for building blocks of certain sizes?", "how is spacing length/thickness and building block size correlated?" *etc.* remain to be investigated systematically.

MSA Assisted by External Forces

For most current MSA works, the macroscopic building blocks mainly rely on external mechanical forces such as agitation, shaking or rotation to have collision and contacting essential for supramolecular interactions. However, these random colliding processes normally provide very short contacting time and thus the binding probability lowers in limited collision events. Besides the above two strategies of either selecting gel systems or introducing flexible spacing coating, another possible manner to promote supramolecular interactions between two macroscopic surfaces is directly applying external mechanical forces. With external pressure, more surface groups may be forced into molecularly interactive distance and thus have more chance for molecular interactions and increased binding strength. In this situation, flexible spacing coating is not necessarily required and slight mobility of the surface supramolecular groups may be enough for MSA. For example, we previously used glass fibers (diameter: 17 μm; length: 500 μm) as building blocks modified with a multilayer of PAA and magnetic nanoparticles (MNPs) and meanwhile modified the glass substrates with a multilayer of PDDA/PAA; guided by magnetic localization, pressed with external force and associated by coordination bonding between MNPs and PAA, the glass fibers could be aligned into arbitrary patterns on the glass substrates (Fig. 10A)[62].

Besides microscale building blocks of glass fibers, Xie's group reported forced assembly of macroscopic epoxy materials by taking advantage of high polymer mobility above its glass transition temperature (T_g)[63]. Taking epoxy resin as an example, they mixed some methanol to the epoxy resin at a temperature higher than T_g to break some internal hydrogen bonding within the resin and simultaneously applied external pressure to attach the surfaces tightly to strengthen the binding force of the interface or alternatively modified polyelectrolytes grafted with hydrogen donor/accepter onto the resin. Similarly, strong cation-π interaction was also used by this group to clarify the adhesion behavior of macroscopic synthetic polymers[64]. Later Kim *et al.* demonstrated underwater adhesion of two silicon wafers

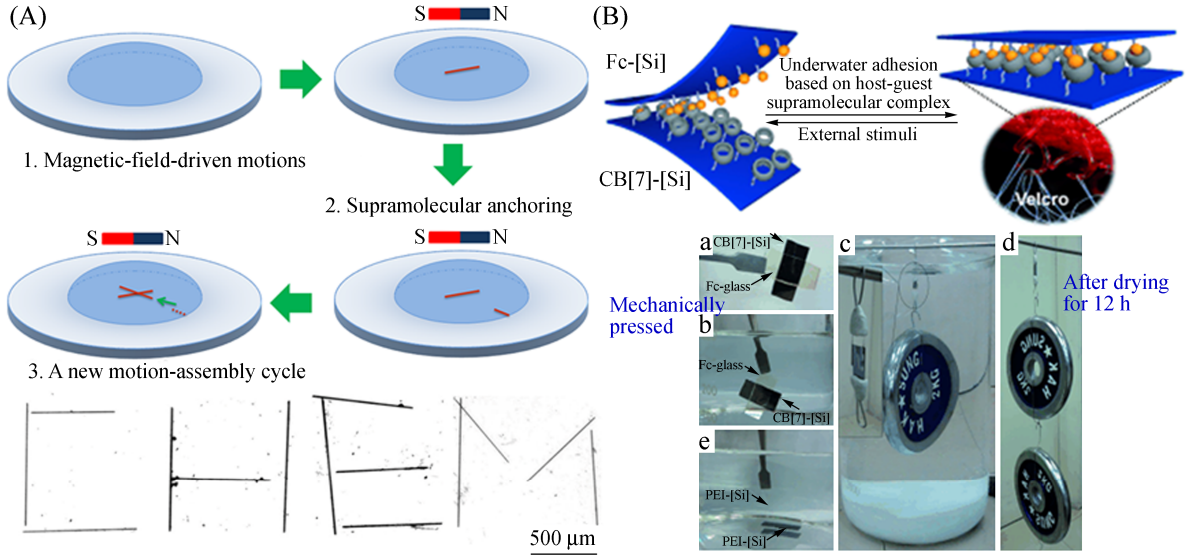

Fig. 10 Supramolecular assembly of (A) microscale glass fibers (Reprinted with permission from Ref. [62]; Copyright (2011) American Chemical Society) and (B) silicon wafers assisted by external forces (Reprinted with permission from Ref. [65]; Copyright (2013) WILEY-VCH Verlag GmbH & Co. KgaA, Weinheim)

of 1 cm^2 through supramolecular interactions assisted by applying extra forces with clip[65]. Before modifying the silicon surfaces with host or guest groups, they pre-coated a thin layer of PEI as a "cushion layer" as a compensation for mechanically forced binding process. The stability of the assembled silicon wafers is shown by being hung with a 2-kg object, which is increased to 4 kg after drying the system (Fig. 10B). These works applied "supramolecular glue" assisted by external mechanical forces for the association of macroscopic objects, providing new solutions to conventional adhesion problems as well as supports for positive effect of external forces on MSA behaviors.

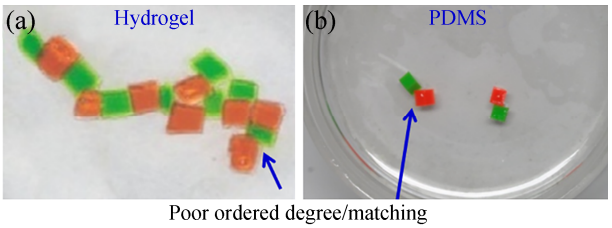

Fig. 11 Mis-matching phenomena in (a) hydrogel and (b) rigid building block systems of MSA (Reprinted with permission from Ref. [21]; Copyright (2010) Nature Publishing Group) (Reprinted with permission from Ref. [20]; Copyright (2014) WILEY-VCH Verlag GmbH & Co. KgaA, Weinheim)

HOW TO REALIZE PRECISE MSA

On the basis of having achieved MSA through the above proposed strategies, we still face a challenge of fabricating functional supramolecular materials for practical uses. However, for most current work relying on rotation or shaking to force the building blocks to collide and assemble, a ubiquitous problem exists that all the obtained assemblies have low ordered degree (Fig. 11)[20, 21]. Although the building blocks modified with host molecules will selectively assemble with those bearing the corresponding guest molecules rather than self-adhesion, the matching degree or associated pattern of the building blocks (*e.g.* contacting area, angle, direction *etc.*) is normally unpredictable and irregular. This is because when the building block size or number increases, the random shaking or rotating processes can lead to growing possibility of different kinetic paths and result in various assembled patterns. Especially in mechanically driven rotation or shaking processes, the parameters regarding the contacting area, collision chance *etc.* are difficult to control. Once the assembled structures have formed, the associated building blocks cannot easily self-adjust to a perfect matching degree. Besides, many supramolecular interactions have short interactive distance (normally nanoscale), which cannot allow macroscopic building blocks to adjust the matching degree before association when they approach to interactive distance. These problems lead to the difficulty in obtaining ordered structures for practical uses as bulk supramolecular materials according to the principle of structure determining performance. Therefore, developing solutions to address these problems is urgent.

To improve the ordered degree of MSA structures, our group applied the strategy of "interactive distance matching size of building blocks" to first adjust the matching degree of the building blocks through long ranged interactive forces and then obtain stable assemblies through short ranged supramolecular interactions. At the same time, we tried to mimic assembly behaviors at molecular level by increasing the random motion and collision of building blocks. Therefore, we designed chemical engines on the building blocks for spontaneous motions. As illustrated in Fig. 12, the PDMS building blocks with a dimension of 8 mm × 8 mm × 2.7 mm are attached with substrates bearing rough platinum structures on opposite or adjacent side surfaces. We considered several factors in the design of the building blocks: (1) the rough platinum can catalyze the decomposition of hydrogen peroxide solutions to release bubbles, which propel the building blocks to move on the solution due to asymmetric

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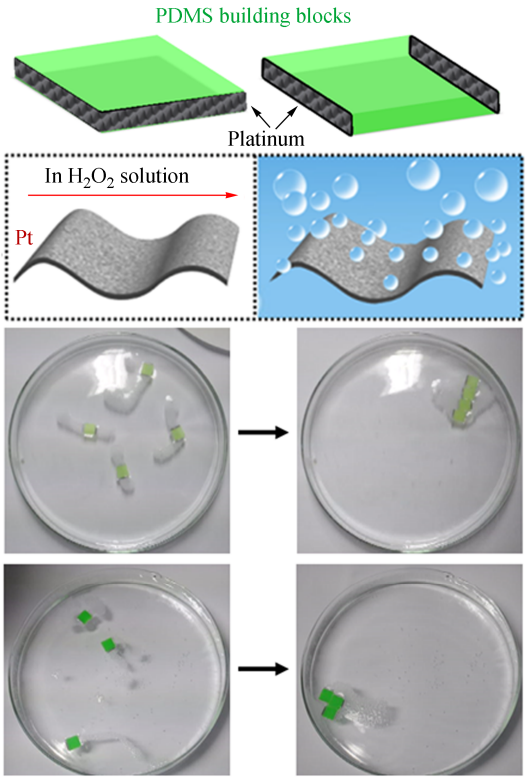

Fig. 12 Fabrication of building blocks with anisotropic wettability and their precise assembly (Reprinted with permission from Ref. [66]; Copyright (2014) WILEY-VCH Verlag GmbH & Co. KgaA, Weinheim)

forces in the bubble generation; thus the building blocks can move in a random way similar to the molecular motions; (2) the attached hydrophilic platinum has different wettability from the original hydrophobic PDMS surfaces, thus contributing to anisotropic wettability to induce capillary force formed by the menisci of hydrophobic surfaces as the long range forces; when two millimeter-scaled building blocks approach to a distance of millimeter level comparable with the interactive distance of capillary force, the building blocks have enough time and space to self-adjust their matching degree before total association; (3) the platinum can be flexibly attached to any surfaces of the building blocks to cause different meniscus locations and assembled patterns: chain-like or triangle structures if the platinum is attached to opposite or adjacent side surfaces (Fig. 12)[66]. In this work, three problems still remain to be tackled: (1) we did not stabilize the obtained ordered structures, which cannot maintain without the interface; (2) some generated bubbles attach to hydrophobic surfaces and hinder tight association of the building blocks; (3) the hydrophobic surfaces are relatively inert to introduce supramolecularly interactive groups.

The above problems have been addressed to further improve the macroscopic supramolecular self-assembly. On the aspect of driving forces to propel the building blocks, we replaced the platinum-hydrogen peroxide system with a bubble free system of Marangoni-effect-driven self-propulsion. The dominant long ranged hydrophobic-hydrophobic interaction has been changed to the design of hydrophilic-hydrophilic interaction for the feasibility of inducing supramolecular groups on the hydrophilic surfaces. Short ranged supramolecular interactions are induced onto the hydrophilic surfaces to stabilize the ordered structures aligned by long ranged forces. In detail, we designed the building blocks as shown in Fig. 13. The PDMS building blocks have anisotropic wettability with two superhydrophobic and two superhydrophilic surfaces, a cavity within the building blocks to store surfactant (*e.g.* ethanol) for the formation of Marangoni effect, and a tiny hole to release the surfactant onto water surface. Upon placing onto water surface, the stored ethanol will be released and soon generate local Marangoni flow, which can propel the building blocks to move randomly. Since both superhydrophobic and superhydrophilic surfaces can generate menisci to induce capillary-force-driven assembly, we adjusted the density of the building blocks to a state of hydrophilic-hydrophilic curvature advantageous over hydrophobic-hydrophobic one at water/oil interface, thus making the selective assembly between hydrophilic surfaces. After assembly driven by long ranged forces, the supramolecular groups on the assembled hydrophilic surfaces can further have short ranged interactions through MSA assisted by the "flexible spacing coating", leading to stable assemblies independent of interface. In this manner, we combined long ranged forces for precise alignment and short ranged supramolecular interactions to stabilize the assemblies, leading to precise MSA[67] and ordered structures promising for further practical uses as supramolecular materials.

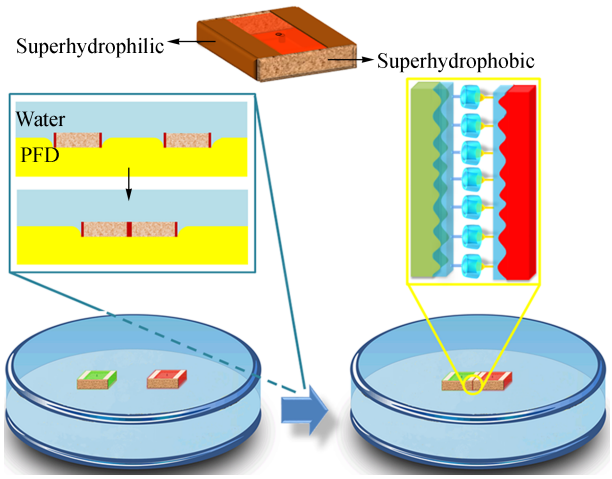

Fig. 13 Precise MSA driven by Marangoni effect (Reprinted with permission from Ref. [67]; Copyright (2015) WILEY-VCH Verlag GmbH & Co. KgaA, Weinheim)

Besides joining long and short ranged forces, tailoring shape of the building blocks to induce anisotropic properties can result in improved ordered degree of MSA structures. For example, compared with cubic building blocks, cylindrical building blocks show anisotropic properties in binding events by taking advantage of the difference in surface area: the top/bottom flat surfaces are favorable for molecular interactions than the curved side surface; especially when the diameter/height ratio of the building block is high, the selectivity is towards the assembly between top/bottom

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surfaces. To clarify this hypothesis, we designed cylindrical building blocks of varied diameter/height (*d*/*h*) ratios: 1, 2, 4 and 6. The building blocks were modified with the flexible spacing coating and supramolecular groups of CD/adamantane (Ad). The MSA behaviors of two cylindrical PDMS exhibit three kinds of assembled patterns: associated by both top/bottom surfaces (face-face), one top/bottom surface and the other side surface (face-side), both side surfaces (side-side). But the percentage of each assembled pattern changed with the varied *d*/*h* ratios as displayed in Fig. 14(a)[68]: with increasing *d*/*h* ratio, the face-face assemblies become dominant with a percentage of 91% in all assemblies. Although simply adjusting *d*/*h* ratio can improve the ordered degree of the assemblies, the matching degree of two cylindrical building blocks is still not 100%. A possible solution may be a combination of both anisotropic surface properties and size/shape design.

The above strategies for precise MSA are mainly focused on the design of building blocks before assembly behaviors to avoid occurrence of error. Actually for self-assembly related methods, error is inevitable because self-assembly is essentially insensitive to errors. Considering the advantages of the reversibility of most supramolecular interactions, we have established a mechanism of self-correction based on dynamic assembly/disassembly processes, which can identify imprecise structures after the assembly processes and selectively correct them[69]. Taking negatively and positively charged cubic hydrogels as a model system, we realized MSA of these isotropic hydrogels under shaking process in water. As expected, both precise and imprecise are present in a random shaking process. Considering that MSA may have accidental results especially regarding the matching degree between the assembled building blocks, we used statistical summary of 100 isolated pairs of interactive hydrogels to check the matching degree after MSA. To distinguish the imprecise and precise structures by the system itself rather than human judge, we found a diffusion-kinetics-dominant disassembly mechanism: the NaCl solution can shield the surface charges to disassociate the assemblies but the consumed time for disassembly differs for assemblies with

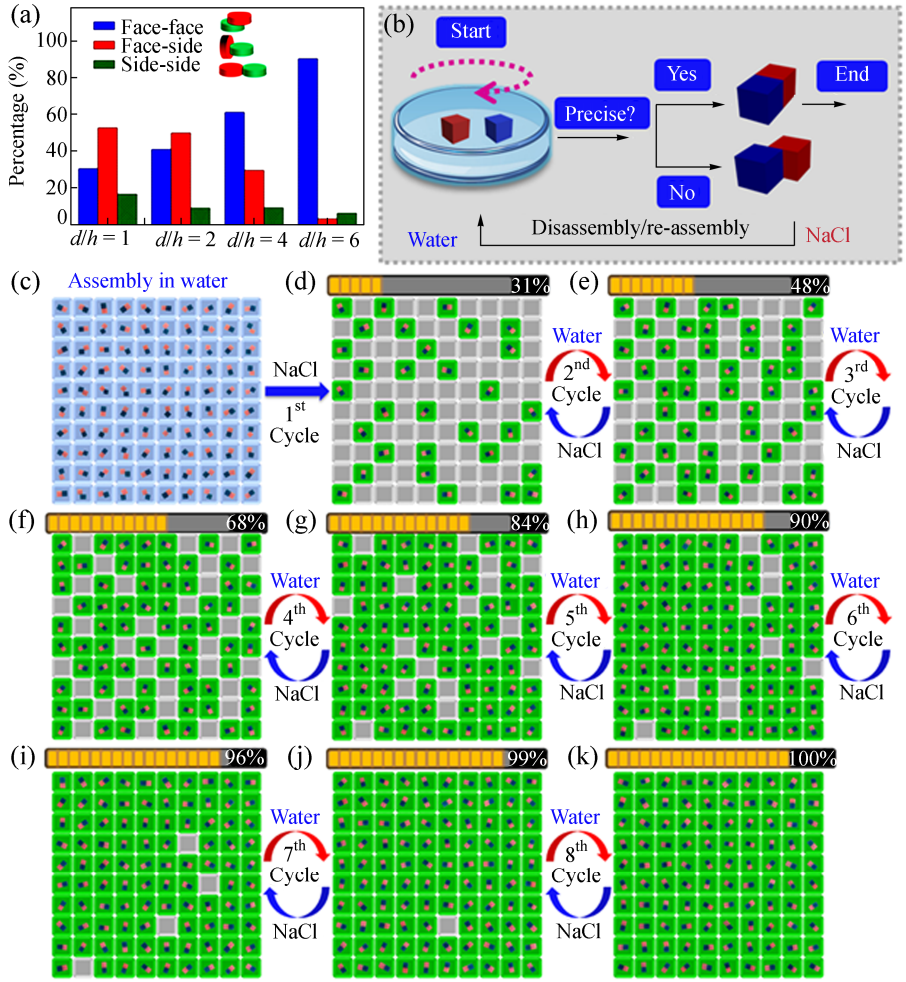

Fig. 14 (a) Anisotropic shape effect on the selectivity of assembled patterns in MSA (Reprinted with permission from Ref. [68]; Copyright (2016) American Chemical Society); (b) Illustrated programmable procedure and (c–k) real implementation of the self-correction strategy to achieve 100% assembly (The dimer in each cube is extracted from photos of the MSA results. The grey cubes indicate disassembled structures (not shown); the green ones show precise structures. The progress bars indicate the self-correction schedule to 100% precise assembly.) (Reprinted with permission from Ref. [69]; Copyright (2017) WILEY-VCH Verlag GmbH & Co. KgaA, Weinheim)

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different matching degrees; for a dimer with low matching degree (< 25%), it takes about 10 min to totally disassemble; when < 50%, the disassembly needs almost 30 min; at > 90%, the total disassembly time reaches 1 h. The difference in disassembly time acts as a selective rule to disassociate imprecise structures while influencing little on precise structures. After disassembly, these separate building blocks have another chance to re-assemble in water to be precise. The iteration of disassembly in NaCl solution and re-assembly in water can lead to gradual self-correction of the system as shown in Figs. 14(b)–14(k): the self-correction mechanism can be illustrated in a computer language of "while loop", *i.e.* a conditional cycled method for iteration and the NaCl solution acts as the judger between yes/no choice; in the beginning a random shaking in water results in various assembled patterns; with the start of disassembly/re-assembly cycles, we can observe that only precise structures remain in NaCl solutions; when the cycle number increases, the percentage of the precise structures increases; after less than eight cycles, all 100 dimers can be corrected. We envision that precise MSA can be completed by the self-assembly system itself; we human being only need to set a cycle number and the exposure time in NaCl/water with automatic mechanical system.

We have summarized two strategies to achieve precise assembly. One is pre-design of the building blocks with anisotropic properties. Thus the assembly process can be directed to the pattern of precise assembly. The other is post-treatment of self-correction mechanism based on iteration of disassembly/re-assembly cycles. The first strategy is challenging for implementation to tailor the anisotropic properties of molecular or nanoscaled building blocks. The second strategy is easier in the aspect of building block preparation. The basic discipline is to introduce appropriate energy form between the energy status of imprecise and precise structures. Therefore, theoretically, it is possible to find suitable energy interference to selectively disassemble imprecise structures while maintaining precise assemblies for both macroscopic and molecular building blocks.

APPLICATIONS OF MSA

Fabrication of Tissue Scaffolds

Based on the understanding of MSA mechanism, we face chances and challenges towards wide applications by applying MSA as a new methodology for the fabrication of supramolecular materials. In tissue engineering[70], methods to fabricate 3D scaffolds with precisely localized chemical or bioactive species are urgently needed[71] especially with requirements in being biocompatible, mild, efficient, precise and flexible in individual design. MSA can well meet these restricted requirements thanks to these unique advantages: (1) mild experimental conditions; most supramolecular interactions such as molecular recognition[72], electrostatic interaction[73], coordination bonding[5, 74], hydrogen bonding[75] *etc.* are quite mild to occur, thus avoiding using tough solvent, heating, UV irradiation; (2) abundant biocompatible molecular recognition systems are available in supramolecular chemistry such as biotin/avidin interaction[76], DNA hybridization[77], which can be used as linkers to incorporate bioactive species; (3) flexible control over the alignment of building blocks and localization of bioactive species designated on specific building blocks.

On the aspect of constructing 3D scaffolds, Xu's group[78] demonstrated MSA of oppositely charged poly(ethyleneglycol) (PEG) hydrogels with a dimension of hundreds of micrometer by using electrostatic interactions. Complementary shapes were designed for interactive hydrogels so that advanced structures were assembled by gently shaking. These microscale hydrogels were further assembled into 3D multilayered spheroid with control over thickness and number of microgels in each layer for potential uses as 3D scaffolds. They have evaluated the biocompatibility of the as-prepared microgel assemblies with fibroblast cells encapsulated within charged hydrogels at varied concentrations of 5% and 10%. The result showed > 90% cell viability. They interpreted that some cell death might be caused by radical species generated by photoinitiator during UV irradiation and such toxicity could be minimized by parameter optimization. Besides, they introduced long ranged forces (magnetic forces[79]) or other energy (ultrasound[80]) to align microhydrogels into complex 3D structures and subsequently crosslinked them for stabilization. The as-prepared hydrogel assemblies show > 90% cell viability for further biological use (Fig. 15). In the presence of magnetic field, the hydrogels loaded with Fe_3O_4 magnetic nanoparticles can induce the alignment of the hydrogels; for acoustic field assisted assembly, they used recognition of complementary shapes under ultrasound field to obtain ordered structures as complex scaffolds for cell growth.

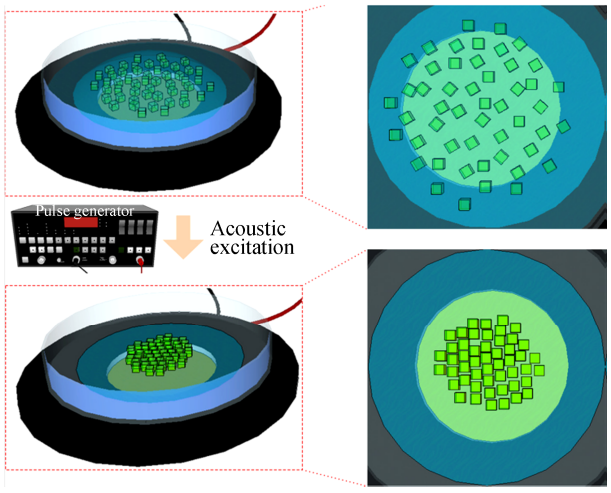

Fig. 15 Assembly of complementary shaped hydrogels under ultrasound field (Reprinted with permission from Ref. [80]; Copyright (2011) Elsevier)

Besides hydrogel systems, other biocompatible materials such as PDMS can also be used for the construction of 3D structures for cell growth. Our group has proposed a methodology of magnetic-field-assisted MSA for the fabrication of 2D patterns and 3D ordered structures in an attempt to prepare complex 3D scaffolds loaded with designated chemical or bioactive species within the structure.

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To handle the problem of precisely localize the building blocks, we modified magnetic responsive species onto the building block surfaces and guided locomotion with magnetic field with sub-micrometer precision. After moved to the targeted locations, the building blocks were fixed through "supramolecular glue", *i.e.* MSA between the building blocks and the substrates. We checked the feasibility of this method with glass fibers (diameter: 17 μm; averaged length: 1 mm) as model building blocks[81]; with stepwise magnetic guidance and supramolecular assembly through CD/Azo (host/guest) interactions, we obtained patterned structures, which could be disassembled with competitive Ad guest molecules (Fig. 16a) due to the reversibility of supramolecular interactions. Constructing 3D ordered structures with targeted modification is significant for applications in tissue engineering. Especially, 3D scaffolds with required growth factors at designated locations are meaningful for cell differentiation and tissue formation. However, quite a few available methods to fabricate 3D ordered structures face problems of keeping biological species active in the fabrication of such complex scaffolds. MSA can normally be done mildly in water in a bottom-up manner; therefore, it is advantageous to fabricate 3D scaffolds with bioactive species. We further demonstrated the construction of 3D structures with PDMS strips (2 mm × 150 μm × 100 μm) by combining MSA based on molecular recognition and magnetic localization (Fig. 16b)[82], leading to periodically stacked layered structures. Adult stem cells (ASCs), human umbilical vein endothelial cells (HUVECs), and human dermal fibroblast (HDF) cells all show good adhesion and growth on the 3D structures. Moreover, PDMS strips modified with biotin could be flexibly aligned to designated locations within the 3D structures for further loading of proteins through the biotin/avidin link.

Multiplex DNA Detection

In molecular detection and diagnose, the demand in multiplex detection with high accuracy and efficiency as well as low error rates is increasing. Conventional lithographic or printing methods can realize these goals but have strong dependence on expensive instruments and skilful workers. We considered about the feasibility of MSA to integrate various building blocks with mild and facile experimental procedures. Therefore, we proposed the magnetic-field-assisted MSA as a new methodology to fabricate DNA microarray for multiplex detection of DNA strands. By using glass fibers as modules bearing different DNA targets, we designed several functional DNA sequences for anchoring onto substrates, detection of targeted DNA and fluorescent signaling of the hybridization results, respectively. Three kinds of targeted DNA sequences related with HIV-1 U5 long terminal repeat, hepatitis B virus and Ki-67 were selected. Correspondingly, complementary DNA sequences for anchoring and fluorescent linking were modified onto substrates and glass fibers. Three types of fluorescent chromophores were grafted onto DNA strands for the visualization of detection results. As shown in Fig. 17[83], three kinds of glass fibers modified with binding sites targeting three types of target DNAs were assembled onto the same substrate by stepwise MSA assisted by magnetic localization, leading to a DNA microarray for the detection of single, double or triple target DNAs. If the targeted DNAs are present in the tested samples (*e.g.* aqueous solution or blood sample) mixed with fluorescently marked DNA sequences, hybridization of the targeting sites on the substrate and the target DNA will occur; subsequently fluorescent DNA can bind to designed residual sequences and then the detection result will be displayed with fluorescent patterns. Cross contamination is avoided and the test is sensitive to error down to one single base, *i.e.* if one base pair of the target DNA is wrong, no strong fluorescence will be observed. MSA has provided an alternate method for the fabrication of DNA microarray and meanwhile multiplex DNA detection shows new chances of MSA towards practical uses.

CONCLUSIONS

As a new branch in supramolecular chemistry, MSA has provided a platform to investigate supramolecular interactions of numerous groups between two macroscopic surfaces and established a methodology to construct bulk supramolecular materials through directly associating large

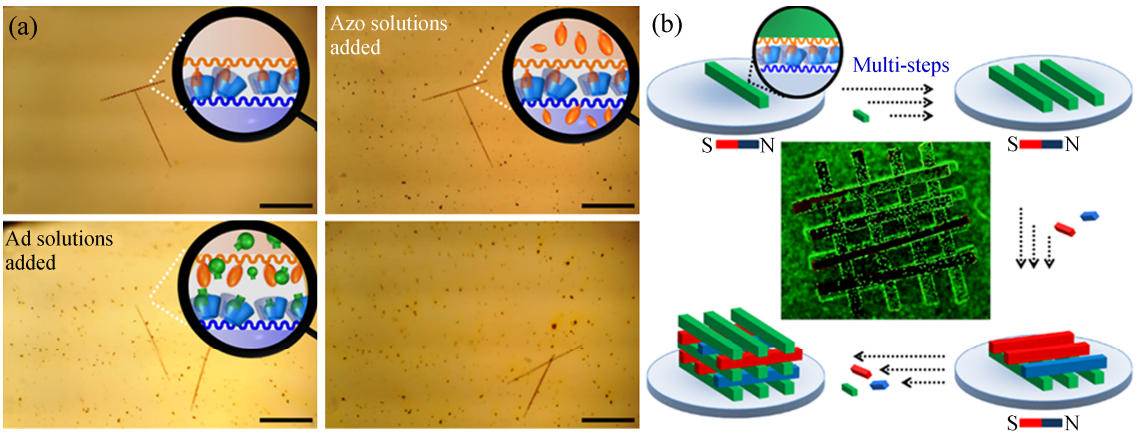

Fig. 16 Magnetic field assisted MSA to construct (a) 2D (Reprinted with permission from Ref. [81]; Copyright (2014) American Chemical Society) and (b) 3D ordered structures (Reprinted with permission from Ref. [82]; Copyright (2015) WILEY-VCH Verlag GmbH & Co. KgaA, Weinheim)

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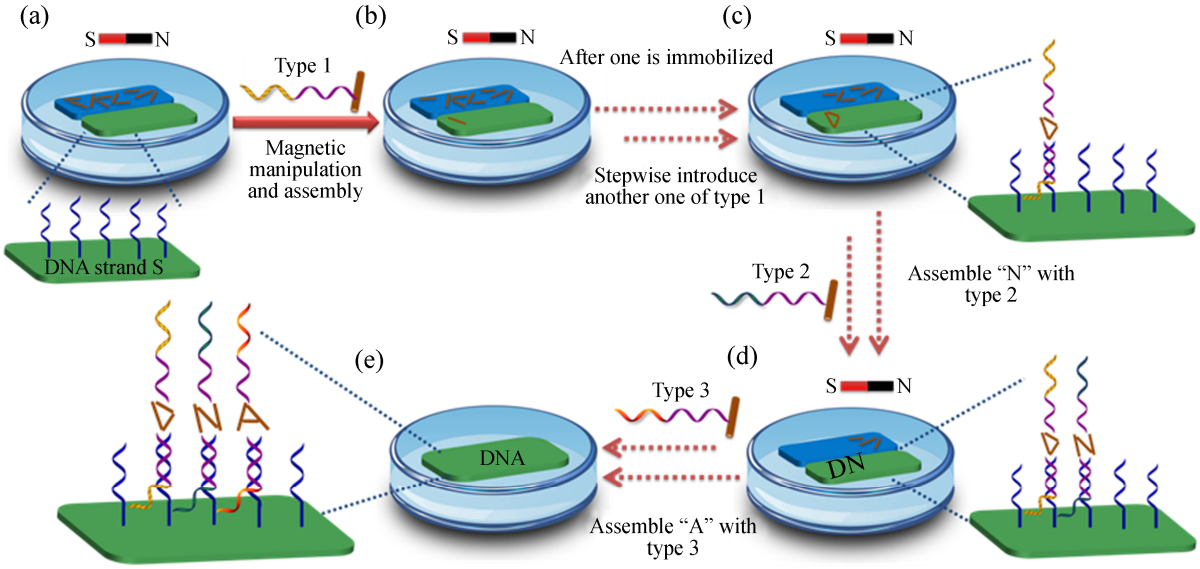

Fig. 17 Illustration of constructing a multiplexed DNA pattern and multiplex DNA detection (Reprinted with permission from Ref. [83]; Copyright (2017) American Chemical Society)

building blocks with supramolecular interactions. This review has covered the history and recent development of MSA, tried to interpret the research content, goals and significance of this area. With the current problems and challenges, we summarize from the angle of design principle and strategies including three solutions to improve the binding events between macroscopic surfaces: (1) selecting highly flowable hydrogel systems for direct assembly; (2) inducing "flexible spacing coating" between the substrate and outmost supramolecular interactive groups; (3) relying on mechanical forces to prolong the contacting time of macroscopic surfaces and the chance of molecular recognition. Based on the implementation of MSA, how to realize precise MSA to improve ordered degree of assembled structures for good material performance and wide applications, remains as new chance and challenges of MSA.

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