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Progressive Macromolecular Self-Assembly: From Biomimetic Chemistry to Bio-Inspired Materials

Yu Zhao, Fuji Sakai, Lu Su, Yijiang Liu, Kongchang Wei, Guosong Chen, and Ming Jiang**

Dedicated to the 20 Anniversary of Department of Macromolecular Science of Fudan University

Macromolecular self-assembly (MSA) has been an active and fruitful research field since the 1980s, especially in this new century, which is promoted by the remarkable developments in controlled radical polymerization in polymer chemistry, etc. and driven by the demands in bio-related investigations and applications. In this review, we try to summarize the trends and recent progress in MSA in relation to biomimetic chemistry and bio-inspired materials. Our paper covers representative achievements in the fabrication of artificial building blocks for life, cell-inspired biomimetic materials, and macromolecular assemblies mimicking the functions of natural materials and their applications. It is true that the current status of the deliberately designed and obtained nano-objects based on MSA including a variety of micelles, multicompartment vesicles, and some hybrid and complex nano-objects is at their very first stage to mimic nature, but significant and encouraging progress has been made in achieving a certain similarity in morphologies or properties to that of natural ones. Such achievements also demonstrate that MSA has played an important and irreplaceable role in the grand and long-standing research of biomimetic and bio-inspired materials, the future success of which depends on mutual and persistent efforts in polymer science, material science, supramolecular chemistry, and biology.

1. Introduction

Humans have admired, learned from, and been inspired by Nature from the beginning of civilization. The dream of mimicking nature is becoming more realistic step by step due to the developments in modern science. In the long march to achieve such mimicry, the birth of biomimetic chemistry in the 1970s marked a turning point where mimicking research in chemistry was really launched. As defined by Ronald Breslow,[1] biomimetic chemistry is the field in which chemists invent new substances and reactions that imitate biological chemistry. In this definition, the intellectual flow from biology into chemistry was highlighted, with the purpose of expanding the scope of chemistry.[1b] At its early stage, biomimetic chemistry was regarded as a branch of organic chemistry and the work concentrated on the level of molecules, formation and cleavage of covalent bonds following the way learning from the living body. Artificial enzymes aiming at fast and high selectivity have been the key research subject in biomimetic chemistry with emphasis on the idea of molecular recognition, which is also the center of supramolecular chemistry. Later, the principle and methodology of biomimetic chemistry have gradually expanded and penetrated to other sub-disciplines with great successes. In polymer science, the achievements in precise polymerization that were developed in the last two decades provide a good example. Now, the preparation of a remarkably diverse and growing range of precise polymers with mimic complex and hierarchical architectures from the natural prototypes become realistic.[2]

Looking back the tremendous progresses of polymer science achieved in the past 30 years, we do admire and appreciate the unusual foresight of Helmut Ringsdorf as shown in his article in *Angewandte Chemie* in 1988.[3] In the paper, which has been cited more than one thousand times so far, Ringsdorf put forward the questions: "where is the future, where are the adventures" of polymer science as it became a classical discipline and a mature science. He clearly presented the answer, "Polymer science finds itself not only on the borderland between chemistry and physics, but also between materials science and life science" and "On the border between the different disciplines of science, adventures are waiting". It meant that polymer science could no longer restrict itself to common plastics and should expand to neighboring science, particularly biology. Along this line, Helmut is a pioneer in practice as well since he designed the first artificial polymeric liposomes, and pointed out possible contributions from polymers to the simulation of cellular processes, such as the stabilization of biomembranes and specific surface recognition.[3] He also pointed out that the functions of biomacromolecules, including polysaccharides and nucleic acids, are in all cases based on the combination of molecular mobility

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and high order. Led and encouraged by such pioneering work, the mimetic research of macromolecular science have gradually moved to materials level, i.e., constructing artificial living elements mimicking the morphology first and then functions turned to the main stream in this area. Among the various research areas of polymers, macromolecular self-assembly (MSA), which emerged in 1970s, no doubt contributes most to the biomimetic chemistry and bio-inspired materials. It is understandable as the central mission of MSA is to constructing well-defined assemblies varying in architectures, size scales and complexities, etc. from macromolecules as main building blocks. MSA experienced an amazing progress and steadily began to contribute to biomimetic and bio-inspired study by its own way. This is the thesis of this review.

This review paper pays special attention to the integration of MSA with supramolecular chemistry and material science under the light of biomimetics.[4] We have to mention that in the past ten years, quite a few valuable review articles picked the topics related to biomimetics focusing on the progresses made in the field of inorganic materials, nanotechnology and nano-engineering, which will not be covered in this article.[5] Regard to applications of assembled objects of macromolecules, no doubt, those towards medicine such as drug and gene delivery, medical imaging, etc. have been the hottest subject currently as thousands papers including timely reviews published per year. So this article will not cover this area. We make this article with a 'beads-on-a-string' structure where MSA is the string which wraps and connects all of the important recent fruits including: (a) a brief introduction of some representative developments of MSA which have been used or have potential usage in the mimic research; (b) artificial basic building blocks of life built by MSA; (c) cell-inspired bio-mimetic materials, mainly vesicles; (d) assembled materials with property of self-healing and self-sorting and a few applications, e.g., template synthesis, nanoreactors etc. We hope that by our elaborate reorganization of the intelligent relevant research papers in literature, the significant role and bright future of MSA as an alternative avenue in achieving biomimetic or bio-inspired materials is clearly and concisely presented.

2. Aspects of MSA Developments

The studies on self-assembly of synthetic macromolecules started in 1960s when block copolymers with well-defined structures in terms of composition, molecular weight and its distribution, and the chain architectures, etc. were attained in laboratory and part of them was commercialized as thermoplastic elastomer. Various different regular morphologies of the block copolymers formed by 'microphase separation' in solution or bulk aroused great interest of polymer community as such regular mesophase structures had not been observed for any synthetic polymers before.[6] Regard to self-assembly of block copolymers, the repulsion between unlike blocks and the cohesive interaction between the like blocks is the main driving force which differs from the specific interactions that are concerned most in supramolecular chemistry. So for a long time, MSA developed with a little influence from supramolecular chemistry. It is interesting to see that the terminology of 'phase separation' describing the most important feature of block copolymers was widely used in polymer literature and was gradually replaced by 'self-assembly' in later 1990s, which reflected the penetration of supramolecular chemistry to MSA

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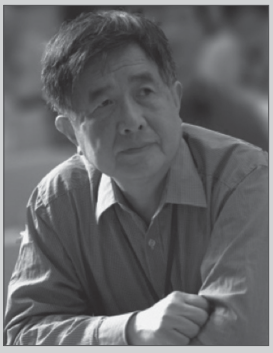

Ming Jiang graduated from the Chemistry Department at Fudan University, China in 1960. Since then he has served within the Chemistry, Materials, and Macromolecular Science Department at Fudan University as assistant, lecturer, and then as associate professor. He was promoted to professor in 1988. He 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.

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and then promoting its further developments. The early studies of MSA focused on a few block copolymers formed by a limited number of monomers, i.e., styrene, butadiene, isoprene and pyridine *etc.*, which were readily obtained by living anionic polymerization. In 1990s, the research of MSA became relatively mature as various different self-assembled morphologies of block copolymers as desired were obtained and the relationships between the morphology and copolymer parameters were clearly explored by theoretical studies. Therefore the subsequent very rapid, nearly explosive development of MSA in this new century, to some extent, is unexpected. Such unusually rapid developments, in our opinion, can be attributed to two main factors: the developments in methodology of polymer synthesis provide a broad range of new macromolecules as building blocks for MSA studies and for constructing new self-assembled objects; learning from biology and orientating the research to biology open up vast new research fields of MSA which will be the central thesis of this review.

In the past two decades, polymer synthesis developed tremendously.[7] Living anionic polymerization has improved itself by expanding the monomers applicable to some acrylates *etc.* and post polymerization modification, which makes producing some polyelectrolyte blocks possible. The most outstanding contributions originate from the advent of controlled radical polymerization (CRP) including ATRP (Atom Transfer Radical Polymerization) and RAFT (Reversible Addition-Fragmentation chain Transfer) polymerization. Nowadays, varieties of well-defined copolymer architectures with designed composition, molecular weight and their distribution *etc.*, can be prepared from the most existing monomers by living anionic polymerization, CRP, cationic and metathesis routes. Some complex copolymers are obtained via a combination of two or more of these polymerization methods. In the context of this review, we would say that the well-defined block copolymers composed of doubly water-soluble blocks prepared by ATRP are particularly significant as such copolymers readily assemble in water by changing environmental conditions, which benefits to their applications in the biological systems. Now we discuss some of the developments in MSA, which have been used or are potentially useful in the bio-related studies.

2.1. New Strategies in Micellization of Macromolecules

Differing from that in the early stage studies of MSA where block copolymers were the overwhelming majority of the building blocks, now random copolymers, dendrons, dendrimers and hyperbranched polymers *etc.* are all able to assemble into nanostructured materials. Many reports are on the 'micellization' of amphiphilic random copolymers in water into nanostructures.[8] Such assemblies may not have clear boundary between the hydrophobic core and hydrophilic shell while hydrophilicity-rich surface exists stabilizing the assemblies. Considering the composition flexibility and the readiness in preparation, MSA of random copolymers is promising in further study for their use in bio-related studies and applications. Hyperbranched copolymers also have aroused interest in MSA because they show peculiar assembly behavior. Zhou and Yan reported macroscopic self-assembly of an amphiphilic hyperbranched multiarm copolymer with a hydrophobic poly(3-ethyl-3-oxetanemethano) core and many hydrophilic PEG (poly(ethyleneoxide)) arms in acetone. The copolymer aggregated into membranes with a lamellar structure as multiwall tubes reaching millimeters in diameter and centimeters in length.[9] Since then there has been an ever-growing interest in MSA of the hyperbranched polymers resulting in various aggregates including physical gels, micro- and nano-vesicles and fibers, etc.[10] In addition, hyperbranched polymers were found to form giant vesicles in a size range of micrometers, which are one or two orders of magnitude larger than the ordinary vesicles of block copolymers. This size is comparable to that of cells so hyperbranched copolymers in spite of their ill-defined structure became favorites in MSA for mimicking cell membranes.[11]

The success in self-assembly constructing nanostructures from homopolymers has been resulted from so-called 'block-copolymer-free strategy' in MSA developed by Jiang's group. This strategy was based on their long-term research on interpolymer complexation via hydrogen bonding of complementary polymers. Usually the complexation in solution leads to irregular aggregates or precipitates. By new molecular design of polymer structures and usage of specific assembly processes, several approaches to polymeric micelles driven by interpolymer hydrogen bond, were developed. In the resultant micelles, the core and shell are connected by hydrogen bond or other interactions. So it is named non-covalently connected micelles (NCCMs).[12] Two typical approaches are addressed below.

1. Localization of the binding sites of hydrogen bonds of homopolymers (or random polymers): As shown in **Figure 1**, **A** is a proton-donating polymer with the donor at the polymer chain end only, **B** is the proton-accepting polymer, on which the acceptors randomly distribute. Then, in a common solvent, hydrogen-bonding graft polymer is formed. After switching the medium to a selective solvent, NCCMs with hydrogen bonds connecting the core and shell form. The micelles are stable for a long period of time and more importantly, the composition, structural factors and size of the NCCMs can be adjusted.
2. Solvent/non-solvent process: In this method, there are no restrictions to the distribution of the proton donors and acceptors on the polymer chains. The key point here is to control the process of the polymers contacting each other and then the assembly process. The two polymers **A** and **B** containing hydrogen-bonding sites are dissolved in their own solvent respectively. The solvent of **B** should be the precipitant for **A**.

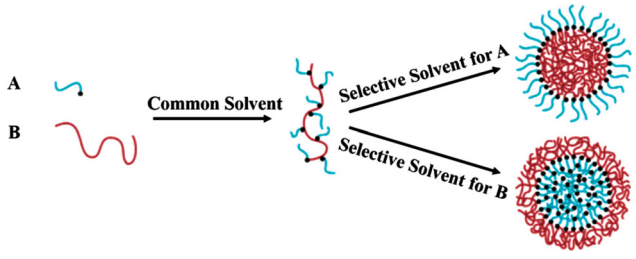

Figure 1. Schematic representation of the formation of hydrogen bonding graft polymers and the corresponding NCCMs. Reproduced with permission.[12] Copyright 2005 American Chemical Society (ACS).

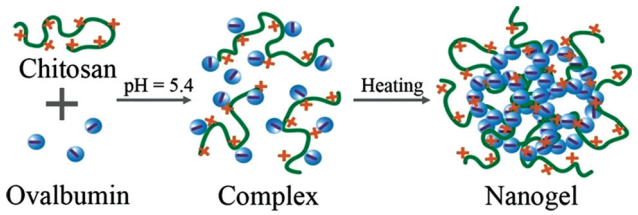

Figure 2. A schematic representation of Nanogels of chitosan and ovalbumin. Reproduced with permission.[14b] Copyright 2006 ACS.

When the solution of **A** is added to that of **B** dropwise, **A** will aggregate immediately while **B** will gather around the aggregates of **A** driven by hydrogen bond. Thus NCCM with **A** as the core and **B** as the shell comes into being. If NCCM shell can be crosslinked and then the core is moved by switching the medium to a good solvent for the core, hollow spheres are obtained. The driving force for these two approaches are hydrogen bonding. NCCMs could also be obtained driven by ligand-metal coordination, one representative paper on this study was presented by O'Reilly et al.[13]

This strategy was further developed and applied in fabricating nontoxic, biocompatible and biodegradable NCCMs composed of bio-macromolecules i.e., proteins and polysaccharides. For example, via adjusting solution pH, formation of the complexes between two different proteins or between a protein and a polysaccharide could be realized. Then the complex solution was heated above the temperature of protein denaturation to induce intermolecular hydrophobic interactions, hydrogen bonding and disulfide bonding, which led to NCCM formation (**Figure 2**). This method is simple and effective. In the process, no chemicals were used except acids and alkalis as pH adjustors. The method has been found widely applicable to fabricate "green NCCMs" with different combinations such as two globular proteins, a globular protein/a linear protein, and a globular protein/a polysaccharide as long as the two components carry opposite charges.[14] Furthermore, the conjugates can be used as carriers to deliver hydrophobic nutriments and drugs.[15] Quite recently, the lysozyme-dextran conjugates prepared via this green route with loaded Au nanoparticles and Doxorubicin were found effective in simultaneous drug release and biomedical imaging.[16]

2.2. MSA Promoted by Host-Guest Interactions

It is only in recent years that the concepts and achievements related to molecular recognition developed from supramolecular chemistry have drawn the increasing attention of polymer scientists and thus greatly promoted the progress of MSA. In this respect inclusion complexation i.e., host-guest interaction has played a major role. One example of the early work of MSA along this line was reported by Wang and Jiang.[17] Here a hydrophobic linear polymer P*t*BA-Ada (P*t*BA, poly(*tert*-butyl acrylate)) containing pendent adamantane (Ada), and a hydrophilic polymer PGMA-CD (PGMA, poly(glycidyl methylacrylate)) containing β-cyclodextrin (β-CD) was found to form micelles with P*t*BA-Ada as core and PGMA-CD polymer as shell. The core and shell was non-covalently linked by inclusion complexation between β-CD and Ada. Such NCCMs were featured by double-scale hydrophobic domains, i.e., the hydrophobic core with a size of about 100 nm and the plenty of hydrophobic cavities of β-CDs with a size of 0.7 nm on the surface. Thus there is sufficient room for further surface modification. Moreover, when the shell was crosslinked and then the core was dissolved by switching the solvent from water to DMF, the micelles were converted into hollow spheres of PGMA-CD. Afterwards, several reports on constructing non-covalently connected block copolymers linked by inclusion complexation emerged. Shi et al. reported that Ada end-functionalized PNIPAM (poly(*N*-isopropylacrylamide)) and β-CD end-functioned P4VP (poly(4-vinylpyridine)) formed a pseudo block copolymer via the Ada/β-CD interaction.[18] Zou and Jiang reported that dendrons with a binding site azobenzene (Azo) group at their apex was able to form a non-covalently connected linear-dendron amphiphile with β-CD ended PNIPAM due to AZO/β-CD interaction.[19] The resultant vesicles from this amphiphile show both optical and thermal responsiveness. Zhang et al. expanded this concept by introducing ion-ion interactions and dynamic hydrogen bonding and performed systematic research on so-called supra-amphiphiles, which has been nicely reviewed.[20] Introducing host-guest interaction into the studies of MSA has obviously promoted MSA in many aspects. In addition to constructing NCCM and supra-amphiphiles, the successes in modification of assemblies, protein-polymer conjugates and hybrid supramolecular hydrogels, etc. are substantial as well. All of these have been reviewed by Chen and Jiang.[21] The most prominent feature of the supramolecular assemblies based on the inclusion complexation is the reversibility of the stimuli-responsiveness. This in fact inherits the perfect reversibility of some inclusion pairs, e.g., Azo/α-CD to light irradiation, ferrocene (Fc)/β-CD to electrochemistry and almost all such pairs responsible to "supramolecular replacement". We would like to emphasis that for such supramolecular assemblies driven by inclusion complexation, the stimuli-responsibility can be realized even when all of the component blocks are inert to environment changes. One of the recent results on such supramolecular hydrogel is shown in **Figure 3**. This hydrogel was fabricated based on the inclusion complexation between β-CD and Fc. Hybrid Inclusion Complex (HIC) with β-CD modified quantum dots as the core and Fc-ended diblock copolymer PDMA-*b*-PNIPAM (DMA: *N*,*N*-Dimethylacrylamide), as the shell formed first driven by the β-CD/Fc interaction. When temperature was increased to above LCST (lower critical solution temperature) of PNIPAM, gelation took place due to the interchain aggregation of PNIPAM. The hydrogel shows multiple stimuli-responsiveness. Besides the thermo-reversibility, gel-to-sol transition can be achieved by addition of either an oxidizing agent or a competitive guest Ada to Fc, where Ada replaced Fc to form inclusion complex with β-CD, and thus made the HIC dissociate.[22]

2.3. Micelle-Vesicle Transitions

Polymeric vesicles have drawn increasing attention in MSA due to their great role in mimicking cell membrane, which will be

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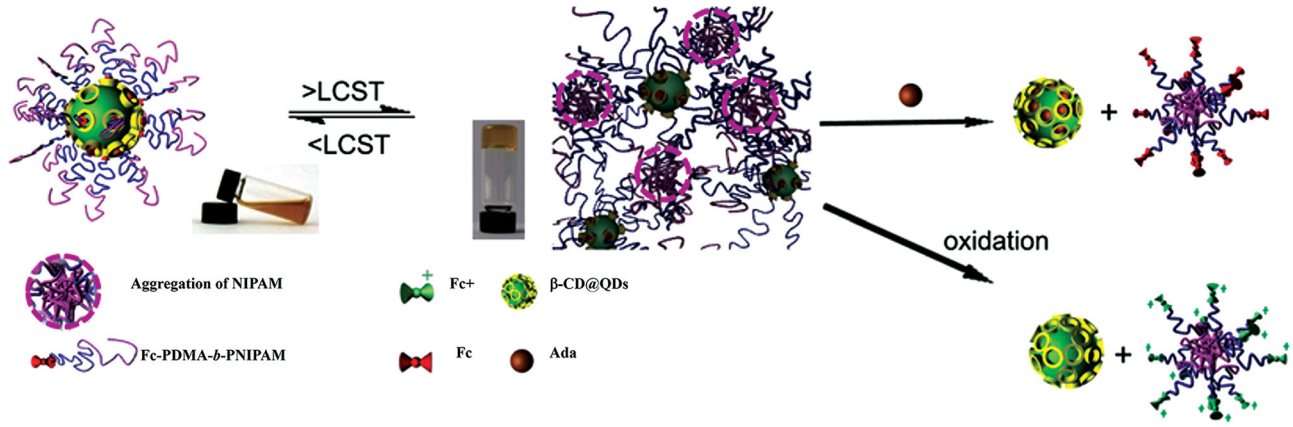

Figure 3. Schematic illustration of the formation and dissociation of the supramolecular HIC hydrogel by temperature change or adding oxidation agent or competitive guest Ada.

discussed in section 4. Most polymeric vesicles studied in literature are formed directly from amphiphilic block copolymers. However, it was also found that vesicles could be attained from spherical micelles of block copolymers via stimuli-induced micelle-vesicle transitions. This kind of research would not only provide useful vesicle materials but also benefit better understanding of the self-assembly mechanisms. In these researches, the thermally induced coil-globule transition of PNIPAM around its LCST (32 °C) has been utilized to adjust the amphiphilic balance of the block copolymers and the packing parameter *p*, leading to the morphology transition. Grubbs and his coworkers reported first that triblock copolymer PEG-*b*-PNIPAM-*b*-PI (PI: polyisoprene) in water formed small spherical micelles at low temperatures, which turned to large vesicles after heating at 65 °C, for as long as 3 weeks. After cooling to 20 °C for about 48 hours, the vesicles returned to assemblies with much smaller sizes.[23] Then O'Reilly et al. demonstrated that diblock copolymer P*t*BA-*b*-PNIPAM, with an quaternary amine end to the PNIPAM block, realized the similar transition at 65 °C, which was faster but one week was needed.[24] Both of the results were successful in realizing the transition, but still suffered from the long duration for the transition and unsatisfactory reversibility. Further efforts from the two groups targeted the problem from different directions. Replacing the hydrophobic P*t*BA block by PMA (poly(methyl acrylate)) with a lower glass transition temperature (T_g), O'Reilly's group achieved even faster morphology transition in about one day.[25] Recently, Grubbs et al. claimed that it was the strong interchain hydrogen bonding between the amide groups of PNIPAM and the high T_g that slowed down further rearrangement, resulting in a week-long transition.[26] This explanation seems not in concert with the well-known fact that the conformation change of PNIPAM around it LCST (32 °C) takes place in hundreds of seconds only. Besides, such a slow and incompletely reversible transition process reported has seriously hindered deep investigation on the transition mechanism and made the applications almost impractical. Chen and Jiang tried to solve the problem from a point of view differing from the previously reported efforts, i.e., to realize the fast and reversible micelle-vesicle transition by greatly reducing the restriction to the mobility of the PNIPAM chains imposed by the solid micellar core.[27] Thus, an asymmetrically end-modified PNIPAM (*C12*-PNIPAM-*CA*) with a short hydrocarbon chain (*C12*) at one end and carboxyl group (*CA*) at the other, was designed and employed. As a result of full monitoring the process by light scattering, the transformation from micelles to vesicles can be realized within 30 minutes, while the reverse process only takes a few minutes. So it is proposed that when the temperature reaches LCST, the micelles as a whole serve as building blocks in constructing the vesicles via processes of combination, fusion, etc., in which only local conformation adjustment of PNIPAM is involved (**Figure 4**). In other words, during the transition there is no micelle dissociation and reorganization involved which may take long time.

This transition mechanism was confirmed by a hybrid system. Chen and Jiang studied such transition of a new HIC composed of a gold nanoparticle (AuNP) core covered with

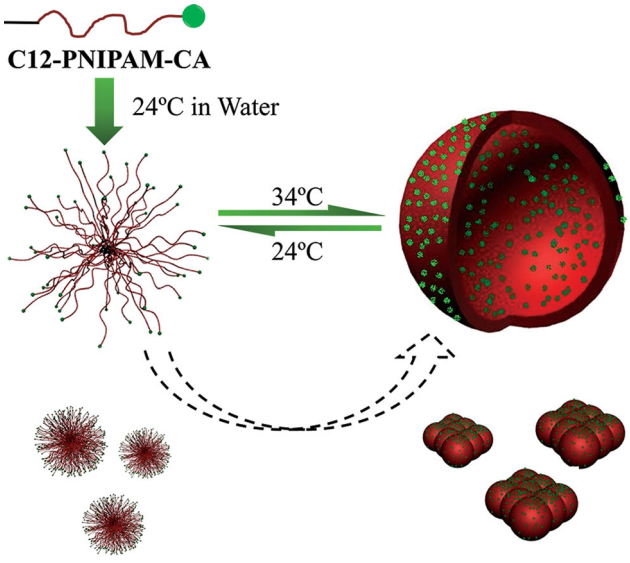

Figure 4. A scheme illustrating the thermal-induced reversible micelle-to-vesicle transition. Reproduced with permission.[27] Copyright 2011 Elsevier.

α-CDs and attached block copolymers of Azo-PNIPAM-*b*-PDMA, which was formed due to the CD-Azo inclusion complexation.[28] The HIC possesses AuNP core and the soluble copolymer shell in water behaving like a micelle. When the solution was heated to around 32 °C, larger, narrowly distributed and stable aggregates formed as the hydrodynamic radius $<R_h>$ drastically increased from 4 nm to 110 nm. TEM and AFM demonstrated the vesicle structure of the resultant aggregates having a monolayer of AuNPs in their thin wall. This soluble HIC-to-vesicle transition was found to be completely reversible and reproducible and could be performed within 30 minutes. The authors suggested that in the transition, HIC as building blocks formed the final vesicles through successive steps of PNIPAM chain collapse, particle fusion to patches and the patches bending.

2.4. Hierarchical Self-Assembly of Well-Defined Polymeric Building Blocks

In the last decade, inspired by the precisely organized complex structures in nature, the study of self-assembly of block copolymers achieved greatly in constructing hierarchical morphologies, particularly the multicompartment micelles (MCMs). Such complex structure of polymers is very intriguing as its possible capacity of incorporating different payloads in individual compartments, which may interact each other biologically or chemically. This will be discussed in Section 4. Lodge and Hillmyer succeeded in fabricating a variety of MCMs including spherical and linear worm-like MCMs and constructed vesicles from ABC miktoarms in selective solvents.[29] Du and O'Reilly reviewed the fabrication and application of multicompartment and patchy polymeric particles.[30] According to their definition, the former has phase-separated domains in the core while the latter has the same in the corona, although in many applications the two terms do not show such clear difference. While variety of MCMs have been attained, one still lacks of a general concept and a scheme to predict and control the architecture, such as the patch distribution, geometry, linear versus spherical aggregates of the resultant MCMs as a function of polymer composition. Along this line, a recent paper by Müller et al. has made significant contributions.[31] The authors used a series of ABC triblock copolymer samples, where A, B and C refer to PS (polystyrene), PB (polybutylene) and PMMA (poly(methyl methacrylate)) respectively, as building blocks to construct MCMs via a well-designed two-step procedure (**Figure 5**). Primary micelles i.e., subunits with B core and compartmentalized corona of A and C were prepared in a non-solvent for B. Such subunits were then dialyzed against a non-solvent for both the block A and B causing the collapse of A. This collapse occurs slowly and leads to consecutive refinement of the A/C corona structure of the intermediate subunits (Figure 5b,c). At some point the insufficient swollen block C cannot stabilize the refining subunits anymore and secondary aggregation is triggered by the unfavorable exposure of the solvophobic A patches. Consequently, initial subunits serve as building blocks for MCMs and induce higher-level aggregation of the subunits into the final multicompartment-core micelles (MCM, (Figure 5e,d)). It is striking to find that the architecture of the resultant MCMs depends on the parameter of the block copolymer, i.e., V_A/V_B, the volume ratio of the two insoluble blocks. The 'linear' MCMs (Figure 5e) is formed when $V_A/V_B \leq 1$, which can further aggregate into long, micron-scale core-segmented linear "colloidal polymers" (Figure 5f). When $V_A/V_B > 1$, spherical MCMs are obtained with defined patch numbers (Figure 5d) depending on the molecular parameters of the copolymers. For example, the population of both "clover" MCMs with 3 patches and "hamburger" MCMs with two patches are above 90%. They are also remarkably monodispersed in size. Therefore, this great success in two-step hierarchical self-assembly of simple linear ABC block copolymers leading to well-defined and controllable complex nanostructure provides very bright perspective for MSA towards their bio-related investigations and applications.

3. Artificial Basic Building Blocks for Life

Nature is powerful at building nanostructures with great complexities via precisely controlling multi-stage self-assembly processes. This highly specific, hierarchical and cooperative chemistry enables the living systems to maintain themselves in a dynamic equilibrium. In biology system, some of the basic building blocks are incredibly complex, and some are elegantly simple. Most of them, such as genes, enzymes, antibodies, chaperones, and even some lower life forms, e.g., virus, exhibit supramolecular features, which can be simply described, to some extent, in terms of molecular recognition, and programmable and hierarchical self-assembly.[32] So chemists, particularly, supramolecular chemists have devoted to mimic the biological processes to produce artificial building blocks of life. Tremendous achievements have been made in constructing artificial enzyme, DNA, antibody, chaperon and virus, although generally they are still in the infant stage.

Among the various kinds of the mimics, the study on artificial enzymes has a quite long history with large accumulation of research results. Looking back the development process of this research area, one may find that in the early stage of the research, the developments were mainly associated with biomimetic chemistry on small molecular level, while nowadays the emphasis has been gradually moved to self-assembled macromolecular materials. Recently, this field has been reviewed comprehensively,[33] so we will not go further in detail; instead just try to describe the development trace from the viewpoint of MSA. Enzymes are remarkably selective catalysts. It binds a particular substrate out of many available compounds in solution, and performs a reaction at a particular position of the bound substrate, showing regioselectivity and stereoselectivity.[34] Inspired by the elegancy of enzymes, chemists have synthesized a large amount of artificial compounds for the mimicry. Among these compounds, CD, one of the well-known semi-synthetic host molecules in supramolecular chemistry, seemed to be the most interesting one. The first modified CD referred as an "artificial enzyme" came out in 1970 (**Figure 6**a).[35] Around the end of 20th century, people began to realize that the macromolecular character of enzymes might play a special role in catalysis, which included shielding the active center from water, changing the pK of acid and base groups in the protein environment, etc.[36] Thus polymers,

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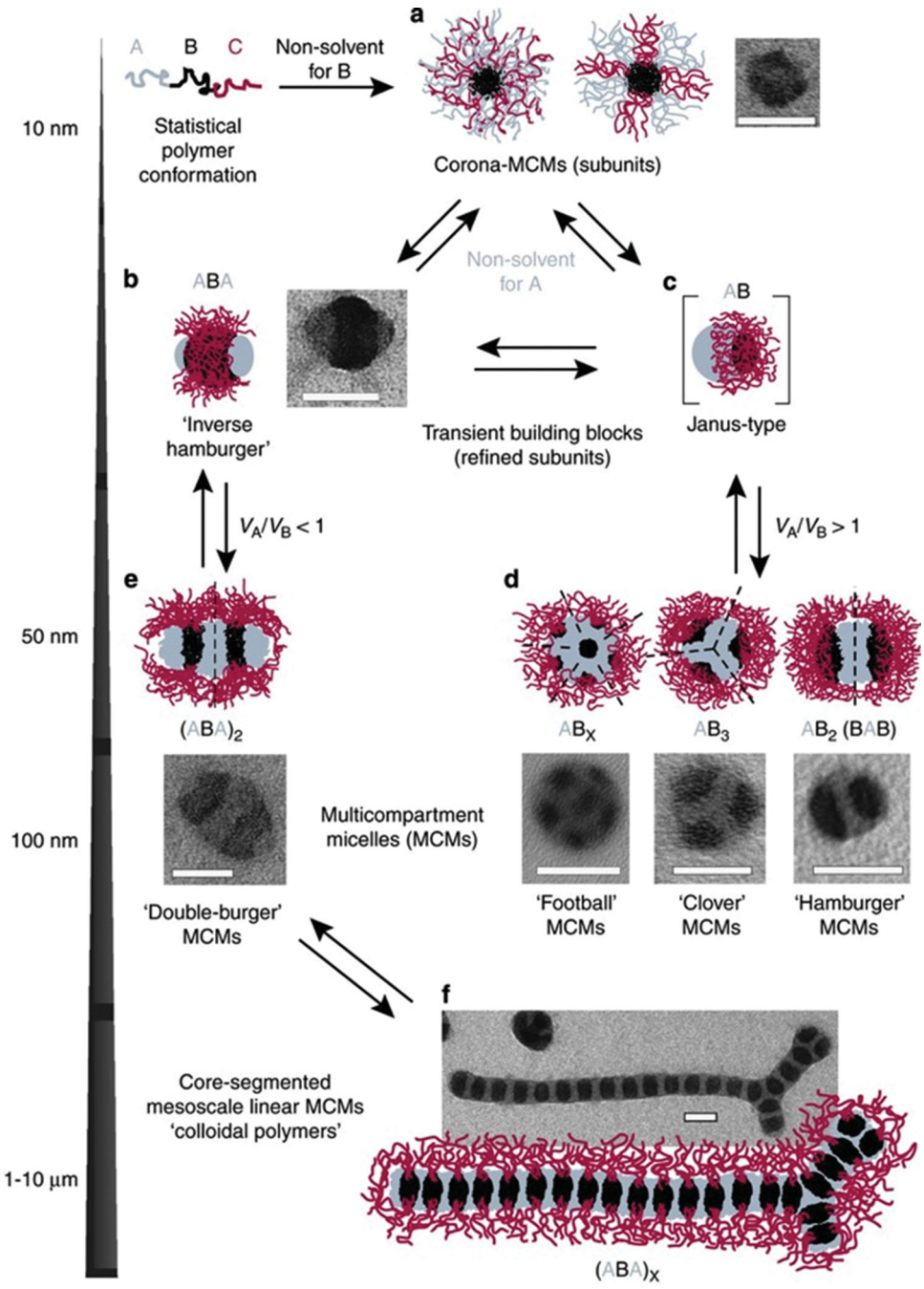

Figure 5. Mechanism for the preparation and directed hierarchical self-assembly of well-defined multicompartment micelles (MCMs). Reproduced with permission.[31] Copyright 2012 Nature Publishing Group (NPG).

especially synthetic polymers began to attract more attention than the simple cavity of CDs did. Among those polymers, commercialized polyethylenimine (PEI) with branched structure was quite popular.[37] Later, more polymers with various architectures, including random polymers, block copolymers, dendrimers and even supramolecular copolymers with covalently attached reactive centers were synthesized and investigated. Fréchet et al. achieved one-pot multi-component asymmetric cascade reactions by using soluble star polymers with catalytic centers integrated (Figure 6b).[38] Meanwhile, self-assembled synthetic block copolymers have been employed. For example, in the case of glutathione peroxidase, active center can be integrated inside self-assembled micelles made of block copolymer[39] (Figure 6c) or directly attached on copolymer chain before self-assembly.[40]

Now we will move to the main parts of the work on mimicking the basic building blocks of life that published recently, including DNA, antibody, chaperone and virus. Most of the

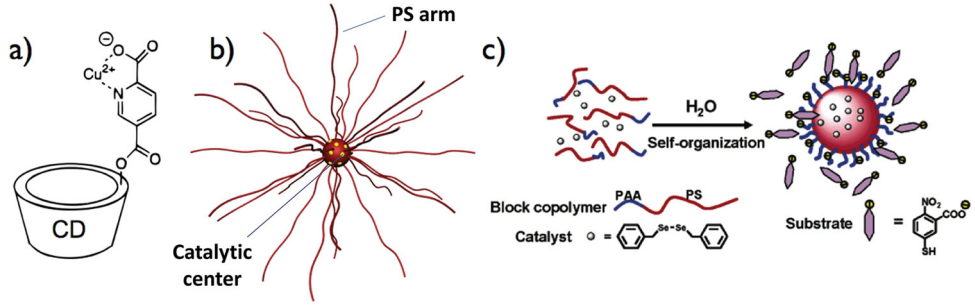

Figure 6. Typical artificial enzymes from the levels of small molecule (a) to polymer (b), then self-assembly (c). (a) Reproduced with permission.[35] Copyright 1998 ACS; (c) Reproduced with permission.[39] Copyright 2006 ACS.

selected systems use synthetic polymers as the major scaffold, and their self-assembly process will be highlighted.

3.1. Artificial DNA

DNA double helix formation is perhaps the most perfect example of MSA process in nature. The driving force is hydrogen bonding between the nucleobase pairs and the formation of double helix structure enables the hydrophobic nucleobase to be stacked in the center of the helix. More importantly, the nucleobase sequence contains large amounts of life information. DNA double helix structure has drawn long-time attention of supramolecular chemists as a fantastic model of chemical information carriers. A large number of approaches have been made on DNA-based self-assembly and DNA mimicking by synthetic building blocks.[41] In fact, combining the structure of double helix DNA with supramolecular chemistry opens a new field of "supramolecular DNA assembly",[42] in which discrete metal arrays in artificial DNA were recently constructed by using metal-ligand interactions;[43] and approaches towards mimicking helix and double helix structures by synthetic molecules or polymers were reported.[44] Considering that the field is quite popular with many published comprehensive reviews, in this section, we mainly focus on a couple of recent polymer-related approaches towards DNA.

3.1.1. ssDNA Templated Self-Assembly

In natural conditions, DNA mostly assembles into double helix, which is relativity stable in aqueous solution, but can disassemble to single-strand form under certain conditions, e.g., heating above its melting temperature. The single-strand form can be recovered into double helix by slowly decrease the temperature. Inspired by this recognition procedure and also promoted by a few remarkable achievements of artificial DNA,[45] a single-strand DNA (ssDNA)-templated self-assembly of synthetic chromophores through hydrogen bonding was reported by Meijer and Schenning.[46] A short oligothymine (dTn) chain was used as the ssDNA template. Through hydrogen bounding between thymine and adenine, a number of chromophores, e.g., adenine-modified naphthalenes (NT), which was achiral itself, presented a positive Cotton effect at the wavelength it absorbed, after its attachment to the dTn chain showing the expression of chirality from its ssDNA template. The structure was stabilized by π–π interaction, resulting in a DNA hybrid. Another chromophore, adenine-modified oligo(p-phenylene) vinylene (OPVT), was converted to helix structure with the same template (**Figure 7**). This approach developed a new strategy towards construction of well-organized nanoscale assembles by hydrogen bonding. Later several different building blocks were synthesized and their assembly behavior with ssDNA was studied.[47] Furthermore, single-stranded peptide nucleic acid (ssPNA) was successfully used as a template for the assembly of a chiral π-conjugated oligo-(p-phenylenevinylene) diaminotriazine derivative in methylcyclohexane, which expanded this template approach to an organic medium.[48]

Although nice artificial double helix was achieved, the chromophore part was only supramolecularly connected, dynamic combinatorial chemistry (DCC) was then introduced to make them polymerize.[49] With polymeric dTn (DP = 40) as template, non-natural dihydrazinetriazine naphthalene guest was assembled and then allowed to react with divalent aldehyde (glyoxal) in a reversible and dynamic manner forming hydrazone in the presence of aniline as a nucleophilic catalyst at 273 K. Thus a new polymer chain formed under low temperature. Generally linear supramolecular polymerization has to overcome cyclization. In this template dynamic polymerization, cyclization could be prevented, when the template length was long enough. Furthermore, the ssDNA template was re-used by heating the mixture in order to remove the polymerized guests from the template. When fresh monomer was then added, its assembly and then polymerization took place again. As a prospective, this renewable template procedure may enable large-scale production of functionalized polymers in an inexpensive and simple way.

3.1.2. DNA/Polymeric Micelle Self-Assembly Mimicking Chromatin Compaction

In eukaryotic cells, most DNA molecules do not exist independently, instead they form complex with histone octamers into chromatin. Histone octamers are disc-shaped nanostructures with positively charged binding sites and can self-assemble with DNA strand into fiber with diameter around 30 nm via two stages. In nature, the crucial step of this complicated self-assembly is the formation of so-called "beads-on-a-string" structure, i.e., a nucleosome (the bead) composed of one DNA segment wrapping around the edge of one histone octamer,

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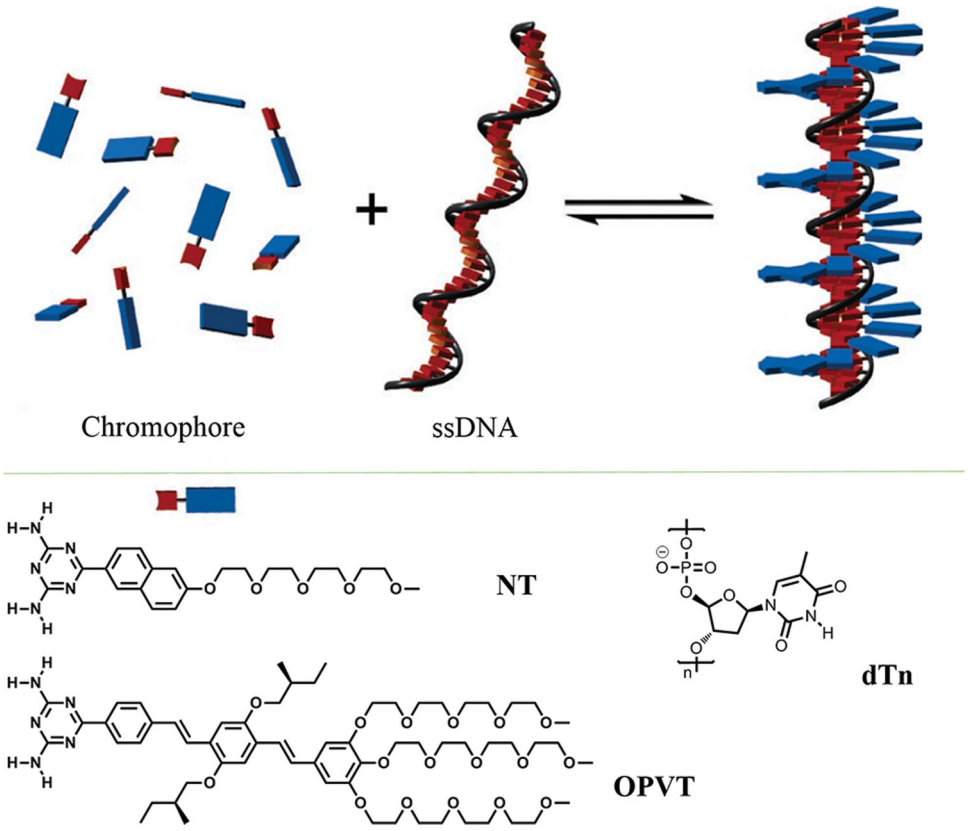

Figure 7. ssDNA-templated preparation of double helix structure. Reproduced with permission.[46] Copyright 2007 ACS.

which is the product of the first-stage assembly and the important building block for the next stage leading to 30 nm fibers. Inspired by such efficient self-assembly process, a number of attempts were performed to mimic the two-step self-assembly of DNA and histone. Inorganic nanoparticles have been used as a primitive model of histone core particles.[50] Very recently, as reported by Chen et al., the self-assembly process was successfully mimicked by using block copolymer micelle and DNA with 5427 base pairs (L5427).[51] Block-copolymer micelles of PEG_{113}-*b*-$P4VP_{58}$ (diameter 17.5 nm, picture B in **Figure 8**) with an inert shell and a positively charged core and mono-dispersed linear double-strand DNA 5427 were mixed in water/methanol. After 0.5 h incubation, the first stage assembly began. Mono-dispersed beads-on-a-string structure (picture C in Figure 8) formed exclusively, which evolved to form shorter strings after 10 h (picture D in Figure 8). In each of the strings, a DNA chain organized the micelles into a string by wrapping around the individual micelles. The second stage of the DNA/micelle self-assembly took place after 48 h incubation in which the strings fused into mono-dispersed nanofibers (picture F in Figure 8), during which the intermediate structure (picture E in Figure 8) between the strings and the nanofibers was also observed. The two-stage assembly process of DNA/micelle observed in the paper deserved more attention, as a high fidelity mimic of the native DNA/histone assembly forming chromatin. Such high precision in nanostructure formation and evolution is almost unprecedented in artificial materials. The work also proves that the synthetic macromolecule is probably able to play a very active and effective role in mimicking natural process, which was unexpected before.

3.2. Plastic Antibody (PA)

Antibody, also known as immunoglobulin, is a large Y-shaped protein produced by B cells that is used by the immune system to identify and response to foreign objects such as bacteria and viruses.[52] They are able to recognize the specific parts of foreign objects, i.e., antigens, in a way with very high selectivity and usually extremely strong affinity. The idea of using antigen as template to direct the assembly of peptide chains around the recognition sites was first suggested by Pauling[53] to explain the formation of antibody, which formed the research basis for the preparation of plastic antibody (PA).[54] In this short section, some of the recent progresses in the research field of PAs will be discussed. Briefly, PA inherits the scientific idea from molecular imprinting (MIP), which has a history of several decades.[55] MIP is a process in which the target molecule (or a derivative thereof) acts as the template, around which interacting and crosslinking monomers are arranged and copolymerized to form a cast-like shell.[56] In this process, the weak interaction between monomers and templates results in the formation of complementary binding sites in the polymer product to the template with specific binding abilities. Despite

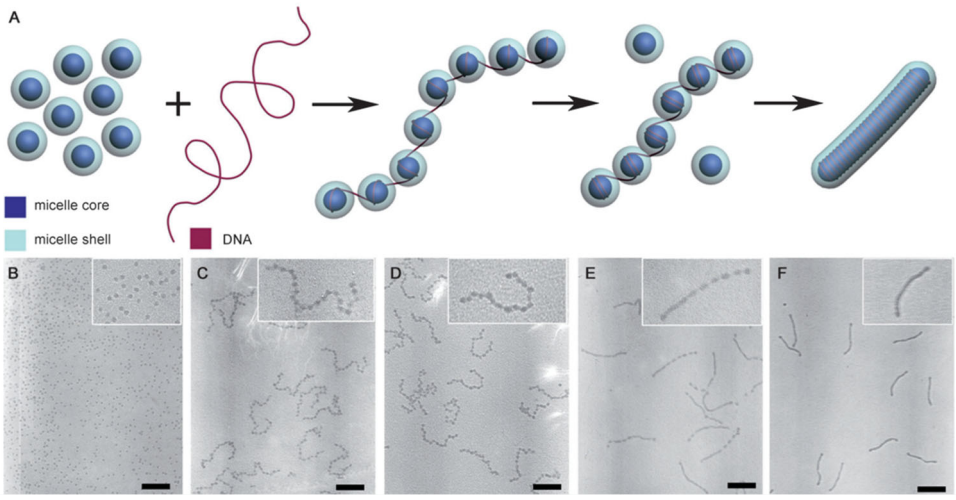

Figure 8. Self-assembly of linear DNA and the core-shell micelles. A) A schematic representation of the assembly process. B–F) TEM images of PEG_{113}-*b*-$P4VP_{58}$ micelles (B), and the nanostructures formed in the mixture of DNA and the micelles after incubation for 0.5 h (C), 10 h (D), 32 h (E) and 48 h (F) (scale bars: 200 nm). Reproduced with permission.[51] Copyright 2012 John Wiley & Sons, Inc (Wiley).

extensive research in this field, the main applications for MIPs so far have been restricted to analytical chemistry, especially as bulk materials for column separation.

The idea of antibody mimic was first proposed in 1993[57] and significant developments have been made recently attaining a high specific binding ability to an antigen, and neutralization to toxicity in vitro and in vivo.[58] Shea et al. used melittin as template molecule to perform self-assembly around the template of functional monomers (**Figure 9**a), e.g., hydrophobic *N*-(*tert*-butyl)acrylamide, negative charged acrylic acid (AA), and *N*,*N*′-methylenebis(acrylamide) as a crosslinker.[59] Based on series of copolymerization of different monomer pairs in a broad range of molar ratios followed by dialysis against water to remove the template molecule, a library of PA particles was established (Figure 9a). After screening of their binding abilities to melittin by QCM (quartz crystal microbalance), both of hydrophobic

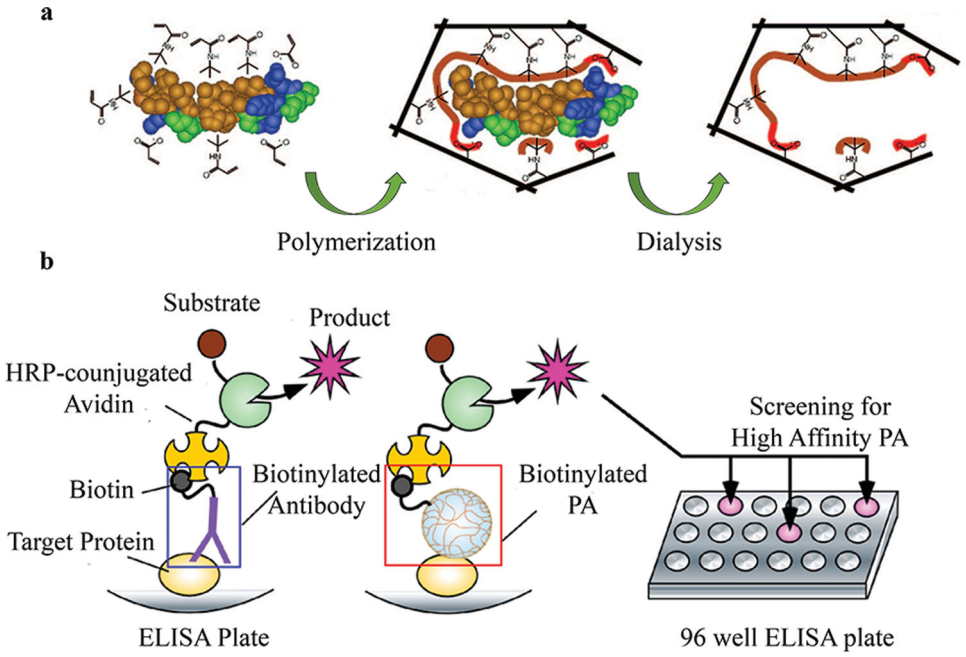

Figure 9. (a) Schematic representation of the preparation of PA to melittin (represented as space-filling model). Hydrophobic, positive/negative charged, and hydrophilic residues are represented in brown, blue/red, and green, respectively. (b) Concept of an ELISA-mimic screening (middle and right): A standard ELISA using a biotinylated antibody is also illustrated (left). (a) Reproduced with permission.[59] Copyright 2008 ACS; (b) Reproduced with permission.[60] Copyright 2012 ACS.

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interaction and electrostatic interaction were found important for preparing PA with strong affinity.[59]

Furthermore, based on this result, a template-free strategy was further developed.[61] Here the obtained series of template-free nanoparticles from combinations of monomers were purified by chromatography with a melittin-immobilized solid phase. The selected particles by this purification procedure were found to have strong affinity with melittin (~10^9 M^{-1}), which was amazingly similar with the native antibody (~10^9 M^{-1}). These nanoparticles successfully neutralized the cytotoxicity of melittin in vitro, i.e., injection of melittin and the PA nanoparticles together into mouse gave almost zero mortality in 40 min, while injection of melittin alone caused 100% mortality. Furthermore, biotinylated PA nanoparticles further replaced native antibody to perform ELISA (Enzyme-linked immuno sorbent assay) with binding ability to Histone and Fibrinogen.[60] This result proved the very promising future of this plastic antibody as a new material to replace native antibody in applications (Figure 9b).

In the first system prepared with the template, the target molecule has hydrophobic, hydrophilic and positive charged sites, which provides a nice platform for playing with different non-covalent interactions in concert. Thus the association of different monomers with the specific sites of the template is crucial, showing the significant effect of non-covalent interactions in molecular imprinting (Figure 9a). However, for those particles prepared by template-free strategy, although the "correct match" of the association of those different non-covalent interactions is really low, the subsequent treatment of passing the resultant nanoparticles through an affinity column, which is convenient and versatile, seems very efficient to find out the "right" particles. With the tools of polymer chemistry in hand, the particles can be further developed into responsive materials with ability to "catch and release" proteins at different temperature.[62] Considering the readiness of the preparation procedure, PA has a good chance to be commercialized to replace the expensive and limited antibodies.

3.3. Chaperone

In molecular biology, molecular chaperones are proteins that assist the non-covalent folding/unfolding or assembly/disassembly of other proteins. Heat-shock proteins (Hsps),[63] the most common kind of molecular chaperones, play an effective role in promoting proper protein conformation, as well as inhibiting unwanted protein aggregation, in response to elevated temperature or other stimulus. The GroEL/GroES complex, a classical Hsp system contains an open barrel with a large central cavity to receive unfolded protein substrates.[64] Inspired by the native occurring chaperones, especially the GroEL/GroES system, a chemical-assisted protein folding strategy has been developed. Rozema and Gellman first described a new approach for controlling the competition between renaturation and aggregation of unfolded proteins *in vitro*.[65] This method employed small molecules to guide the folding process. These low molecular weight assistants were referred as "artificial chaperones".[65] Early approaches on chaperone mimicking used mainly surfactants and CDs, and also water-soluble polymers such as PEG.[66]

Compared to the complex structure of the GroEL/GroES system having an open barrel for accommodating denatured proteins, the cavity of CD with a diameter less than 1 nm diameter seems too small. Thus designing an artificial host with a nanocage to bind denatured proteins and control the dynamics of catching and releasing proteins are necessary for simulating the function of molecular chaperones (**Figure 10**a). Early approaches towards chaperone mimicking at a nanostructure level were performed by Akiyoshi et al.[67] As shown in

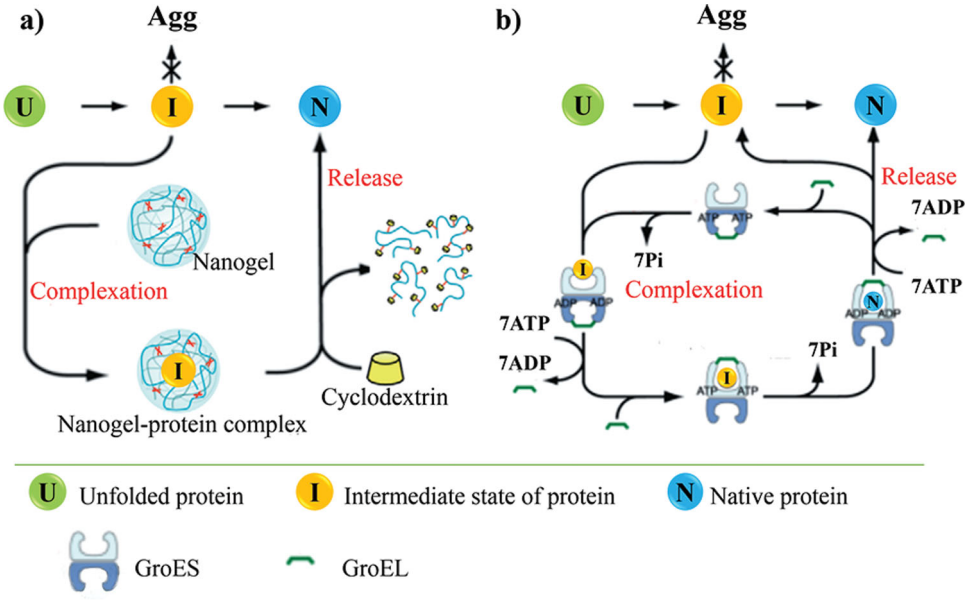

Figure 10. Comparison of the mechanisms of artificial (a) and natural (b) molecular chaperones (U: unfolded protein; I: intermediate state of protein; N: native protein; Agg: aggregated protein). (b) Working mechanism of GroEL/GroES involves reversible complexation between GroEL and GroES, with the required energy from consumption of ATP to ADP and Pi. Reproduced with permission.[67] Copyright 1999 ACS.

Figure 10, cholesteryl group-bearing pullulan (CHP) nanogels with flexible binding area were used to complex with carbonic anhydrase B (CAB). The CAB was complexed quantitatively by the nanogel in an intermediate state of heat-denatured form above its denaturation temperature. Then the intermediate-denatured protein was effectively released and refolded into its native form in the presence of β-CD, which was able to bind to the hydrophobic cholesteryl group and stimulate the release process. The whole process is very similar to the two-step mechanism of a native molecular chaperone (Figure 10b).[68] Further attempts of the nanogels mimicking chaperone such as those based on photo-stimulated spiropyrane-bearing pullulan (SpP)[69] and methacryloyl group-bearing CHP[70] are prepared. Similar approaches based on the two-step system by using smart copolymers[71] and highly anionic nanoparticles[72] in chaperone mimicking were also reported. Recently, an amphiphilic enzymatically synthesized glycogen was also employed.[73]

Most recently, mixed-shell polymer micelles were introduced to chaperone mimicking by Shi et al.[74] The mixed-shell polymeric micelles prepared by PLA_{100}-*b*-PEG_{45} (PLA: poly(lactide)) and PLA_{125}-*b*-$PNIPAM_{180}$, in which the reversible PNIPAM domains can be reversibly turned on or off through switching temperature, were used in preventing unwanted aggregation of model protein CAB and assisting the refolding of denatured proteins, similar to the ATP-driving conformation change in the GroEL/GroES complex. At room temperature, the PNIPAM chain remained hydrophilic, thus there were no interactions between CAB and the micelle. After heating to 50 °C, the collapse of PNIPAM formed hydrophobic domains among hydrophilic PEG phase on the micellar shell, but CAB still remained in its natural state without any interaction with the micelle. When the temperature reached as high as 70 °C, CAB switched to its intermediate state (i.e., unfolded peptide chain) with the hydrophobic area exposed, and then bound to the hydrophobic PNIPAM area on micelle surface and resulted in the formation of micelle/peptide complex. The complex was stabilized by the stretched PEG chains to prevent further aggregation of the peptide. In the cooling process, the PNIPAM chain transferred from hydrophobic to hydrophilic state and resulted in gradually disassembly of the complex, during which the unfolded intermediate protein departed from the micelle surface and started to refold into the native form (**Figure 11**). The presence of PEG on the mixed shell enhanced protein renaturation by interacting with the unfolded intermediate, which was prone to aggregation. During the long journey to prepare practical artificial chaperone, this achievement is a significant progress as the cycle is fully temperature driven without addition of any small molecules. More importantly, in this process, the hydrophilic part and the hydrophobic part of the micelle shell worked together to make their individual contributions to chaperone mimicking.

3.4. Virus-Inspired Materials

Virus can be regarded as a perfect self-assembled object. In this respect, tobacco mosaic virus is the most famous example, which is in a rod-like shape made of self-assembled 2130 coat protein molecules and one genomic single strand RNA with 6400 bases. Virus is a small infectious agent that can replicate itself only inside living cells. Virus particles are composed of two or three parts, i.e., genetic material made of DNA or RNA, a protein coat protecting the genes, and perhaps an envelope of lipids surrounding the protein coat. Virus is too simple to afford metabolism independently, hence its multiplication, including DNA replication and biosynthesis of the capsid proteins, totally relies on organelles of the host cell. Research on artificial virus has great potential in application, e.g., the tunable antigenic epitopes on capsid of artificial virus can trigger specific immune response in vivo as a versatile vaccine. Meanwhile, the inherent gift in transportation would make the artificial virus a reliable drug-delivering vehicle in therapeutics. These features make artificial virus gain so much attention for decades.[75] In this section, we attempt to address some of the studies on artificial virus from the view point of MSA, focusing on the self-assembly process in which synthetic polymers are involved. Thus virus-like particle (VLP) and polyplex, which are inspired by the immunogenic capsid protein and the delivery of nucleic acid segment, respectively, will be introduced in the following part.

3.4.1. Virus-like particles (VLP)

VLP is a common name of various classes of nanoparticles with virus-mimicking features, in which native capsid protein (CP) is employed as a building block. With identical or modified structures to the native CP, VLPs made of CPs have been demonstrated as a reliable and commercially available nanomaterial. Although they are typically used as artificial vaccines with tunable antigenic epitopes on surface,[76] their aggressiveness to cells inherited from the native virus makes them promising gene vectors as well. Meanwhile, VLP is also a valuable building block for constructing more complicated self-assembled materials, which was recently summarized.[77] In this part, we tend to focus on special contribution of MSA in this flourishing field.

The capsid of native virus is generally assembled under the help of coulombic interaction between nucleic acid and CPs. Thus ionic strength is naturally a determinant parameter in self-assembly. Naturally, the empty capsid of a well-characterized virus, cowpea chlorotic mottle virus (CCMV), without RNA can be obtained by self-assembly of its CPs at low pH (about 5) but cannot form in neutral conditions. Cornelissen and coworkers used polystyrene sulfonate (PSS) instead of RNA and investigated its interaction with CP at neutral pH in different stoichiometric conditions.[78] Mono-dispersed icosahedral nanoparticles with diameter of 16 nm were obtained, similar in shape with but smaller than the native CCMV capsid with a diameter of 28 nm (**Figure 12**). In further studies, with the purpose of increasing the stability of VLP in water, PEG was used to modify CPs and surround the self-assembled VLPs. But because the PEG chains sometimes are too close to each other, they brought thermodynamic instability to the self-assembled VLPs because of the steric interference. The negatively charged PPS existing inside the capsid was proved to be able to overcome this instability. This provides a new method to control the structure of VLP, by which the outside and inside of the VLP can be modified with synthetic polymers at the same time, both

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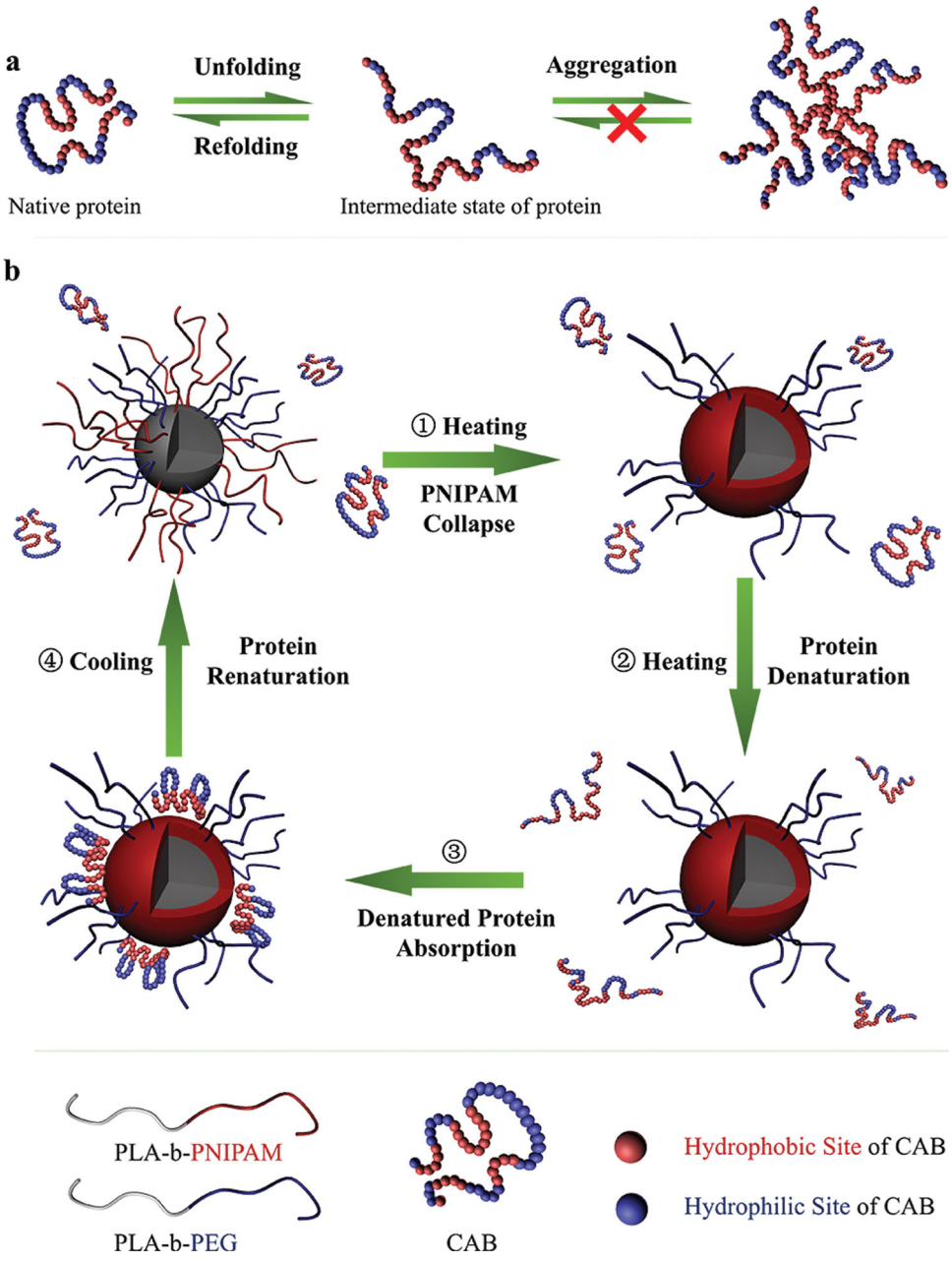

Figure 11. (a) Schematic representation of the denaturation process of a protein in native, unfolded and aggregated states. (The hydrophobic and hydrophilic domains are in red and blue, respectively). (b) Mechanism of the stabilization of the heat-denatured proteins and refolding, assisted by the mixed-shell polymeric micelles.

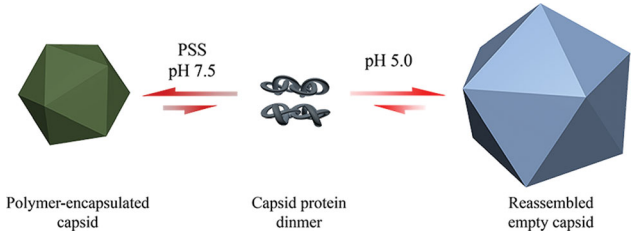

Figure 12. The presence of PSS induces the formation of smaller particle from modified CP (left) at pH = 7.5, whereas larger particles are formed at pH = 5.0 in the absence of polymer (right).

of which will contribute to the final self-assembled structure.[79] Furthermore, another negatively charged polyelectrolyte, polyferrocenylsilane (PFS) containing redox active ferrocene moieties was encapsulated instead of PPS as a responsive switch to redox reaction.[80] Besides synthetic polymers, nucleic acid is of course an ideal polyelectrolyte to drive the self-assembly of VLPs. Cornelissen and Herrmann et al. thus employed micelles formed by DNA amphiphiles as template to induce the formation of CCMV capsid. An advantage of this design is that it can simultaneously entrap a large number of small oligonucleotides existing in the micellar template. Furthermore, preloading

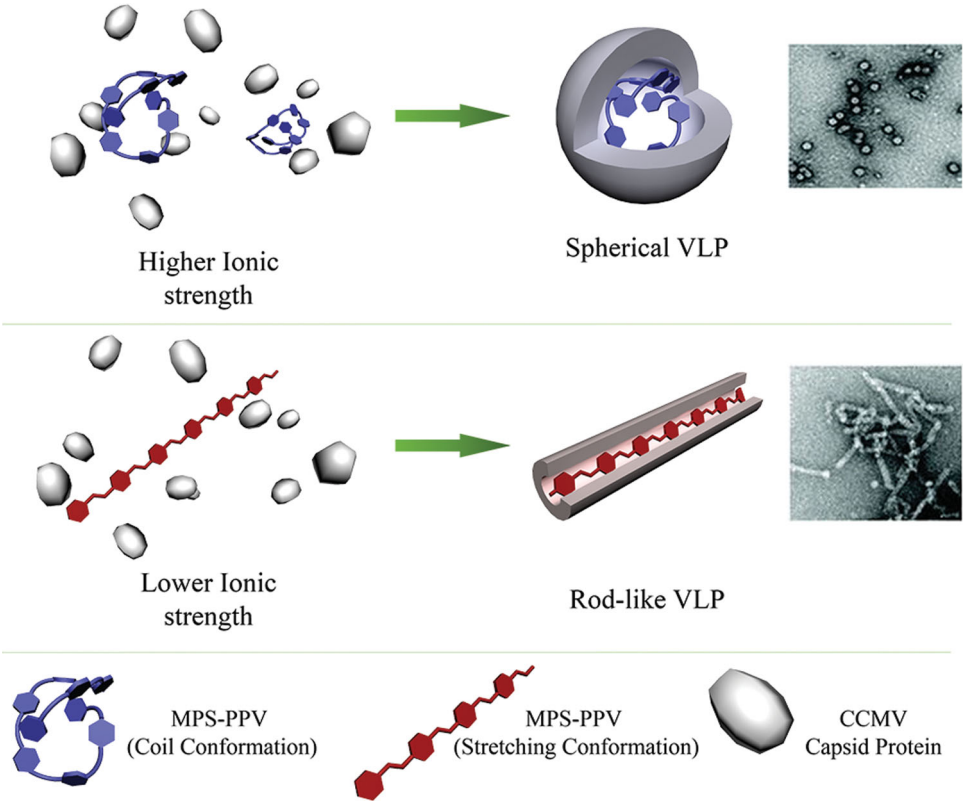

Figure 13. Mechanism of the synergy of synthetic and biological systems with different ionic strength.

of the micelles with hydrophobic entities in the core and hydrophilic entities by DNA hybridization enables encapsulation of various small molecules inside the artificial virus.[81]

Besides the spherical icosahedral morphology, the CP of CCMV can also self-assemble into non-native rod-like structures by varying the property of the encapsulated polymers. In order to study the effect of polymer on forming non-spherical morphologies, Tolbert et al. use a fluorescent polyanionic semiconducting polymer, poly-2-methoxy-5-propyloxy sulfonate phenylene vinlyene (MPS-PPV) as building block to construct VLPs.[82] MPS-PPV shows a broad range of conformations in aqueous solutions depending on ionic strength, which can be reflected by its fluorescence behavior. Meanwhile, the morphologies of the resultant VLP can be monitored by TEM (**Figure 13**). The results illustrated that at a higher ionic strength, the polymer assumed coil conformation favoring the formation of spherical VLP with blue emission, while at a low ionic strength, the polymer took stretching conformation favoring rod-like VLP with red emission (Figure 13). The results showed the synergy of synthetic and biological systems: polymer conformation drove the morphology of this hybrid composite; in turn the VLP structure modified the polymer optical properties. This synergy has a bright future for development of biomimetic and bio-inspired materials with special functionality. The following work using MPS-PPV by Cornelissen and coworkers indicated that the synergy between polymer conformation and capsid protein assembly resulted in an unexpected selection of molecular weight of polymers, where longer conjugated MPS-PPV chains could not sufficiently coil for being accommodated in a single VLP.[83]

In desire to expand the family of VLPs to a much more diversified platform, Robinson et al. devoted to synthetic virus-like particles (SVLPs) in which the native capsid proteins were replaced by synthetic building blocks.[84] The basic building block comprised a lipopeptide containing a "coiled-coil" sequence. The peptide chain firstly self-assembled into parallel helical bundles, and then these bundles continued to assemble into stable SVLPs. With multiple copies of desired antigens attached to the C terminus of the lipopeptide building blocks, the SVLPs not only retained advantages of naturally derived VLPs as antigen delivery vehicles, but also gained the possibility to be optimized using a myriad of synthetic chemical methods. The method was expanded further into a common one[85] to form hollow spheres with calcium phosphate, and to explore different applications to generate immune response.[86]

3.4.2. Polyplex

Polyplex is another type of virus-inspired materials, which is generally used as synthetic delivery vehicle of nucleic acid to pass through the cytoplasmic membrane and to prevent the susceptible nucleic acids from enzymatic degradation in the body. In contrast with VLPs being self-assembly of CPs containing foreign cores, polyplex is typically a "core-shell" polyion complex (PIC) of polycation and plasmid DNA (pDNA). Polyplex can be prepared by simply mixing a polycation with pDNA in

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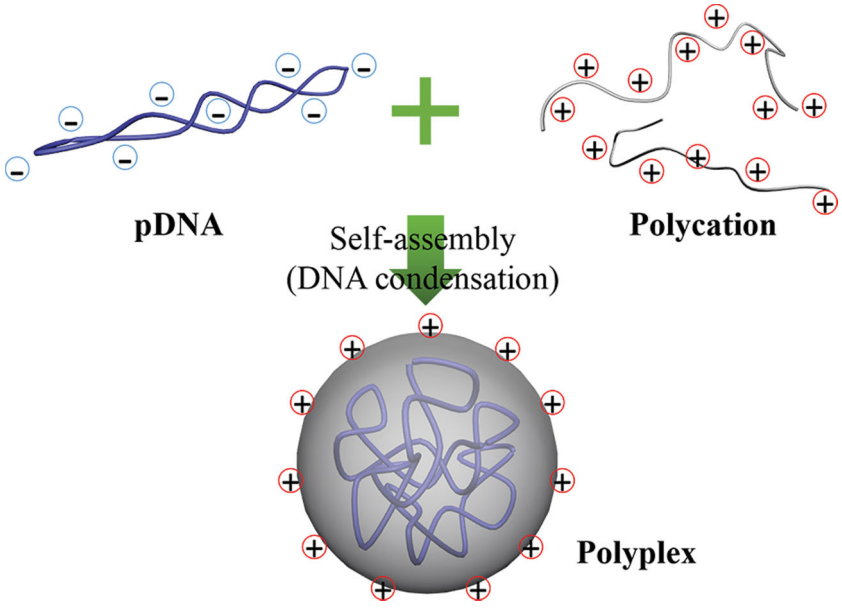

Figure 14. Common concept of polyplex.

an aqueous milieu through electrostatic interaction to generate polyion pairs, accompanied by liberation of small counterions to gain entropy (**Figure 14**). As a topic extensively developed for nearly two decades, the abundant works on polyplex have been systematically summarized by previous researchers.[87] Here we would like to introduce some latest developments focusing on new features of polyplex achieved by MSA procedures.

As a delivery vehicle, polyplex needs to fulfill some requirements. Polyplex should have low immunogenicity, high selectivity to the target cell type and reversible deshielding properties. These are the prerequisites to achieve its virus-mimic function of gene delivery. What's more, in order to avoid aggregation *in vivo*, hydrophilic polymer shell made of synthetic polymers, such as PEG or *N*-(2-hydroxypropyl)-methacrylamide (HPMA), is normally incorporated onto polyplex.[88] Recently, more efforts have been made on increasing both the stability of the polyplex outside the target cell and the release efficiency after entering the cell as well.

Pun et al. delicately designed and synthesized a block copolymer for polyplex, starting from a reducible double-head agent consisting of a disulfide-linked RAFT agent and an ATRP initiator (**Figure 15**a).[89] Thus a multifunctional well-defined block copolymer P(OEGMA)-SS-P(GMA-TEPA) was obtained through RAFT polymerization of oligo(ethylene glycol) monomethyl ether methacrylate (OEGMA) and ATRP of GMA, followed by post-polymerization modification for attaching the tetraethylenepentamine (TEPA) to the PGMA block. The block copolymer effectively condensed plasmid DNA into salt-stable polyplex with the P(GMA-TEPA) block as the core and P(OEGMA) block as the shell. Furthermore, the polyplex was dissociated via cleavage of the S-S bond on the polymer main chain under intracellular reducing conditions. Additionally, a neuron-targeting peptide (Tet1) was conjugated to the terminus of the block copolymer, resulting in increased transfection efficiency in vitro (Figure 15b). Moreover, Miyata and Kataoka et al. recently reported their stabilized and functionalized PEGylated polyplex encapsulated in a hydrated silica rather than polymersome.[90] The silica outer layer substantially improved the stability of the polyplex against counter

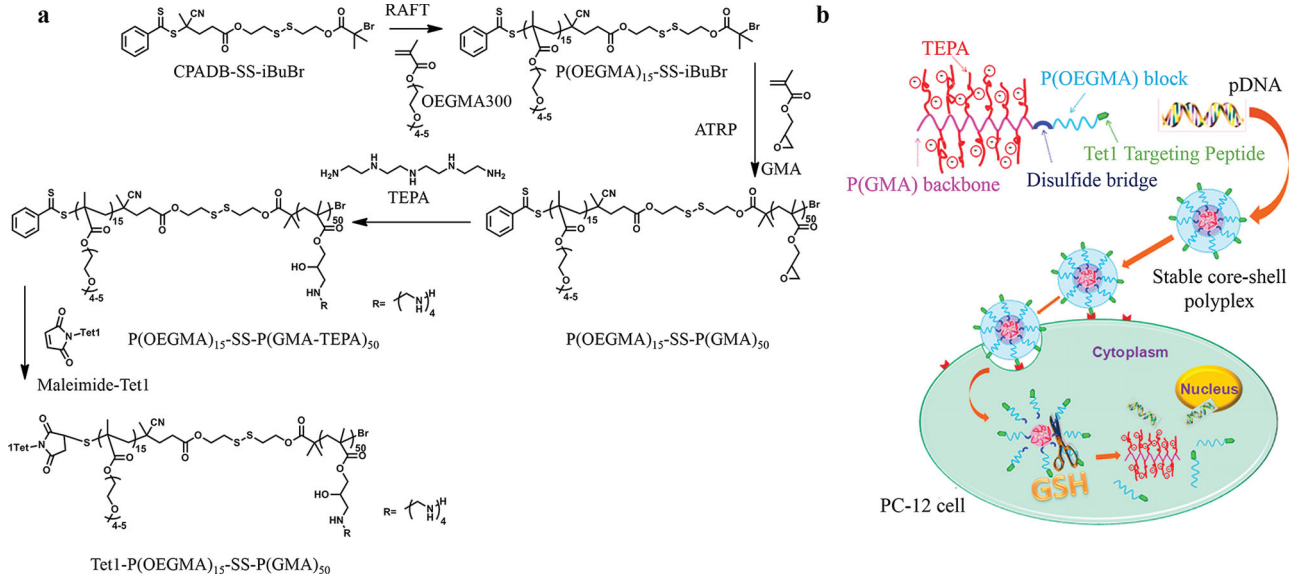

Figure 15. (a) Synthetic steps of P(OEGMA)-SS-P(GMA-TEPA) and (b) the mechanism of formation and dissociation of the polyplex. Reproduced with permission.[89] Copyright 2012 ACS.

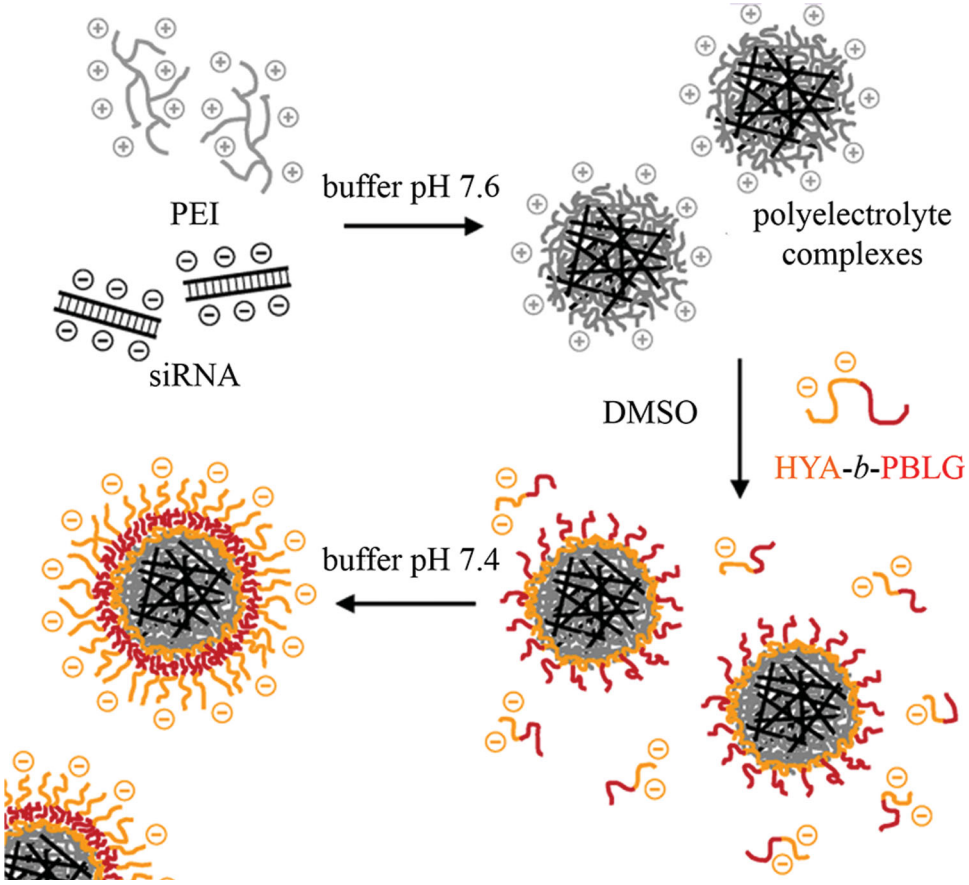

Figure 16. Preparation procedure of copolymer-modified polyplex complex with two layers of HYA-*b*-PBLG. Reproduced with permission.[91] Copyright 2012 ACS.

polyanion-induced dissociation under non-reductive condition, with responsive gene release triggered by disulfide cleavage.

Schatz and coworkers provided another strategy to gain enhanced stability and functionality of polyplex by encapsulating it into a self-assembled capsid-like shell of an amphiphilic block copolymer (**Figure 16**).[91] They first prepared positively charged polyplex consisting of branched PEI and siRNA in aqueous solution, and then neutralized the excess surface charges by complexing the polyplex with negatively charged hyaluronan blocks of a diblock copolymer hyaluronan-block-poly(c-benzyl-L-glutamate) (HYA-*b*-PBLG) in DMSO, which is a good solvent for both of the blocks. The particles were finally transferred into buffer at pH 7.4, where the outer layer PBLG of the particle formed in DMSO became insoluble, thus the free HYA-*b*-PBLG polymer would self-assemble onto the particle surface again with HYA pointing outside (Figure 16). From the experimental results, a higher gene silencing activity of the copolymer-modified complexes over the nude complexes was obtained showing the potential of this new type of polyplex for biological applications.

The role of sugar on the surface of polyplex was also investigated.[92] Reineke et al. reported a novel polyplex employing supramolecular host-guest interaction in order to demonstrate whether glycopolymer was a better hydrophilic material than the commonly used PEG.[93] The polymeric capsid was self-assembled via non-covalent interaction between Ada-conjugated glycopolymer poly(2-methacrylamido-2-deoxy glucopyranose) (Ada-pMAG) and "click cluster" (PEI-modified CD via click chemistry), which assembled further with pDNA to form polyplex with Ada-pMAG as shell (**Figure 17**a). Compared with a Ada-conjugated polymer (Ada-PEG) covered polyplex (Figure 17b) as control, Ada-pMAG-coated polyplex provided improved colloidal stabilization under physiological conditions, while the toxicity of the "click cluster" appeared to be significantly decreased by Ada-p(MAG). However, the uptake and reporter gene expression of pMAG-coated polyplex were much lower than its PEG-coated counterpart in HeLa cells.

4. Cell-Inspired Bio-Mimetic Materials Constructed by MSA

Cells are basic units of life, in other words, they are the smallest structures that can support metabolism individually. Under artificial culture condition, a cell can achieve heredity, breed, motion, environmental response, and self-regulation by itself. Cells can be divided into two categories, i.e., the relatively simple prokaryotic cell, which constructs bacteria and archaeans, and the complex eukaryotic cell, the basic structural and functional unit of most organisms on earth. Eukaryotic cell

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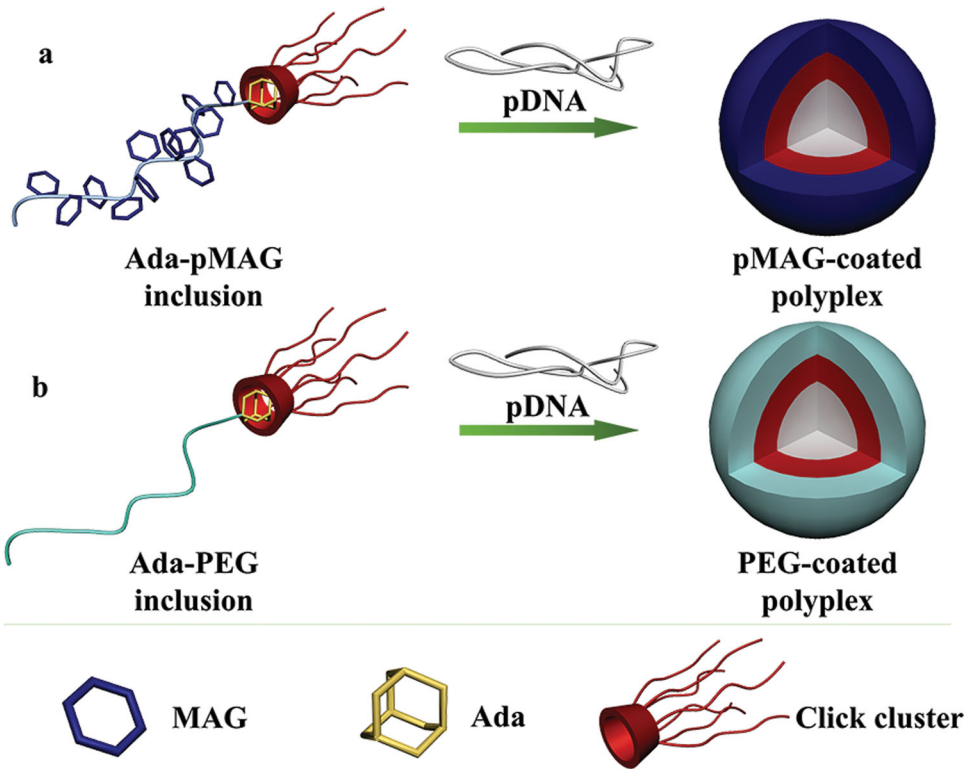

Figure 17. Supramolecularly design of polyplex to demonstrate the role of glycopolymer. (a) pMAG-coated polyplex, (b) PEG-coated polyplex.

has various organized components as containers for different biochemical reactions, which attracts high level of interest in chemical research, leading to the birth of the studies of cell structure mimicking and cell-inspired materials. The cell-mimicking study was initiated decades ago and achieved great progress, in which various molecules including phospholipid, small molecular surfactant, peptide and macromolecules were employed as raw materials to construct simplified skeleton of eukaryotic cells. Among these, phospholipid serving as building blocks has the longest research history and reached the most significant achievements, mainly because it is the building block that constructs the biological bilayer membrane of native cells.[3a] For example, a self-reproducible cationic giant vesicle of phospholipids with DNA encapsulated was found to perform growth and spontaneous division, accompanied by a re-distribution of the amplified DNA to the daughter giant vesicles. In particular, amplification of the DNA accelerated the division of the giant vesicles.[94] Other outstanding achievements include exocytosis of the daughter vesicles, in which the membrane proteins were delivered to the outside of the giant vesicles,[95] and sugar synthesis in a lipid vesicle leading to a cell signaling response in bacteria.[96]

However, the defects of the phospholipid systems are obvious as well. In natural cells, the cytoskeleton constructed by microtubules and fibers of proteins acts as anchor to stabilize the multicomponent membrane. Stabilization to the lipid membrane can also be promoted by saccharides and proteins located on and/or inserted in the membrane. However, in the pure phospholipid model, lacking of cytoskeleton and other structural elements results in instability of the artificial membrane. So to reconstruct a cytoskeleton in an artificial eukaryotic cell remains a great challenge. That is why there are few phospholipid-based mimicking systems having found their applications as bio-inspired materials.

As a large category of alternative material to mimic cell, amphiphilic polymer constructing polymersome enjoys its own advantages. As a latecomer, mimicking work employing polymersome is far behind that of liposome and the constructed models are relatively simple. Compared to liposomes, the membrane of polymersomes are much thicker with intrinsic structure, which confers on polymersome a higher mechanical stability, lower permeability and equal biocompatibility comparing with liposome, and a higher loading capacity to hydrophobic components can be achieved as well.[97] Additionally, the morphologies and membrane properties can be controlled via traditional approaches in MSA and membrane modification. These methods, to a certain extent, compensate some of the disadvantages of polymersomes, e.g., low fluidity and poor permeability, and therefore make polymersome a trustworthy and grateful material of cell-mimicking in recent years.

Although the structure and chemical composition of polymeric membranes are far from their natural prototype, polymersomes, with the advantages described above, can be employed to construct a well-defined platform to study the detailed mechanism of a given biochemical process. What's more, with self-assembly and modification approaches, some cell-inspired materials of polymersomes with specific functions can be designed and brought to real applications. To our opinion, although such polymersomes might not be the best building blocks for the final target of synthetic lives, they are

ideal materials for both theoretical and practical studies of biomimicking. Considering the great complexity of cell, establishing a cell-mimicking or cell-inspired model is a long-term and stepwise process. This section will focus on the construction of cell-mimicking structures with polymersomes, which include shape and morphology, fluidity of the membrane and functionality located on and inserted in the membrane.

4.1. Formation of Artificial Cell

As mentioned above, the research of cell mimicking mainly focuses on establishing models of eukaryocytic cell, especially animal cell without cell wall. For a typical eukaryocyte, membrane is undoubtedly the most important structural element. A cell can be simplified to a system in which different matrix are closed and divided by different membranes. Semi-permeable membranes surround cytoplasm, nucleus and most of the organelles as well, which are known as endomembrane systems. In this case, the prerequisite of a perfect artificial model of eukaryocyte is to construct a well-defined membrane system. Fortunately, vesicle is one of the common morphologies of macromolecular self-assemblies, which generally is not hard to obtain. In this section, we focus on the formation of multicompartment structures similar to the endomembrane system and a special type of cell structure, i.e., stomatocyte.

4.1.1. Multicompartment Structure

Compartmentalization is an essential and unique character of eukaryocyte. A compartmentalized structure is the basic description of eukaryotic cells containing organelles inside. This type of structure enhances the surface area immensely, and provides segregated spaces for different biochemical reactions to occur in an orderly way at the same time, thus endows the eukaryocyte strong metabolism ability. Therefore, to construct this multicompartment structure through a self-assembly strategy, i.e., a vesicle-in-vesicle model at different levels of complexity instead of a simple polymersome is a long-standing task in MSA. The efforts on this topic were initiated by the work of Chiu et al. via a double emulsion approach.[98] Quite recently, Lecommandoux et al. intensively reviewed polymersomes as well as capsosomes covering a broad subjects from their constructions to functions.[99] In this section, we mainly focus on technologies employed to construct polymersomes with multiple aqueous compartments via MSA together with a brief description of other frequently used compartmentalization methods.

In a normal condition, these multicompartmentalized architectures are prepared in a multi-step process: the inner vesicles are usually formed first and then embedded into a larger outer vesicle. Thus the outer vesicle plays as the cell membrane, while the inner ones act as that of the organelles. This sequential stepwise process provides some extra benefits. For instance, if the inner and outer vesicles are formed in different solvent compositions or with different additives, different "matrix" will be encapsulated into each compartment. What's more, with the inner and outer vesicles of different polymers, the permeability of the compartments can be designed to mimic the cellular process or engaged in application more intentionally. In short, with these advantages, one can achieve both "organelles" and "cytoplasm mimics" in one system.[97,100]

Nallani and coworkers used such sequential self-assembly to prepare compartmentalized polymersomes.[101] In this method, two different block copolymers, i.e., poly[-(2-methyloxazoline)-poly-(dimethylsiloxane)-poly-(2-methyloxazoline)] (M-D-M) and poly[styrene-*b*-poly-(L-isocyanoalanine(2-thiophen-3-yl-ethyl)amide)], (PS-PIAT) were employed. The vesicles of M-D-M were firstly formed through film rehydration, which possessed a tightly packed membrane structure that limited transport across the membrane, Subsequently, PS-PIAT polymersomes were formed in the presence of M-D-M polymersomes by adding the THF solution of PS-PIAT into the solution of the preformed polymersomes in buffer. Thus a vesicle-in-vesicle structure comprising at least two different compartments finally formed (**Figure 18**a,b).

A significant drawback of this method is the polydispersity of the products. The encapsulation of the inner vesicles is a random process leading to three populations of vesicles, i.e., the individual M-D-M vesicles, individual PS-PIAT vesicles and the target PS-PIAT vesicles encapsulating M-D-M vesicles. This is probably the Achilles' heel of the traditional self-assembly strategies.

Layer-by-layer (LbL) approach is another classic strategy of self-assembly, featured by using a template and being driven by electrostatic interaction. Caruso et al.[102] employed LbL as

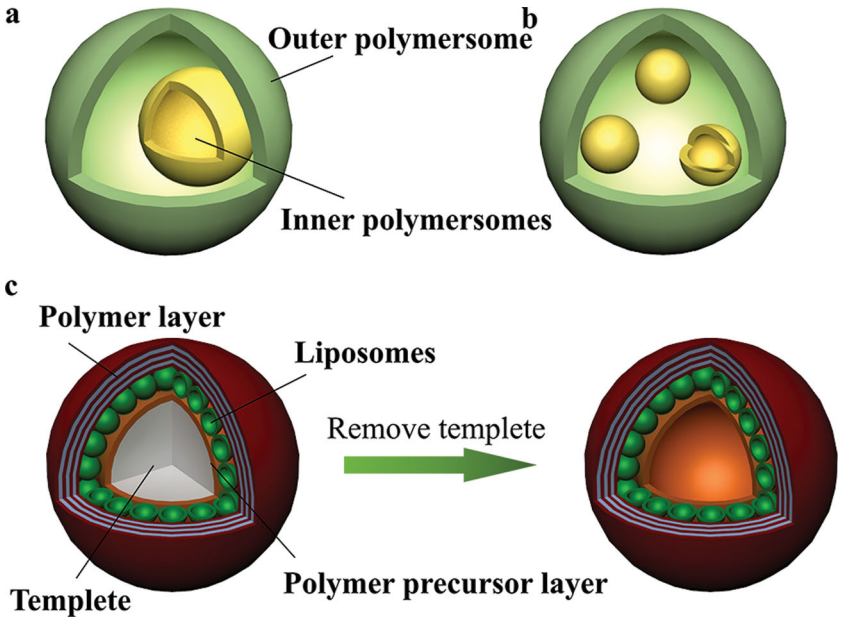

Figure 18. Various structures of multicompartment vesicles. (a,b: typical vesicle-in-vesicle structures; c: Capsomes via layer by layer approach.

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a reliable method in precise design and preparation of capsosomes (sub-compartmentalized polyelectrolyte capsules with liposomes inside).[103] The LbL assembly of capsosome involved the deposition of a polymer precursor layer onto a sacrificial colloidal template, followed by the alternating assembly of liposomes and polymer separation layers. After the adsorption of a polymer-capping layer, the assembly of capsosome finished and the template particle was removed (Figure 18c). An optimized capsosome assembly employed cholesterol-modified polymers as precursor to form separated and capping layers for stably incorporating the liposomes.[104] Different hydrophobic components can be preloaded into liposomes to obtain multifunctional capsosome.

However, the current popular approaches to prepare multicompartment polymersomes are mostly related to nanotechnology, not self-assembly. Besides, the microfluidic approach was demonstrated as a very valuable pathway with high controllability.[105] Recently, Lecommandoux and coworkers presented a new approach, in which the polymeric subcomponents were first formed by nanoprecipitation, i.e., precipitation of nanoscale vesicles, then loaded into larger polymersomes through emulsion-centrifugation technique.[97,106] Currently, among variety of the approaches to multicomponent structures, MSA in solution seems to lag behind the others due to the low polydispersity control to the resultant vesicles. However, as many well-defined structures of assembled objects have been achieved by MSA for many different purposes, one is still confident that, MSA will become a much more reliable strategy in near future.

4.1.2. Stomatocyte-Type Vesicles

Besides round-shape cells, there are many types of cells with abnormal shapes, which play crucial roles in life processes. Stomatocyte-type vesicle is one of the representations. Natural stomatocyte is in the shape of fish mouth, which is not typical for a eukaryocyte. Currently polymer scientists show strong interest in achieving the similar morphology of stomatcytes, although the related bowl-shaped polymeric assemblies were reported decades ago without any bio-related aims.[107] Jiang et al. also reported "dimpled beads" of polymeric vesicles with shallow cave on their surface formed by collapsing of the vesicle walls.[108] Eisenberg et al. named fully collapsed hemispherical vesicles "Kippah" and studied their formation mechanism.[109] They indicated that at least one of the factors, i.e., relative flexibility of the vesicle wall, pressure gradient, or surface tension might contribute to this interesting morphology.

Recently Van Hest and coworkers succeeded in constructing such special morphology with interesting functions from a very common diblock copolymer PEG-*b*-PS.[110] Here the PS block is a high-molecular-weight glassy segment at ambient temperature, whose behavior can be kinetically controlled, thus the shape transformation of the whole vesicle can be adjusted and then specific morphologies can be captured. The mimic stomatocytes were prepared through a selective solvent approach. It started from a solution of PEG-*b*-PS in dioxane and THF (1:1 v/v), and cloudy suspension was obtained after addition of water, followed by dialysis. The DLS characterization indicated that during the dialysis the average diameter of the aggregates decreased while the PDI (polydispersity index) stayed almost unchanged, which suggested a reduced overall volume of the formed polymersomes without significant vesicle fission. The TEM images of the dried polymersomes after dialysis suggested a complete change of morphology from spheres to stomatocytes. The proposed mechanism of morphology transformation is shown in **Figure 19**a. Dialysis of the polymersome against water would cause a rapid expulsion of the organic solvent molecules, which was held within the inner compartment of the polymersome, through the solvent-swollen fluidic PS membrane due to osmotic pressure, while the unfavorable energy barrier between water and PS would hinder the penetration of water through the swollen PS membrane and replacement of the space occupied by organic solvent molecules, which would consequently decrease the volume of the inner compartment of the polymersomes.[111] Afterwards PS collapsed into the glassy state to form a rigid membrane, which locked the morphology and then stopped removal of the organic solvent. Thus the osmotic pressure difference between the inside and outside of the vesicle induced the formation of the opening. Further research indicated that the size of the opening could be adjusted by changing the flexibility of the starting vesicles, which depended on the composition of the solvent mixture and PS segment length.[110] That is to say, through raising the ratio of THF or shortening the length of PS segment, the locking of the morphology will be delayed resulting in a decrease in the size of the opening because of the increase of membrane flexibility.

In an interesting further step of van Hest and his coworkers, the artificial stomatocytes were employed to make a "miniature monopropellant rocket", with pre-formed active catalyst, platinum nanoparticles (PtNPs) entrapped during the shape transformation of the polymersomes into the stomatocytes with small opening (Figure 19b).[112] The 'locked' stomatocyte structure with entrapped PtNPs was clearly visualized by TEM images (Figure 19c-e). The resultant stomatocyte performed as a rocket when hydrogen peroxide was added as the fuel that decomposed under the catalysis of PtNPs. The discharged oxygen came out from the cavity and then drove the stomatocyte in autonomous movement.

4.2. Morphology Transformation of Artificial Cells

Fluidity is one of the most typical characters of natural phospholipid bio-membrane and is also the prerequisite of some important cell growth processes, including endocytosis, exocytosis and cell division. As mentioned above, MSA has provided assembled objects with different morphologies inspired by various cells, while exploring the functions of these resultant structures, especially fluidity and dynamic evolution, is another important topic. Fortunately, a great advantage of synthetic polymersome is controllability, which helps ones to tune its morphology and function.

4.2.1. Shrinking and Swelling: Breathing Vesicles

Swelling and shrinking and the accompanying change in volume and permeability are basic and well-known phenomena of eukaryotic membranes, which reflect fluidity at

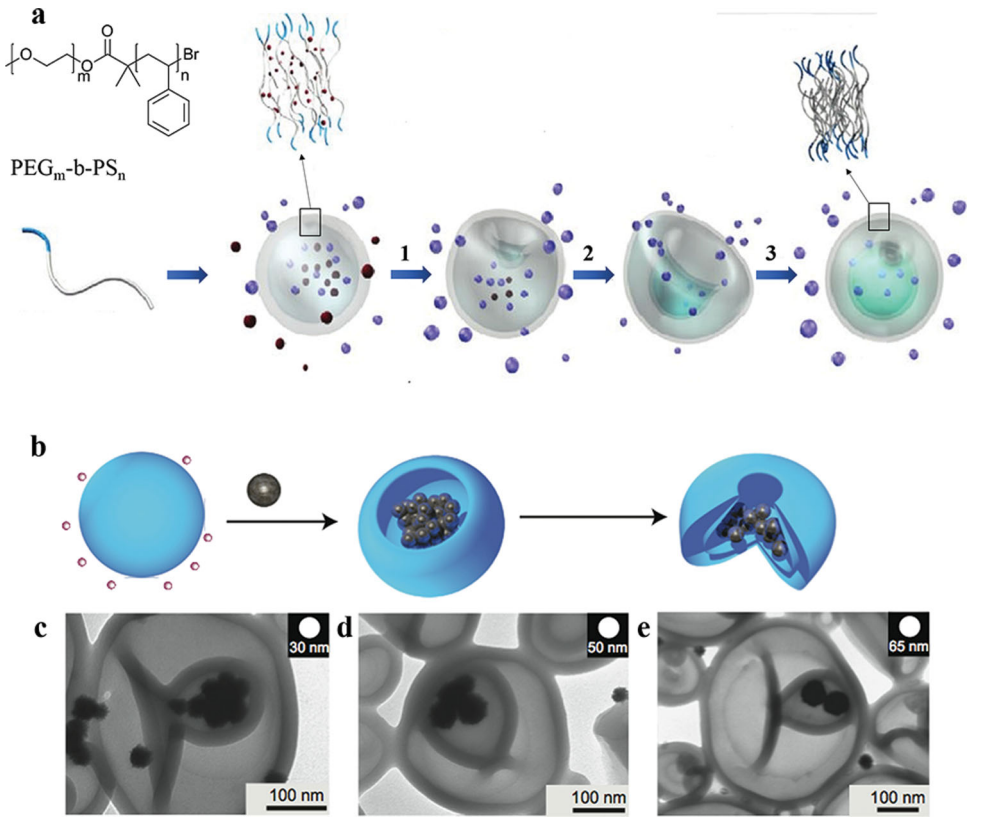

Figure 19. (a) Shape transformation of polymersomes during dialysis of organic solvents (dark red spheres) against water (blue spheres) through a solvent-swollen bilayer membrane. (b) Strategy for entrapping preformed PtNPs during the shape transformation into stomatocytes. (c) - (e) TEM images show the entrapment of PtNPs of different sizes during the shape transformation of polymersomes. (a) Reproduced with permission.[111] Copyright 2010 ACS; (b) Reproduced with permission.[112] Copyright 2012 NPG.

a macroscopic scale. Usually swelling or shrinking can be observed, when the eukaryotic cells are in hypotonic or hypertonic solutions, respectively. Polymersomes process similar behavior as a response to solution environment.[113] This behavior, i.e., the reversible shrinking and swelling of polymersomes, was reported much earlier than it was named "breathing vesicles" by Eisenberg.[114]

Eisenberg and his coworkers investigated pH-induced "breathing" vesicles of a triblock copolymer in detail.[115] The copolymer PEG-*b*-PS-*b*-PDEA, where PDEA denoting the pH responsive block of poly(2-diethylaminoethylmethacrylate), self-assembled into vesicles at a strong basic condition where the PDEA block remained insoluble and behaved like a hydrophobic unit along with PS. The vesicle is special of its three-layered "sandwich" membrane structure, i.e., two external continuous PS layers and one thick PDEA layer in the middle. When pH decreased from 10.4 to 3.4, the size of the vesicles increased dramatically as a result of the intermediate PDEA layer becoming protonated and hydrated. The swelling of the PDEA layer further increased the immiscibility between PDEA and PS and thus sharpened the interface between them. Finally PDEA chains broke the heavy layer of PS and extruded into its favorable solution, i.e., water. The meticulous Cryo-TEM studies made the process visible (**Figure 20**). The images of the aggregates at pH 3.4 showed very special structure of the walls: two

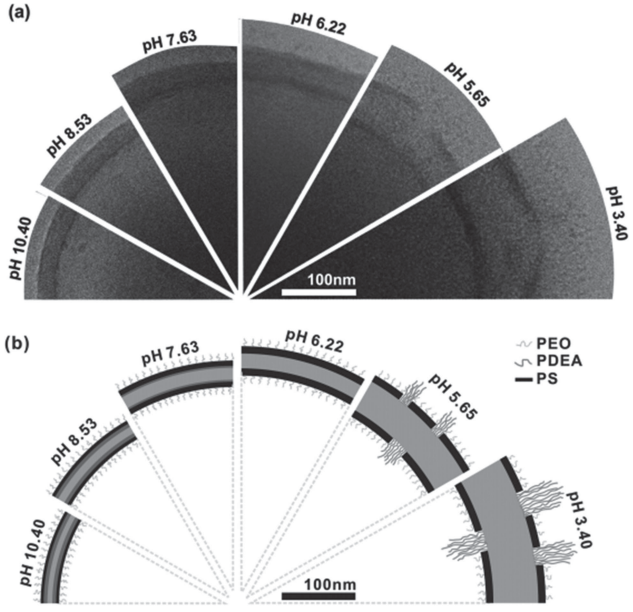

Figure 20. Breathing vesicles (a) cryo-TEM images of vesicle wall structures at pH 10.4, 8.53, 7.63, 6.22, 5.65, and 3.40, respectively; (b) Schematic illustrations of the vesicle structures at corresponding pH values. Reproduced with permission.[115] Copyright 2009 ACS.

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thin PS layers on the wall surfaces cracked and some chains of PDEA from its middle layer extruded through the cracks in the PS layers into the solution. When pH of the solution increased, the vesicle shrinking was observed. Such swelling-shrinking process was highly reversible with a relaxation time of about 1 min. Recently a few reports followed this work focusing on its application in drug delivery, which took advantage of the permeability changes.[116] While the breathing process of the vesicles was demonstrated successfully, resulting in the changes of permeability of the membrane, in literature the major way to regulate the permeability of the membranes has been counted on the channels inserted in the membranes, which will be introduced later.

4.2.2. Fusion and Fission

Fusion and fission of cell membrane are fundamental biological processes.[117] They participate in cell division, endocytosis and exocytosis and some transport processes between different intracellular compartments. Studies of shape transformations and topological changes, such as the fusion and fission of vesicles, have no doubt a very important physical and biological significance. However, the kinetic and mechanistic details of these processes remain incompletely understood. Moreover, to observe such phenomenon directly in experiments is challenging due to the complexity of membranes and the high energy-cost of these processes.[118]

Fusion and fission of polymersomes is not a new topic in MSA. The first study on dynamics was performed by Eisenberg et al.[119] The morphologies in transformation were captured by TEM from quenched systems in different steps. It was encouraging to find that the morphology transformation of polymersomes during fusion and fission was similar to that in the biological processes in cell membranes. For fusion process, it was proposed that, contact and adhesion of vesicles would appear first, followed by coalescence and formation of a connecting wall. The reverse process, fission, contains a series of steps, i.e., vesicles elongation, formation of an internal waist, narrowing of the external waist and final complete separation.[120] In their following work, the kinetics of this vesicle fusion after addition of water was measured by solvent turbidity as a function of time, and the relaxation times were extracted from the resulting turbidity *vs* time plots.[121] The result indicated that the kinetics of vesicle size increase was quite slower than that of water content increase. Increasing the initial polymer concentration or the PAA (poly(acrylate acid)) block length caused an increase in the rate of vesicle fusion.

Differing from the first attempt on polymersome fusion and fission, which was patched up by TEM images captured from different quenching steps, Yan and Zhou employed their admirable giant vesicles (100 μm diameter) of hyperbranched copolymer and achieved real-time monitoring of polymersome fusion triggered by sonication with optical microscopy.[122] In their study, the content mixing process inside vesicles was observed directly from the images of rhodamine-encapsulated vesicles by fluorescence microscopy. These giant vesicles were then successfully used in capturing a real-time description of a specific cooperative fission system as well.[123]

Optical microscopy has great advantages than TEM to perform a real-time monitoring of vesicle fission or fusion. Zhang et al. reported another kind of giant vesicles made of a diblock copolymer composing of PNIPAM and an Azo-containing block.[124] Though the resultant vesicles were smaller (diameter 5 μm) than the giant vesicle of hyperbranched polymers, their morphology could be readily observed by optical microscope as well. It was found that the photoisomerization of the Azo units endowed these vesicles with a photosensitive fusion behavior. As the current trigger, UV irradiation was more controllable than sonication, so the fusion rate of the vesicles was precisely adjusted.

Battaglia et al. reported another visible fusion process triggered by addition of homopolymers.[125] The initial polymersomes were formed by self-assembly of PEG-*b*-PBO (PBO: poly(butylene oxide)) in water. When homopolymer PEG was added, the swelling of PEG domains perturbed the vesicle membranes, thus disrupted the original stability resulting in aggregation. With lower molecular weight PEG, the process happened in a small scale with fusion from 2–3 vesicles into a larger one. With PEG of higher molecular weight, the added PEG rapidly disrupted the vesicle dispersion to induce mass aggregation of the vesicles. When the aggregates formed became too large to be supported in solution, the system jammed and formed gel.

Temperature induced fission/fusion of vesicles was reported by Lecommandoux et al.[126] The building block used in this case was a well-defined copolymer PTMC-*b*-PGA (poly(trimethylene carbonate)-*b*-poly(L-glutamic acid)), of which PTMC is a semicrystalline hydrophobic block with a melting endotherm around 34–35 °C in vesicular dispersions. This property made it possible to achieve both fusion and fission/budding of vesicles by tuning temperature. Specifically, when temperature was increased to above the melting point of PTMC block, the original crystal lattice was disrupted, creating an excess volume in the membrane, which finally resulted in a budding/fission process. Oppositely, when temperature was decreased, the amorphous PTMC began to form crystalized domains in the membrane, thus fusion process occurred due to the membrane defects arising from the variation in PTMC membrane packing during crystallization.

4.3. Biomimetic Functionalities Decorated On/Inserted in Artificial Membranes

Cell membrane is a systematical non-covalent combination of lipid, protein, and carbohydrate. The lipid bilayer serves primarily as a structural backbone of the membrane and provides a barrier preventing random movements or transfer of water-soluble materials into and out of the cell, while the proteins of the membrane, on the other hand, carry out most of the specific functions.[127] Carbohydrates, which are mostly covalently linked to lipid and/or protein components, play a crucial role in mediating cell-cell and cell-medium communications. In short, lipid bilayer mostly contributes to the structure of the eukaryotic cells, while protein and carbohydrate are related to functions. In the following part of this section, we will focus on functionalities attached on or across the membranes, which include ligands or receptors for specific recognition, mimicking of glycocalyx and lipid rafts, and trans-membrane proteins.

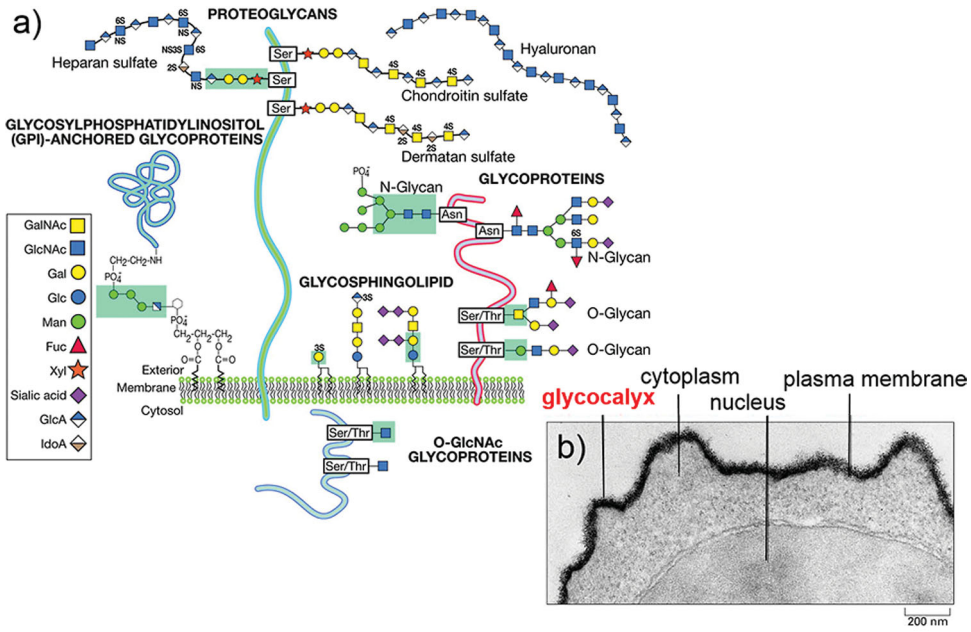

Figure 21. (a) Common classes of animal glycans;[133] (b) TEM image of cell surface.[134] Reproduced with permission.[133] Copyright 2009, The Consortium of Glycobiology Editors, La Jolla, California. Reproduced with permission.[134] Copyright 2008, Garland Science, Taylor & Francis group.

4.3.1. Common Binding Sites

To establish simplified models of on-membrane functions or to design cell-inspired self-assembly materials with biological functions on membranes, one of most direct and common strategies is introducing synthetic molecular recognition sites on the surface of polymeric vesicles. This strategy can be achieved via attaching ligands/receptors to amphiphilic copolymers with covalent or noncovalent bonds, or decorating ligands/receptors on surface of previously prepared polymersomes. One kind of the most commonly employed ligand/receptor pairs is composed of supramolecular host and guest, probably because of their well-established synthetic strategy and relatively high binding constants.[128]

In nature, proteins manipulate most of the specific functions on membrane surface. However, there are only a few well-established polymersome systems with functional proteins decorated on surface.[129] In contrast, in artificial systems, proteins are usually involved as specific receptors in binding with ligands decorated on membranes, which probably can be attributed to the difficulty in avoiding denaturation of proteins during the preparation and storage. For example, streptavidin was immobilized onto polymersome surface via the interacting with biotin group modified on the outer layer of the vesicle.[130] Streptavidin-biotin is well known for years as a strong non-covalent binding pair, but without further biological functions of their own. From the aspect of cell-mimicking and bio-inspired materials, we would like to pay more attention on something natural on cell surface, e.g., carbohydrates, which will be discussed in the next section.

4.3.2. Polymeric Vesicles Mimicking Glycocalyx (PV-Gx)

Glycocalyx, which is known as a dense layer of carbohydrates of glycoproteins, glycolipids and proteoglycans, etc., is found universally existing on both prokaryotic and eukaryotic cells (**Figure 21**).[131] The carbohydrates of glycocalyx play an irreplaceable role in a variety of cellular events, including proliferation, recognition, intercellular communication and immunoregulation, etc. For example, it is well known that human blood types (A, B, AB, and O) originate from the presence of different oligosaccharides on erythrocytic surface. And recent achievements confirm that the formation of human zygote, starting from sperm and egg binding, relies on the recognition of the glycoproteins on the sperm to tetrasaccharide (Sialyl-Lewis^x) of the glycocalyx of the egg.[132]

In fact, in the 1980s, research with thorough insight in glycocalyx overthrew the old concept that carbohydrates only served as fuel and structural materials, and gave birth to an emerging subject, Glycobiology.[135] Glycobiology, coined by Raymond Dwek, is a subject focusing on chemical structure, biosynthesis and biological functions of carbohydrates in organism. In the view of glycobiology, saccharide is another substance that encodes information besides protein and nucleic acid, with the name of "glycocode".[136]

Due to the diversity of oligosaccharides, glycocode is considered as the most complex coding system in organism, which contains large amounts of information. Encoding and decoding of information in glycobiology generally rely on intermolecular binding between oligosaccharide ligands and their specific protein receptors, i.e., lectins, which has been demonstrated as an important basis of life. As a major topic of glycobiology, carbohydrate-protein interaction has raised a great interest in different research fields in the last few decades.[137] It's worth indicating that the binding constant for a 1:1 carbohydrate-lectin pair is rather low, thus the apparent high activity and specificity in the system is a result of multivalent interaction.[138] Actually, some of the known lectins are homo-oligomer assemblies consisting of two to four identical subunits, each with a recognition site for a single carbohydrate.[139]

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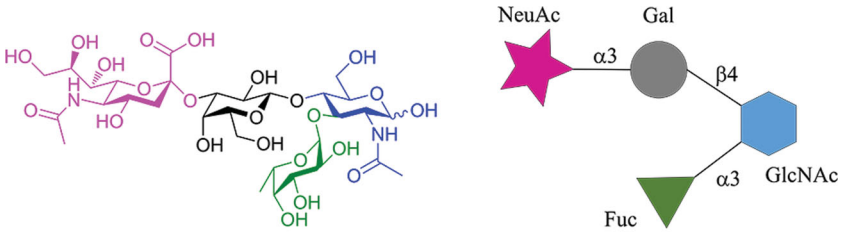

α-NeuNAc-(2→3)-β-D-Gal-(1→4)(α-L-Fuc-[1→3])-D-GlcNAc

Figure 22. A typical tetrasaccharide structure Siayl-Lewis^x. (Different sugars are in different shape and color with their initials. α or β represents the stereoselectivity and numbers represent constitutional selectivity of glycosidic bond.) The chemical structure is crucial to its binding ability.

Although more than 30 years have past, the progress of glycobiology is still rather slow compared with that in protein or nucleic acid biochemistry. The major problem is related to the extreme structural diversity of saccharides, which has frustrated scientists when they try to define oligosaccharide expression patterns on proteins or cells and set up the structure-function relationships. In cells, oligosaccharides are synthesized in a step-wise fashion in endoplasmic reticulum and then Golgi apparatus, which affords products with significant microheterogeneity. As a result, it is difficult to obtain homogeneous and chemically defined glycoconjugates from biological sources. Without such materials in hand, biological functions of sugars are difficult to unravel.[140]

Nonetheless, regard to the synthesis of oligosaccharides, an alternative strategy to the enzymatic route is chemical synthesis, which may lead to products with stereoselectivity and constitutional selectivity. Various methods have been developed to form stereoselective glycosidic bond and useful protective groups (an example of complex oligosaccharide structure is shown in **Figure 22**). Thus chemical glycobiology emerged as a new subject. Chemical glycobiology is capable of not only synthesizing a variety of pure natural oligosaccharides but also establishing unnatural oligosacchride architectures, which provide opportunities to design bio-inspired materials as required for both theoretical models and practical applications. Thus carbohydrate chemistry began its sweet-talking with material science. Synthetic glycopolymer is an outstanding language in this talking, which has been demonstrated as a valuable material with diverse applications.[141] As a material employed to mimic natural sugars, it has multiple binding sites acting as a multivalent ligand binding with lectin.

Synthesis of glycopolymer started with ring-opening polymerization by Kiessling,[142] and grew really fast as promoted by the breakthrough of controlled radical polymerization. The preparation of tailor-made glycopolymers with controlled structures can be mainly performed via two effective strategies: (1) polymerization of monomers bearing oligosaccharide moieties named as "glycol-monomers"; (2) modification of reactive polymer precursors with glycosyl donors. Cameron and Davis et al. prepared glycol-monomers as methacrylate derivatives via glycosylation of 2-hydroxyethyl methacrylate (HEMA) with acetyl protected glycopyranosyl bromide and galactopyranosyl bromide.[143] The targeted deprotected polymers were obtained by two parallel ways: either polymerization of the protected monomers followed by deacetylation or polymerization of the deprotected monomers. Further characterization of the products indicated that the latter led to a well-defined composition (**Figure 23**a). Haddleton and coworkers decorated various azide-functionalized carbohydrates onto polymers prepared by ATRP containing alkyne side chain via copper(I)-catalyzed Huisgen

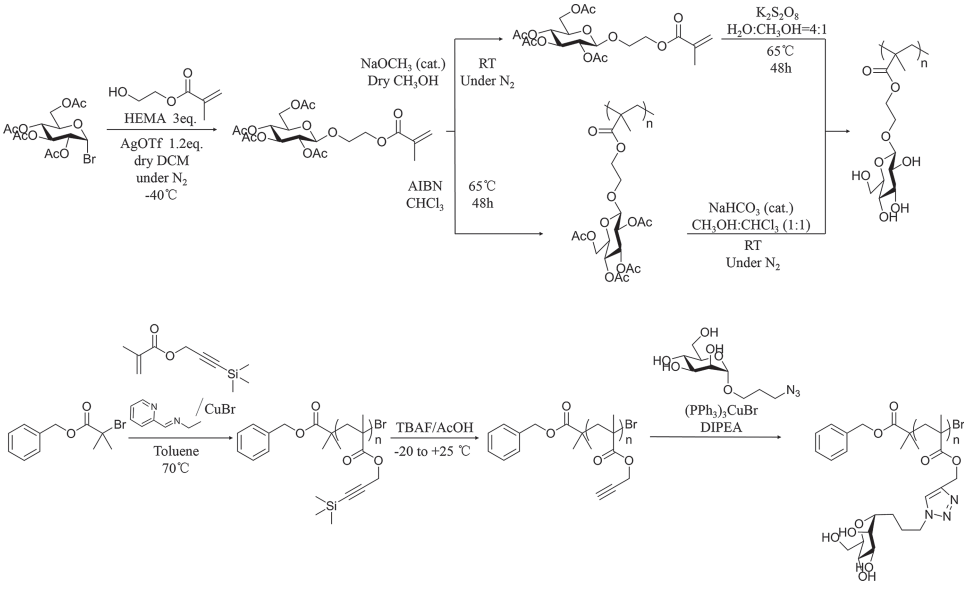

Figure 23. Typical synthetic routes of glycopolymers (a) glycol-monomer, (b) post-polymerization modification.

1,3-dipolar cycloaddition, i.e., "click" chemistry.[144] Following this "co-click" synthetic protocol, they provided a strategy to establish a library of multivalent ligands (Figure 23b).

Although plenty of glycopolymers have been reported in literature, their self-assembly study is still limited.[145] In fact, self-assembly of glycopolymer-containing copolymers in water may induce formation of vesicles with heavy layer of sugars on their surface, which may serve as an artificial model of glycocalyx. Compared with carbohydrate-coated nanoparticles (NP),[146] such polymeric vesicle mimicking glycocalyx, PV-Gx, the name suggested by Chen and Jiang,[147] enjoys its great superiority, e.g., the parameters of the assemblies including size, sugar density, flexibility, are all tunable and can be much closer to the natural glycocalyx. New attempts have been involved into this promising field in recent years, providing several models of "sweet" vesicles[148] with successful communication with bacteria.[149] Nevertheless, considering the complexity of carbohydrates in their chemistry and biology, constructing desirable PV-Gx systems with well-defined chemical structure being able to replicate the behavior of natural glycocalyx in its sweet taking with lectins or cells is still challenging and has a long way to go.

To our point of view, to establish a qualified system of PV-Gx, the following factors should be carefully considered. First, orientation of the hydroxyl groups of pyranose rings is different in various saccharides, e.g., glucose, mannose and galactose are constitutional isomers with only one or two configuration differences of the hydroxyl groups. Moreover, the aldehyde carbon generates another chiral center named anomeric carbon with two configurations (α- and β-) in the pyranose form, which have great effect on the binding ability of sugars to lectins. For example, the well-known lectin Con A only binds α-Mannopyranoside and α-Glucopyranoside, not to their β-form and any form of Galactopyranoside.

Additionally, the chemical stability of glycol-monomers before and after polymerization is of great importance during preparation. This issue brings unexpected difficulties to polymer chemists. For example, acetate is the most widely used protective group in carbohydrate chemistry. It is useful to prepare sugar modified (methyl) acrylate monomers, which are wildly used as glycol-monomers in ATRP and RAFT polymerization. But the ester bond can be hydrolyzed unavoidably during deacetylation, which can be a significant uncertainty at the stage of glycopolymer, due to the difficulty in characterization. In summary, correct type of glycosidic bond and definite stereochemistry are significant requirements of PV-Gx.

Considering the above important factors, efforts have been made by Chen and Jiang to design and prepare PV-Gx with a desired sugar layer fulfilling these demands. The employed glycopolymers are prepared via RAFT polymerization of tailor-made glycol-monomers. These monomers are derivatives of acrylamide containing *N*-linked galactopyranoside (β-Gal) and glucooyranoside (β-Glc) of definite configuration. Moreover, the acrylamide is stable enough to resist hydrolysis under basic condition to remove acetate after polymerization. The PV-Gx is prepared via NCCM strategy, which has been introduced in section 2.[12] In this work of PV-Gx, the two complementary homopolymers are a thermal responsive PNIPAM with a phenylboronic acid (BA) end (BA-PNIPAM) and a hydrophilic acrylamide-type glycopolymer (**Figure 24**a). The two building blocks first form a "graft like" complex linked up with a reversible boron-oxygen cyclic ester bond via the reaction of BA and the diol fragments of carbohydrates along polymer chains in basic solution. When temperature was raised to 33 °C, the PNIPAM grafts collapsed and induced the formation of PV-Gx, with glycopolymer on its outer and inner surface and PNIPAM as the middle layer. Dynamic light scattering (DLS) was employed for the first time to monitor the carbohydrate-protein interaction (Figure 24b). The binding result of β-Gal and β-Glc on different PV-Gx and three lectins i.e., Arachis hypogaea (PNA), Erythrina cristagalli (ECA) and Concanavalin A (Con A), showed clear specificities in these sugar-protein interactions, i.e., only pairs of V-PGal with PNA and ECA display the interactions while the other pairs do not, which are consistent to the results known from glycobiology. Thus the PV-Gx showed reliability and great potential in serving as a platform to study the glycobiology of artificial glycocalyx.

4.3.3. Lipid Rafts

Lipid Raft is a kind of newly recognized structure within cell membrane. As the name implies, lipid rafts are specialized regions or microdomains that possess a distinctive composition, i.e., dynamic clustering of sphingolipids and cholesterol, which can float within the fluid bilayer. Recently, the crucial function of lipid raft has been revealed. For example, they are platforms for attachment of proteins when membranes are moving around inside the cell and during signal transduction.[150]

Establishing an artificial model of lipid raft started recently, enriching the cell-mimicking systems. Polymeric vesicles composed of two or more kinds polymer chains on the vesicle surface are promising materials for this mission due to the phase separation of the polymer chains. For example, Discher et al. first prepared spotted vesicles by mixing PAA-PBD (PBD: poly(butadiene)) and PEG-PBD, sharing PBD as the common hydrophobic block, driven by the crosslinking of PAA blocks in the presence of Ca^{2+} cation.[151] Nowadays, several model rafts based on polymer/polymer or polymer/lipid hybrid vesicles have been reported, which will be described in this section.

Battaglia and coworkers took a significant step in engineering polymersomes that spontaneously organized their surface into controlled domains.[152] Two amphiphilic diblock copolymers PEG_{16}-*b*-PBO_{22} and $PMPC_{25}$-*b*-$PDPA_{70}$ (poly((2-methacryloyloxy) ethylphosphorylcholine)$_{25}$-block-poly(2-(diisopropylamino) ethylmethacrylate)$_{70}$) were mixed together to obtain polymersomes with surface domains. Two different preparing methods resulted in phased-separated vesicles in micrometer scale and nanometer scale, respectively. The phase separation behavior of the former was measured by confocal laser scanning microscopy (CLSM) and 3D reconstruction after fluorescent labeling (**Figure 25**a), while the latter was captured by cryo-TEM (Figure 25b). Further cell-incubation of the vesicles showed that although both of the hydrophilic blocks were protein-repellent, the existence of PMPC block did promote their endocytosis efficiency. Additionally, this raft-mimicking system can be selectively modified with streptavidin to one of the phases by treatment of the vesicles composed of biotin-labeled PMPC block with streptavidin-modified AFM tip in buffer.

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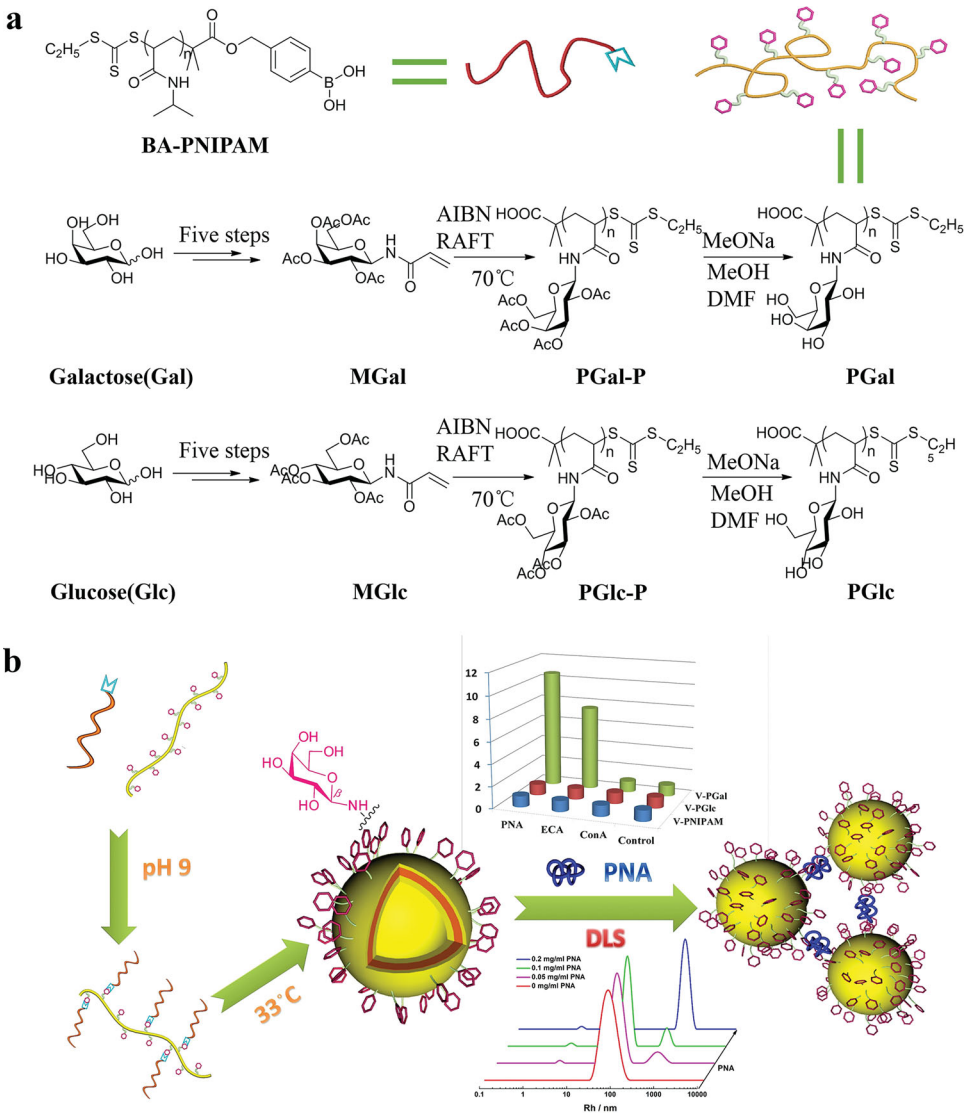

Figure 24. Synthetic routes of acrylamide glycopolymer (a) and its self-assembly via NCCM strategy with BA-PNIPAm, followed by binding test with lectins monitored by DLS (b).

Meanwhile, hybrid vesicle composed of amphiphilic copolymer and lipid is employed as another artificial model of lipid raft on membrane. Fournier et al. studied the mixing behavior of amphiphilic copolymers with lipids and the feasibility of forming mixed lipid-polymer nanoparticles.[153] Later by mixing various lipids and block copolymers, many new vesicles with phase-separated domains were obtained, including either isolated "copolymer domains"[154] or isolated "lipid domains"[155] by adjusting the physical property and molar ratio of the components. Recently, by using different lipids with different melting temperature to control the fluid or gel state of the lipids, Sandre and Meins et al. prepared hybrid vesicles with different surface structures.[156] Among these, the "raft-like" object they obtained was the vesicle, having block copolymer as major component and isolated lipid spots in its gel state.

More recently, Bacia and Binder et al. established a hybrid vesicle system with a great potential in biological study and cell-inspired materials.[157] They employed an amphiphilic block copolymer PIB-*b*-PEG (PIB: polyisobutylene) and a natural lipid, 2-dipalmitoyl-*sn*-glycero-3-phosphati-dylcholine (DPPC) as the major components. Then hybrid giant unilamellar vesicles (GUV) were obtained by a modified electroformation method.[158] The phase segregation of fluorescent-labeled hybrid vesicles with different molar ratio of PIB-*b*-PEG/DPPC was captured by confocal microscopy images. The result indicated that the hybrid vesicles presented homogeneous membranes when the molar content of PIB-*b*-PEG is below 20% or above 30%, while phase-separated hybrid membranes containing microscopic domains were obtained as PIB-*b*-PEG contents were in 20 to 28 mol%. Later, the authors stepped further to study the effect of the hybrid membrane morphology on protein binding behavior, where the glycosphingolipid is a large kind of natural glycolipids locating on cell surface. GM1 is a representative member in this family, which can strongly

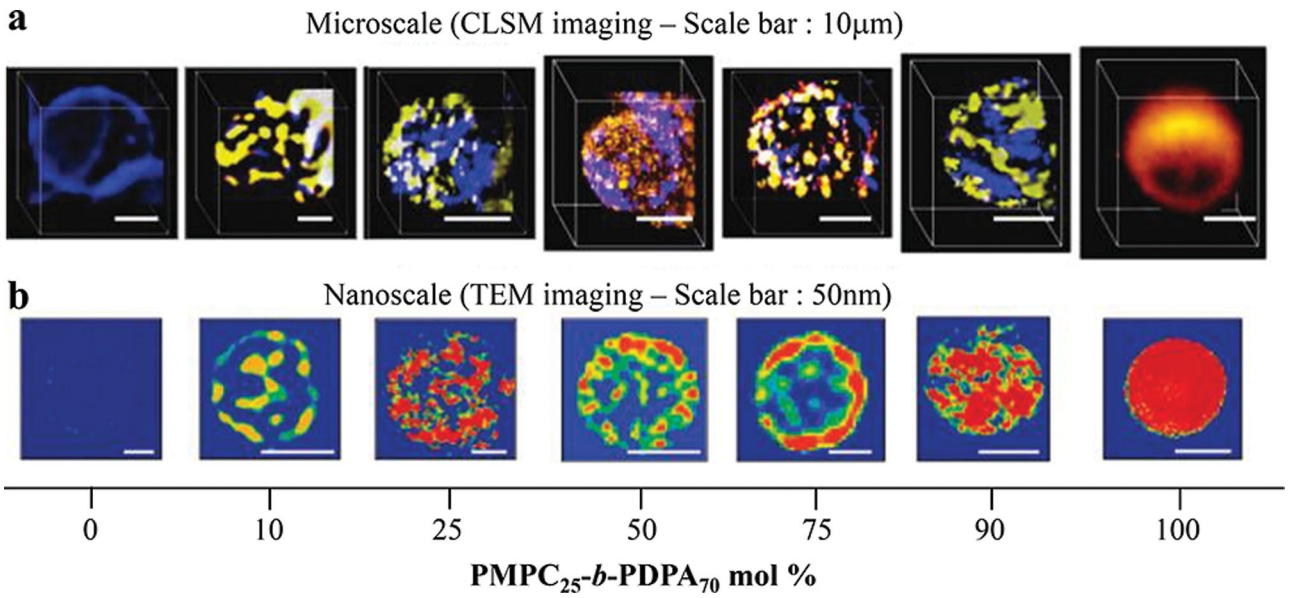

Figure 25. Hybrid $PMPC_{25}$-*b*-$PDPA_{70}$/PEG_{16}-*b*-PBO_{22} polymersomes prepared at different binary compositions. (a) The 3D images calculated from CLSM optical slices showing the microscale morphology. (b) The FFT-filtered (fast Fourier transform) TEM images obtained for selectively stained polymersomes showing the nanoscale morphology. Reproduced with permission.[152] Copyright 2011 ACS.

bind to cholera toxin B (CTB), a pentameric protein, in GM1:CTB 5:1 ratio. The authors prepared GUVs of PIB-*b*-PEG and DPPC containing GM1 (0.1 mol%). It is worth to mention that a small amount of GM1 did not lead to changes in the surface phase state of GUVs. According the confocal microscopy images, it was found that when the content of PIB-*b*-PEG was lower than 20 mol%, CTB bound over the entire homogeneous GUV surface (**Figure 26**A). For the case of 20–28 mol% of copolymer, CTB bound over the phase-separated hybrid membranes as well, which indicated that GM1 incorporated into the polymer-enriched phase and the lipid-enriched domains as well (Figure 26B). More interestingly, within minutes after protein incubation, protein binding and formation of large GM1-enriched lipid domains were observed in GUV containing 30% PIB-*b*-PEG (Figure 26C), which indicated that the highly cooperative binding of the multivalent CTB led to the formation of a more ordered GM1-enriched lipid domain segregated from the surrounding hybrid bilayer. Such hybrid membrane systems provide a nice biomimetic model to understand biological receptor/ligand recognition on hybrid vesicle, which can be fine-tuned in their lateral organization and mobility by varying the DPPC/PIB-*b*-PEG composition.

4.3.4. Biomimetic Functionalities Inserted in Artificial Membranes

In nature, the role of plasma membrane is not limited to provide a closed environment for all living activities. It also allows the necessary exchange of materials between inside and outside of the cell. In other words, cell membrane has some special provisions, which allow the movement of nutrients, ions, other products, and wastes, in and out of the cell. This process can be divided into two types: passive transport by diffusion and active transport coupled by energy.[127] Both of them strongly depend on the channels inserted in membrane, which are majorly made of proteins. Therefore, to design well-established protocells with high fidelity to such trans-membrane functions via MSA, it is necessary to insert natural trans-membrane proteins or artificial proteins into polymersome.

Meanwhile, the protein inserting strategy is a majority approach to prepare polymeric nanoreactors, which becomes one of the most popular research topics in bio-inspired materials during the last decade. Quite a few reviews focused or kept an eye on the protein inserting and nanoreactors with comprehensive citations.[159] Considering this situation, in this section, only some well-established polymeric systems are briefly described as examples.

As far as we know, Meier and coworkers are pioneers in the study of protein insertion into membrane of polymersome.[160] Their system was mostly established on vesicles of a tri-block copolymer M-D-M (of section 4.1) and its derivatives. Here the hydrophobic middle block PDMS is extremely flexible, which may allow the block copolymer membrane to adopt the specific geometrical and dynamical requirements issued by the membrane proteins to keep their functionalities.[161] With different integral proteins inserted, the vesicles were functionalized with a variety of trans-membrane channels, from non-specific to specific ones.[162] Besides, the insertion of bacterial water-channel protein Aquaporin Z (AqpZ) resulted in a large enhancement in water permeability of up to 800 times higher than that of pure polymeric vesicles.[163] This mimicking system has been developed into a well-established polymersome platform, which is a valuable nanoreactor design. Alternatively, using artificial proteins, which usually form helical pores via self-assembly of dendritic dipeptides and dendritic esters, would not require special flexibility for the constituent polymer chains.[164]

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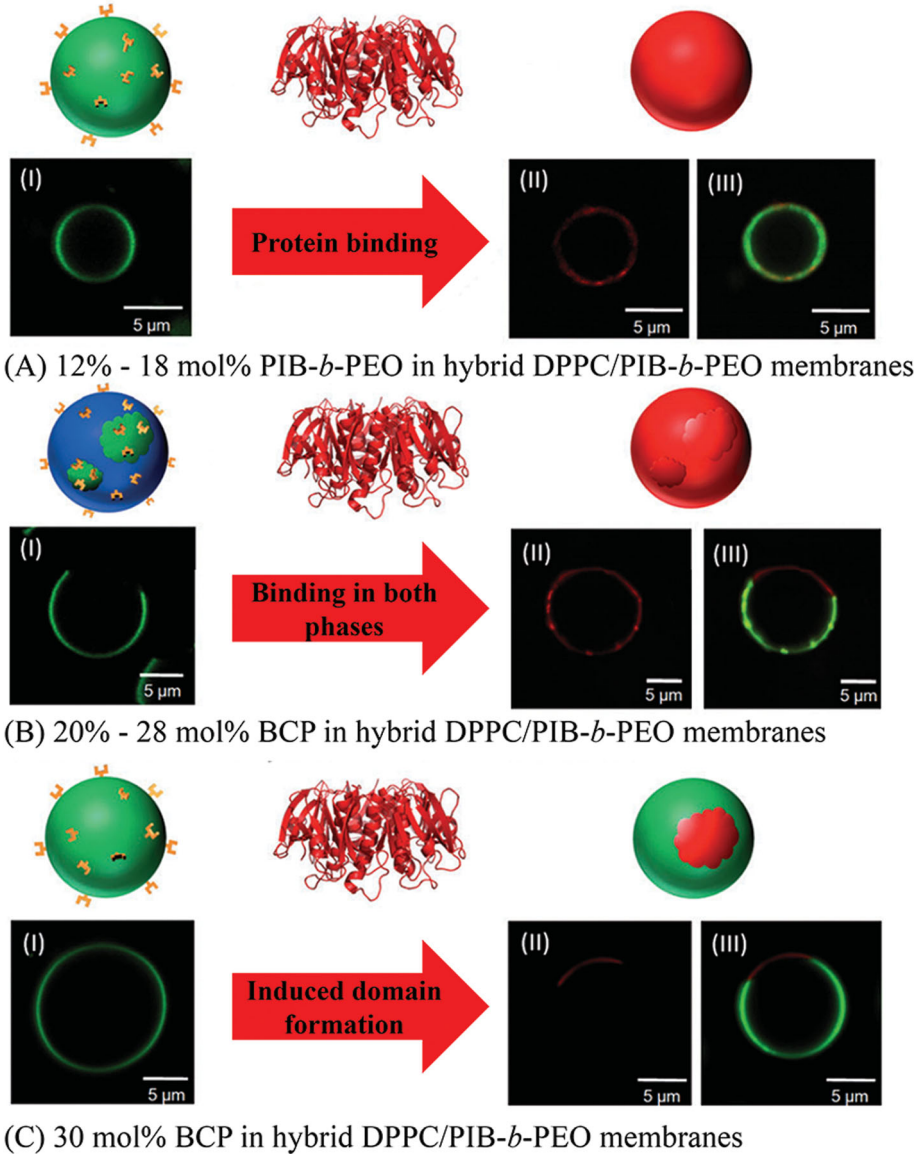

Figure 26. Effect of the hybrid membrane morphology on the protein (CTB) binding behavior. Fluorescence signals came from Rh-DHPE (green, preferential incorporation into polymer-enriched phase), and Alexa488-labeled CTB (red). Mixed DPPC/PIB-*b*-PEG formed membranes in different composition: PIB-*b*-PEG 12 to 18 mol% (A), 20 mol% (B), more than 28 mol% (C). (I) before and (II) after CTB binding, (III) the corresponding overlay image of both dyes after binding. Reproduced with permission.[158] Copyright 2013 Wiley.

5. Macromolecular Assemblies Mimicking the Functions of Natural Materials and Their Applications

5.1. Self-Healing and "Smart" Materials

Self-healing is one of the remarkable features of most plants and animals, which increases their survivability and lifetime. This property is usually unable to be attained from simple covalently connected materials since the permanent break of chemical bonds during macroscopic fracture or cutting event cannot be recovered. Great efforts have been made to establish[165] a series of successful and prevailing strategies to construct self-healing materials, which can be broadly classified into two: The first one is capsule or vascular based strategy, in which healing agents are incorporated in capsules or vesicles embedded in materials.[166] This approach is successful but does not belong to the field of MSA. The second is an intrinsic reversibility based strategy, standing on the reversible character of dynamic covalent bonds and non-covalent interactions.

Dynamic covalent bond has been regarded as an appropriate tool to realize the reconstruction of damaged polymeric materials.[165c] For this propose, several kinds of dynamic covalent bonds are utilized, such as Diels-Alder reaction, acylhydrazone bond exchange, disulfide bond, and Schiff base reaction.

Introduction of Diels-Alder for preparing self-healing materials was reported by Wudl et al.[167] They polymerized molecules with four diene groups and molecules with three dienophile groups by thermal cycloaddition reaction to obtain polymeric materials with mechanical property comparable to epoxy resin. The film showed good healing property by attaching the broken surface after tensile test. However, in this case thermal treatment was still needed. Afterwards, various dynamic covalent bonds were reported to reach similar self-healing potential. Acylhydrazine and aldehyde, which were first successfully used by Lehn to make dynamers,[168] react to form acylhydrazone linker under the presence of acidic catalyst. Chen et al. prepared PEG with acylhydrazine at its two ends and a molecule with three aldehyde groups tris[(4-formylphenoxy)methyl] ethane.[169] Their mixture in DMF with a catalytic amount of acetic acid formed organogel, which showed self-healing property when two freshly cut parts were kept contact for 7 h. Schiff-base based self-healing hydrogel was reported by Tao and Wei et al., in which dibenzaldehyde-terminated telechelic PEG and chitosan are mixed in an aqueous solution in order to form crosslink of Schiff-base between the aldehyde on PEG and amino group on chitosan.[170] The mixture in aqueous solution immediately formed hydrogel with self-healing property. Recently disulfide bond was also introduced to construct self-healing gel and thermoset.[171] Klumperman and Goossens et al. revealed that the self-healing property of their thermoset was based on the exchange between disulfide and free thiol, not disulfide-disulfide exchange reactions.

Besides the polymeric materials held by dynamic covalent bonds, even non-covalent bonds were found to be able to form supramolecular polymers and networks with the self-healing ability, which are of growing interest.[172] They are hydrogen bond,[173] metal coordination,[174] π–π stacking,[175] and host-guest interaction.[176] Hydrogen bonding pairs employed in self-healing materials could originate from ureidopyrimidinone, nucleobases, barbituric acid, Hamilton wedge, etc., which were nicely summarized in a recent review.[177] Among those functional groups, urea is the simplest and oldest one, but seems to exhibit the highest potential for producing self-healing materials in a large scale. Leibler et al. firstly exploited supramolecular network to fabricate novel rubber-like material, in which hydrogen bonding sites were distributed to both of the main chains and the crosslinks. The cut pieces of the resultant network could self-heal when they were brought into contact for some time at room temperature without heat or strong press. The mended samples were able to sustain large deformations and recover their shape and size when stress was released. Self-healing was efficient because many non-associated hydrogen-bonding groups were present near the fracture surface, i.e., it was not hard for free groups to find their "partners". Such hydrogen bond based new polymeric materials have a great potential with many advantages, including low cost, easy preparation in large scale and efficiency of the healing process. The method was further modified by introducing chemically compatible micro-nickel particles to fabricate multi-functional composites with both self-healing and pressure-/flexion-sensitive properties.[173c] After the cut parts were placed to contact under gentle pressure, both the mechanical and electrical properties were recovered at room temperature.

Birkedal et al. built self-healing gel by metal coordination.[174] A catechol-functionalized polyallylamine was mixed with Fe ion in aqueous solution. The catechol is known to coordinate with Fe(I), Fe(II) and Fe(III) ions to form 1:1, 2:1, and 3:1 complexes respectively, thus the mixture formed gel at alkali condition. The gel showed self-healing property at pH 8. Huang et al. used orthogonal assemblies of supramolecular polymers with both host-guest interaction and metal coordination interaction.[176] They prepared bis(benzo-21-crown-7)-based monomer as a host and bis(dialkylammonium salt)-based monomer as a guest, and thus obtained alternating supramolecular polymer through the host-guest interaction. Subsequently, addition of Pd ion led to the coordination of triazole groups from different supramolecular polymers, resulting in the formation of gel, which displayed self-healing property. It is known that copolymers containing π-electron-deficient diimide units in the backbone can adopt chain-folded conformations on interacting with π-electron-rich aromatic molecules such as pyrene. Colquhoun et al. utilized this property to obtain a polymeric blend with thermo reversible property by mixing the chain-folding copolymer and pyrenyl-terminated polyamide.[175] The intercalation of the pyrenyl end-group between the polyimide backbones was identified by the color change due to the complementary π–π stacking and charge-transfer. The blends showed an obvious enhancement in mechanical properties than their individual components due to this physical crosslinking, and showed desired healing properties as well upon heating.

We noticed that all of the self-healing materials mentioned above except the composite with Ni particles, have a same feature, i.e., homogeneous structure at molecular level, in this respect it is similar to the conventional polymeric materials. This is because the basic idea to realize self-healing is just to substitute the conventional covalently linked/crosslinked polymer chains by supramolecular ones with non-covalent interactions. However, some reports suggest another route to reach self-healing by exploiting heterogeneous structure of the material, which is carefully designed through MSA strategy. Okay et al. realized the self-healing in gel using dynamic hydrophobic association between amphiphilic copolymers and surfactant micelles.[178] In the presence of NaCl, sodium dodecyl sulfate (SDS) formed large worm-like micelles, which could accommodate hydrophobic monomer with a long hydrophobic chain, i.e., stearyl methacrylate (C18) inside. After copolymerization of the C18-containing monomer and hydrophilic acrylamide in this SDS micellar solution, a gel formed with the hydrophobic C18 side group stabilized by the micelle with the non-covalently crosslinked structure (**Figure 27**a). The fractured surfaces of the gel was found to heal at room temperature with the original extensibility of about 3600% (Figure 27b). DLS measurements revealed that the gel containing SDS micelles exhibited, in addition to a fast mode, a slow relaxation mode and time-dependent elastic modulus; while the gel after SDS micelles were extracted showed only a fast relaxation mode and time-independent elastic modulus, similar to covalently crosslinked gels.[179] The slow relaxation mode and time-dependent modulus indicated the temporary nature of the hydrophobic associations with a lifetime in the order of seconds to milliseconds, reflecting the reversible crosslinking nature due to the local stablization of the hydrophobic group in SDS micelles. In short, when the

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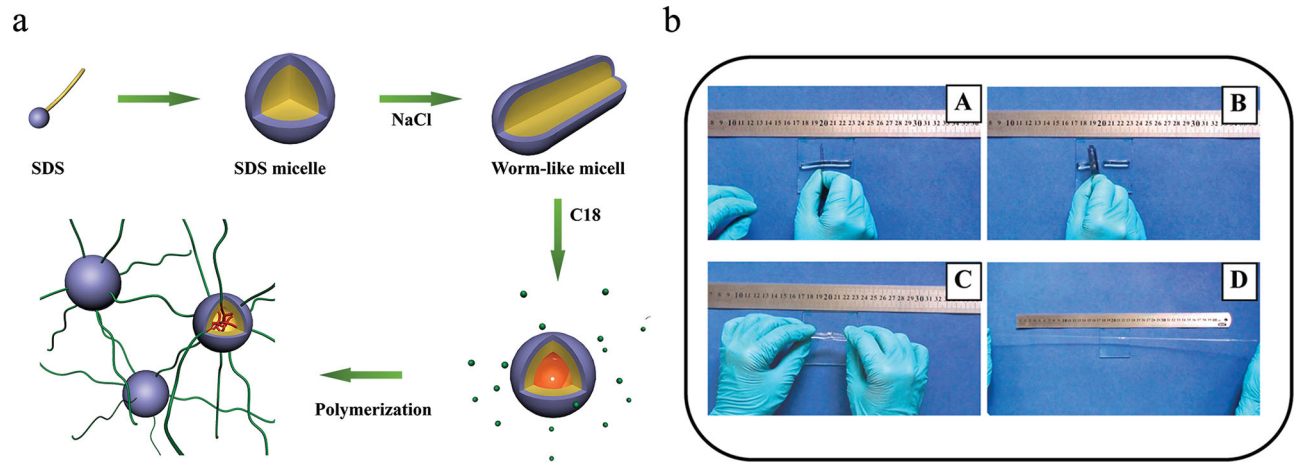

Figure 27. (a) Cartoon showing the formation of surfactant containing physical gels in aqueous SDS–NaCl solutions via hydrophobic C18 blocks. (b) (A–D) Photographs of a gel sample. After cutting into two pieces and pressing the fractured surfaces together for 10 min, they merge into a single piece with the original extensibility. Reproduced with permission.[179] Copyright 2012 ACS.

micelles are present, the hydrophobic interactions are weakened, resulting in an increase of the viscoelastic dissipation in the gel sample. Without the micelles, the hydrophobic interaction was too strong to reversibly associate. This is the key factor for this self-healing behavior.

Contributions from heterogeneous structure to self-healing are not limited to this micelle-containing system. As discussed in section 2, microscope phase separation of block copolymers has been known for years. Recently, the phase separation property of supramolecular polymer connected by hydrogen bonding was demonstrated.[180] Aiming at light-driven self-healing materials, Rowan et al. used a functionalized oligomer, i.e., a polymer backbone of PE-co-PB (poly(ethylene-co-butylene)) with 2,6-bis(1′-methylbenzimidazolyl)pyridine (Mebip) ligand at its both terminals (**Figure 28**a). With addition of $Zn(NTf_2)_2$, which can form 1:2 complex with Mebip, the oligomers were linked into a supramolecular copolymer (Figure 28a). Furthermore, the hydrophobic polymer backbone and the polar metal-ligand motif self-assembled into clear lamellar morphology, which was proved by SAXS (small-angle X-ray scattering) and TEM (Figure 28b). When the metal-ligand core was electronically excited, the absorbed energy was converted into heat, leading to temporary disengagement of the metal-ligand center and a concomitant reversible decrease in the molecular mass and viscosity. Therefore, quick and efficient self-healing process was achieved (Figure 28c).[181]

Furthermore, the phase-separated "hard" phase was employed as physical crosslinking domain for self-healing materials. Guan et al. fabricated self-healing thermoplastic elastomer through micellization of an amphiphilic brush polymer and its further assembly.[182] The brush polymer composed of a PS backbone and poly(5-acetamidopentyl acrylate) (PA-amide) brushes firstly assembled into globular morphology in polar methanol solution, as a result of collapse of the hydrophobic PS backbone. Then with evaporation of the solution, the polymer particles coalesced into bulk material, which still

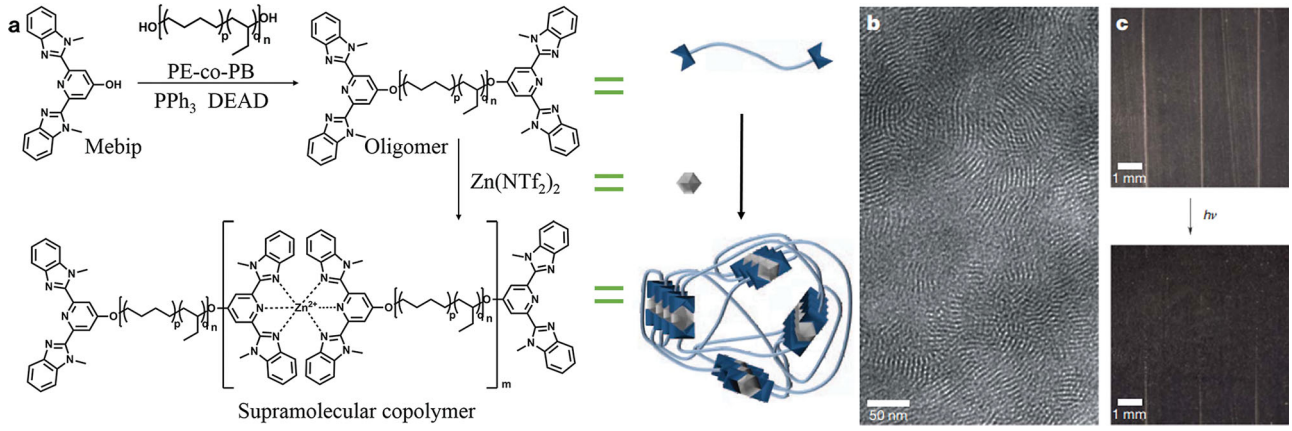

Figure 28. (a) Synthesis of macromonomer and polymerization by addition of $Zn(NTf_2)_2$. (b) Representative TEM micrograph showing the lamellar morphology of the supramolecular polymer. (c) Optical healing of the supramolecular polymer on exposure to light in the wavelength range 320–390 nm for 30 s twice at an intensity of 950 mW cm^{-2}. The damage was prepared by applying well-defined cuts with a depth of ~50–70% of the film. Reproduced with permission.[181] Copyright 2011 NPG.

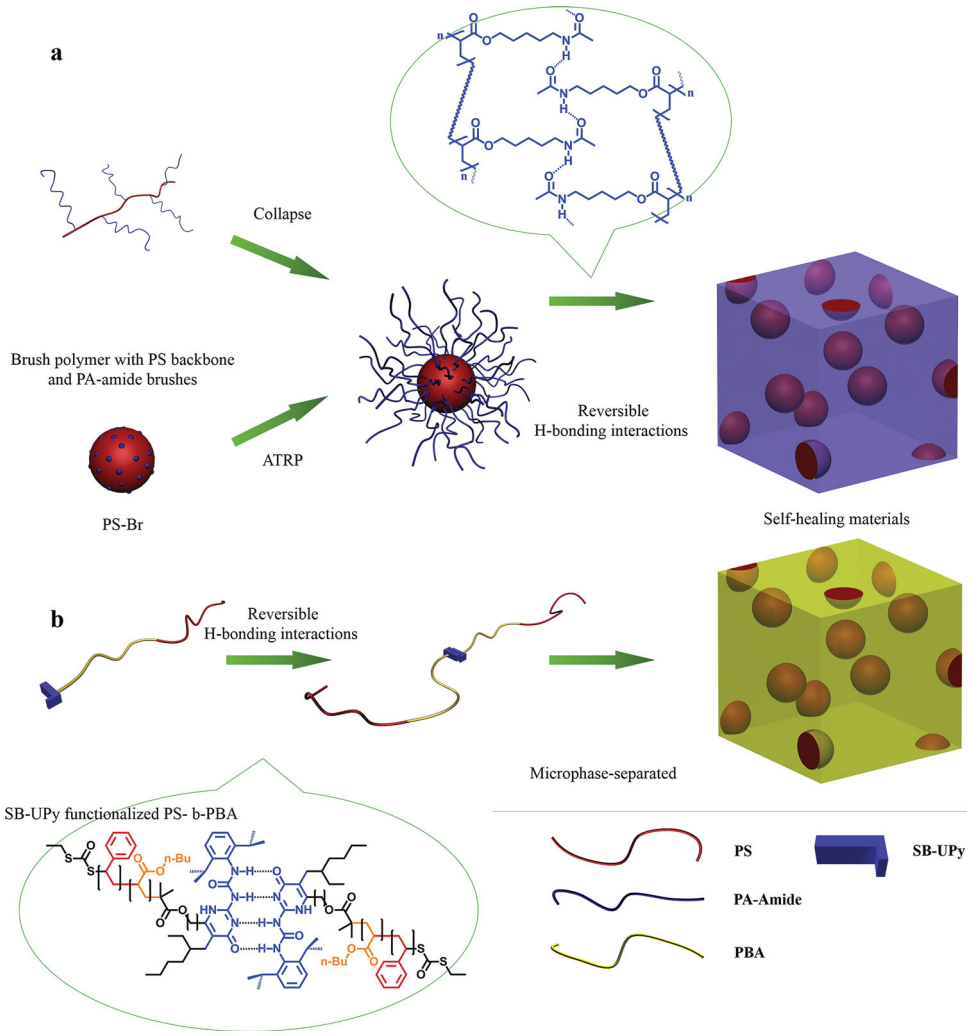

Figure 29. Design concept for the multiphase self-healing polymer system. (a) The hydrogen-bonding brush polymer self-assembles into a two-phase nanostructure morphology during processing. The PS phase can be replaced by PS particles covered by the same brush polymer. (b) PS-*b*-PBA with hydrogen bond linkage at its end undergoes similar microphase separation. The hydrogen bonds are individually dynamic, but polyvalent clusters of covalently linked associative hydrogen bonding interactions result in a mechanically stable connection that behaves like a permanent covalent linkage.

preserved the microphase-separated structure inside. The isolated domains of PS act as hard phase while continuous PA-amide phase acts as soft matrix in which the amide groups form dynamic hydrogen bonds for intermolecular crosslinking. Therefore the cut surfaces showed spontaneous self-healing property as a single-component solid material without any external stimuli and chemicals (**Figure 29**a). Very recently, PS nanoparticles with grafting PA-amide on their surface were also employed by the same group.[183] In the new material, the dynamic shell connected by hydrogen bond conferred self-healing properties while the hard PS particle provided stiffness as crosslinked core. This microstructure was evaluated by TEM, showing that the core–shell nanoparticles self-assembled into well-defined two-phase nanocomposites. In another work, a supramolecular block copolymer with PS block and quadruple hydrogen bonding junction has been used for self-healing materials (Figure 29b).[184] Here UPy (2-ureido-4-pyrimidinone) end-functionalized PS-*b*-PBA (PBA: poly(*n*-butyl acrylate)) was prepared which would form supramolecular triblock copolymer by hydrogen bond between UPy. The supramolecular triblock copolymer was found to phase separate as its covalent counterpart did. Moreover it achieved self-healing behavior due to the reversible hydrogen bond, which was superior compared to the covalent tri-block. In short, this method not only provided a new strategy to realize self-healing property, which took the fully advantage of conventional MSA, but also achieved materials with high modulus and toughness with spontaneous healing capability due to the self-assembled hard/soft two-phase system.

5.2. Materials Based on Self-Sorting

The previous in vitro experiments of self-assembly were mainly conducted in ideal and simple conditions that only components for one kind of assembly exist in a system. However,

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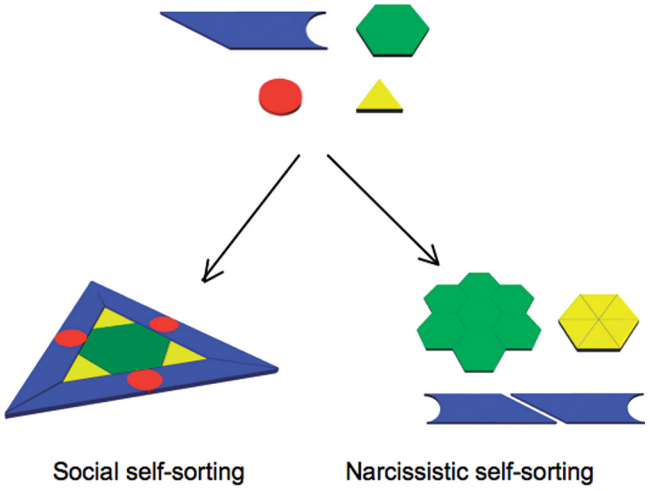

Figure 30. Social and narcissistic self-sorting definition described in reference 186. Reproduced with permission.[186a] Copyright 2011 ACS.

in nature usually numerous kinds of assembling components coexist in one system, e.g., in cells, protein, DNA and sugar act as building blocks independently or coordinately in multiple self-assembly. This principle can find many good examples in nature such as replication of DNA and crystallization of racemates into conglomerates, i.e., mixtures of enantiomerically pure crystals of one enantiomer and its opposite. Isaacs and coworkers suggested the word "self-sorting" to describe such recognition phenomena in multicomponent mixtures at the level of synthetic supramolecular chemistry, which can be defined as high fidelity recognition between molecules within complex mixtures and becomes one of the recent important concepts in self-assembly.[185] Self-sorting can be classified in two categories: 1) narcissistic self-sorting (self-recognition), in which each building block selectively assembles with themselves without mutual disturbance, and 2) social self-sorting (self-discrimination), in which different building blocks coordinately assemble into one defined structure (**Figure 30**).[186] With this classification in mind, in this section we will pay more attention on self-sorting systems from synthetic polymers, while the successful self-sorting systems of small molecular gelator will be excluded.

Self-sorting is often taken into consideration in fabricating complex supramolecular polymer systems. Briefly, when two different monomer units are put into one system, if they form identical supramolecular copolymer with an alternating sequence of the two monomers, it can be regarded as social self-sorting;[187] if they form two individual supramolecular polymers, it is a narcissistic self-sorting process.[188] For example, Huang et al. demonstrated both the narcissistic and social self-sorting by combining two individual host-guest interactions of C10/PQ pair and C8/DBAS pair (chemical structures shown in **Figure 31**). When C10 and DBAS were attached via covalent bond (C10-DBAS), as well as C8 and PQ (C8-PQ), the mixture of this two compounds generated an alternating supramolecular polymer as a social self-sorting process (Figure 31a), due to the selective molecular recognition between C10 and PQ, and C8 and DBAS as well.[187b] On the other hand, when the hosts were covalently linked with their own guests (C10-PQ and C8-DBAS), two individual supramolecular polymers were generated in the mixture, which belonged to narcissistic self-sorting (Figure 31b).[188] In fact, similar self-sorting system was achieved earlier by Harada, using the inclusion complexation between α-CD/β-CD and various guests.[186,187]

Self-sorting is also an important concept in fabrication of supramolecular gel, since it often brings multiple responses to the material. Weck et al. explored the methodology via preparing a linear norbornene-backbone copolymer by ROMP (Ring-Opening Metathesis Polymerization) first, which carried different non-covalent interaction sites for hydrogen bonding,

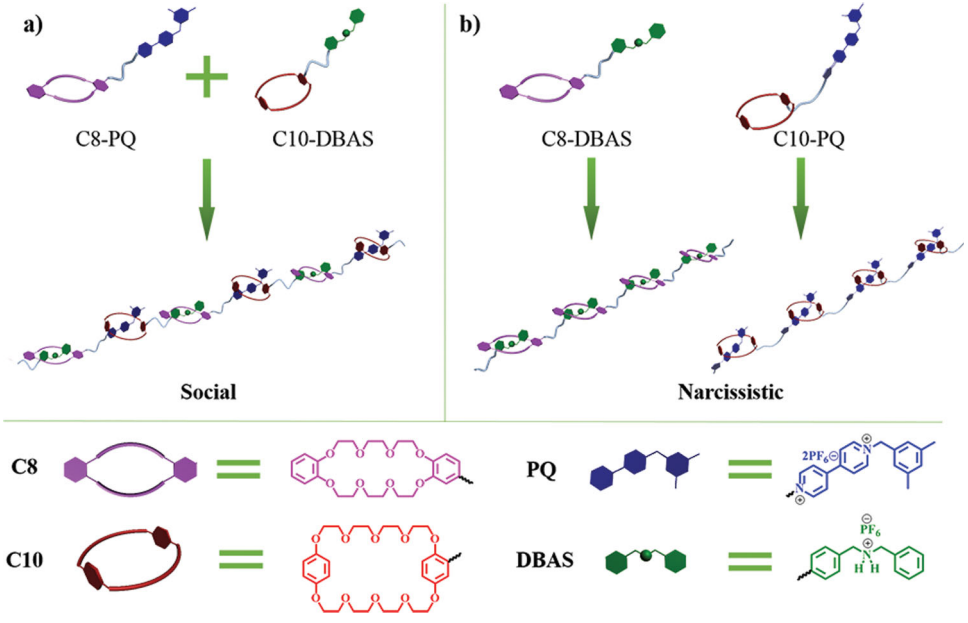

Figure 31. Social (a) and narcissistic (b) self-sorting demonstrated by supramolecular polymer.

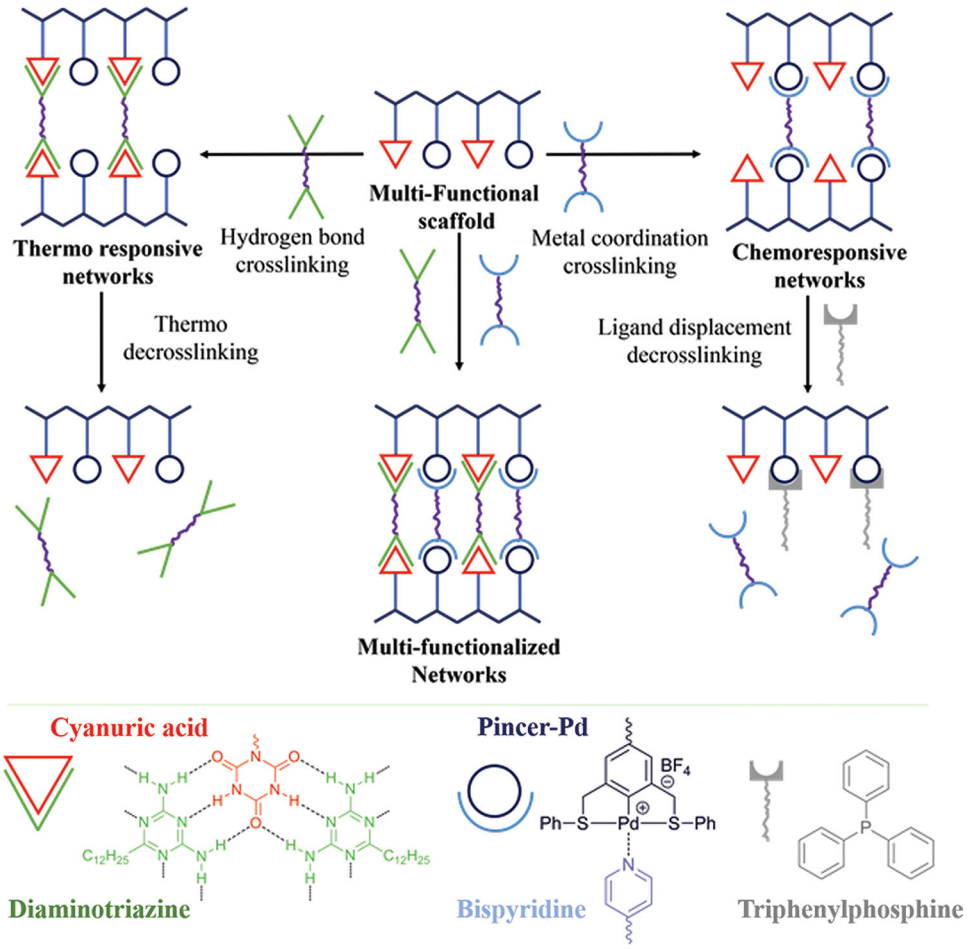

Figure 32. Social self-sorting to form polymeric hydrogel and various de-crosslinking methods. Reproduced with permission.[190d] Copyright 2011 ACS.

metal coordination, and host-guest interaction.[189] Then the polymer was crosslinked via different molecular recognition interactions by adding divalent compounds with complementary interaction sites to the polymer solution.[190] For example, the copolymer chain carrying cyanuric acid group and pincer-Pd ligand can be crosslinked by either diaminotriazine via hydrogen bond with the former or bispyridine via metal-ligand interaction with the latter (**Figure 32**).[190c] The resultant network can be regarded as a social self-sorting gel, which was partially dissociated by either thermal de-crosslinking of hydrogen bond or addition of ligand displacement compound to de-crosslink the metal-ligand interaction. In short, self-sorting has been utilized to realize multi-responsive gelation.

Life in fact is a symphony of multiple recognition pairs with various affinities from strong to weak; in other words, each performs its own functions, and in many circumstances, the relatively weak binding pairs play even more important roles than the stronger ones. For example, rolling of lymphocytes on endothelial cells are elegantly controlled by weak binding at first while the stronger binding will be activated afterwards, which prevents further rolling and induces migration of lymphocytes to infection sites. Thus self-assembly systems with biological molecular recognition, such as protein-sugar interaction[191] or protein multimerization,[192] are introduced to social self-sorting systems. Chen and Jiang paid more attention on carbohydrate-protein interaction due to its crucial role in many biological events although it is a rather weak molecular recognition pair. A complex system was designed and achieved successfully, which included three different molecular recognition interactions, i.e., Con A/α-Mannopyranoside (Con A–Man), β-CD/Adamantane (β-CD–Ada), and α-CD–PEG (**Figure 33**).[191] In the system, the key compound was α-Man modified β-CD (β-CD-Man), which served as a multifunctional linker, connecting lectin Con A with Ada-PEG (Ada modified PEG) via both Con A/Man recognition and CD/Ada complexation. The orthogonality of the two interactions was proved by ITC. After addition of α-CD to the complex, which can thread onto the PEG chain due to the third molecular recognition interaction, the solution turned to a hydrogel. The modulus of the hydrogel was three magnitudes higher than that of the hydrogel without Con A. Thus this work presents a good example of social self-sorting assembly dealing with three different molecular recognition interactions.

The narcissistic self-sorting in elastomer was also achieved. Sijbesma et al. investigated the assembly of motifs with hydrogen bond in polymer backbone and reported the self-sorting effect depending on the length between two binding

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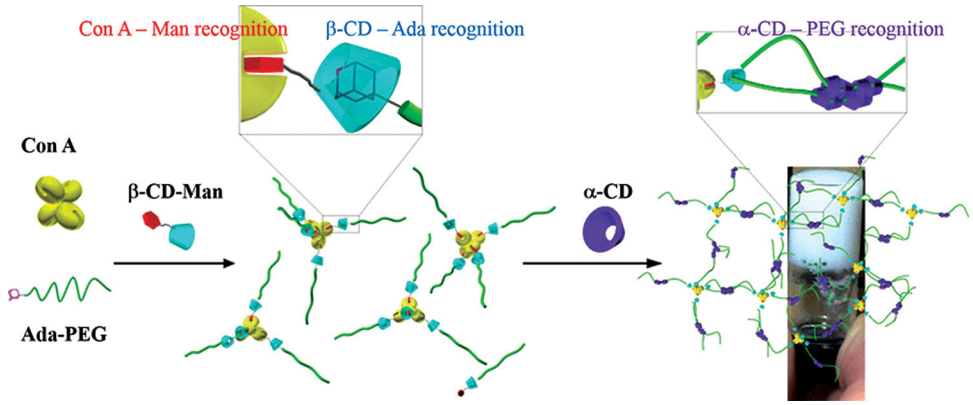

Figure 33. Social self-sorting of three molecular recognition interactions. Reproduced with permission.[191] Copyright 2013 ACS.

sites (**Figure 34**).[193] Urea motifs generally display self-association since it can be concurrently a hydrogen bond donor and acceptor. When two urea groups are linked by an alkyl chain (bisurea segment) and then connected with p(THF) (poly(tetrahydrofuran)) alternatingly, the bisurea segments would associate with themselves to form hard fiber-like segment, subsequently the system exhibited thermoplastic elastomeric property. Interestingly, if the two urea motifs in a bisurea segment were linked by alkyl chains with different length (UpU, p = 4, 6, 7), the UpU segment displayed narcissistic self-sorting, i.e., one associates with those composed of the linker with the same length exclusively. Specifically, when the copolymers with different UpU segments with linker carbon number of four, six and seven were mixed together, the UpU segment with the same linker length formed individual ribbon-like hard segment (Figure 34).[194] Similarly, in another work, benzen-1,3,5-tricarboxamide (BTA) motif and UPy motif were modified to the ends of PE-co-PB separately, forming fiber-like self-assembly.[195] Here the BTA motif and UPy motif performed narcissistic self-sorting in bulk. As a parallel experiment, the two motifs were modified to the ends of elastomers separately. The blend of the two elastomer exhibited individual assembled domains in bulk state. After the addition of small amount of compatibilizer with BTA and UPy at its end (BTA-UPy), this BTA-UPy molecule crosslinked the two assemblies, which increased the modulus of the blend to one order of magnitude higher than the blend without the crosslinker.

Harada et al. recently applied the self-sorting concept, which was developed in molecular level, directly to realize macroscopic selective adhesion of hydrogels.[196] It is known that t-butyl (t-Bu) and n-butyl (n-Bu) groups are the guests for β-CD and α-CD respectively. Harada et al. found that the t-Bu acrylamide-based gel cubic stuck to the gel cubic containing β-CD exclusively, while those containing n-Bu groups did the same to those containing α-CD (**Figure 35**). Obviously, this smart self-sorting process was induced by the selective host-guest interaction between the CDs and the guest groups exposed at the surface. Furthermore, such self-sorting partners can be controlled by thermal,[197] photochemical,[198] or solvent conditions[199] for the systems with the appropriately selected guest groups such as benzene, Azo, or pyrene.

5.3. Template Polymerization

Template polymerization is the key point in the process of the genetic information flow in nature, namely, the transcription of DNA into messenger RNA, followed by translation into peptides and proteins using ribosome. The process is labeled with fidelity and precise control. Polymer scientists have dreamed endowing these features to synthetic polymers for years, i.e., precise control on molecular composition, degree of polymerization, molecular weight distribution, monomer sequence, etc. To this goal, different synthetic, semi-synthetic and even bio-molecular templates have been employed. A very simple example is using CD as a template for ring-opening polymerization of lactones to give polyesters, because the monomer lactone can be accommodated in CD cavity and the hydroxyl group on the cavity rim can activate the carbonyl oxygen of lactones during initiation.[200] Recently, sequence control in living radical polymerization was performed by template-bearing initiators

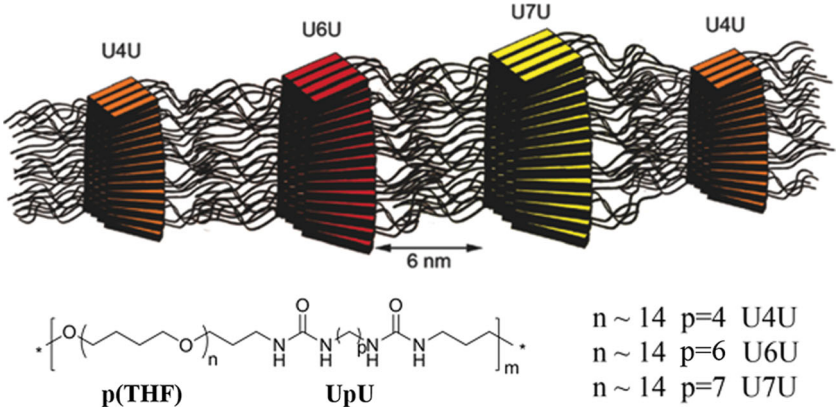

Figure 34. Cartoon of perfect self-sorting in a bisurea thermoplastic elastomer. In a mixture of pTHF-UpU segmented copolymers (UpU) with varying spacer length between urea groups, the hard blocks phase separate. Reproduced with permission.[194] Copyright 2010 ACS.

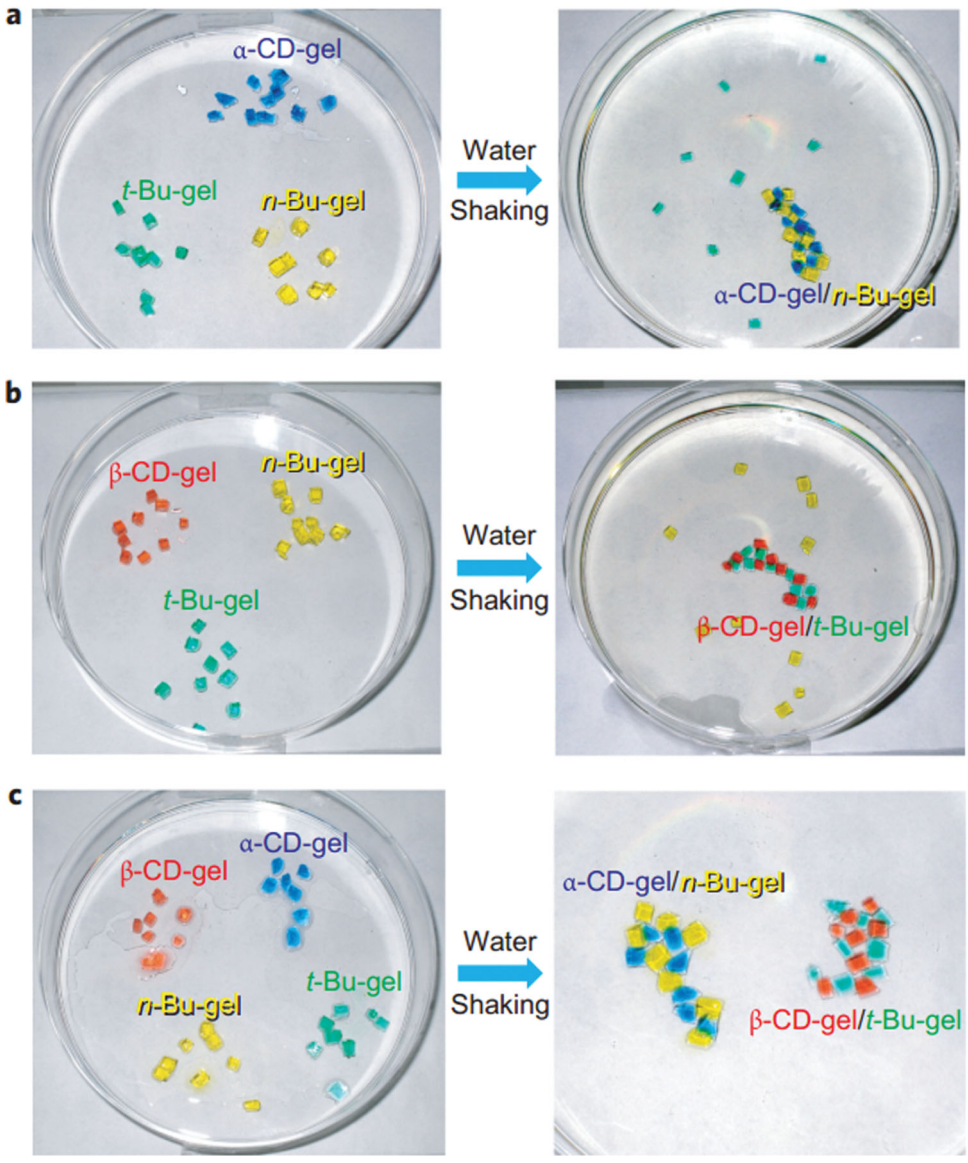

Figure 35. Visualization of self-sorting events on a macroscopic scale based on specific molecular recognition interactions. Reproduced with permission.[196a] Copyright 2011 NPG.

coupled with metal catalysts.[201] Another example came from the work of Sleiman and coworkers, who used nucleobase-containing polymer as template to perform a Sibigashira polymerization, leading to a daughter polymer with a narrow molecular weight distribution and a chain length nearly equivalent to that of the parent template.[202] In this process, the hydrogen bond between the nucleobase from template polymer and daughter polymer directed the polymerization. However, it turns out that during template polymerization, precise control over PDI and sequence is still a persistent task.

Very recently, a significant progress has been made in template polymerization by using self-assembled polymeric micelles, which proved the power of MSA to achieve this biomimetic goal. O'Reilly and coworkers combined nucleobase-mediated template polymerization with self-assembly induced segregation to achieve unprecedented control over free-radical polymerizations to high molecule weight (up to 400 000 g/mol) with extremely narrow polydispersity (PDI ≤ 1.08).[203] Specifically, PS_{115}-*b*-$PVBT_{18}$ (poly (styrene-*b*-vinylbenzyl thymine)) was prepared using TEMPO-mediated polymerization, and self-assembled into micelles by direct dissolution in $CHCl_3$ at room temperature (**Figure 36**a). Uniform, spherical micelles (R_h = 26 nm and PD.I = 0.1) were obtained. Once the complementary monomer vinylbenzyl adenine (VBA) was added, some of the PSt_{115}-*b*-$PVBT_{18}$ dissociated from the micelle and formed complex with VBA as unimers due to the hydrogen bond between VBT and VBA. VBA polymerization was initiated on these unimers and the product then re-inserted into the micelle core, polymerization continued inside the core among different template polymers, and finally gave out

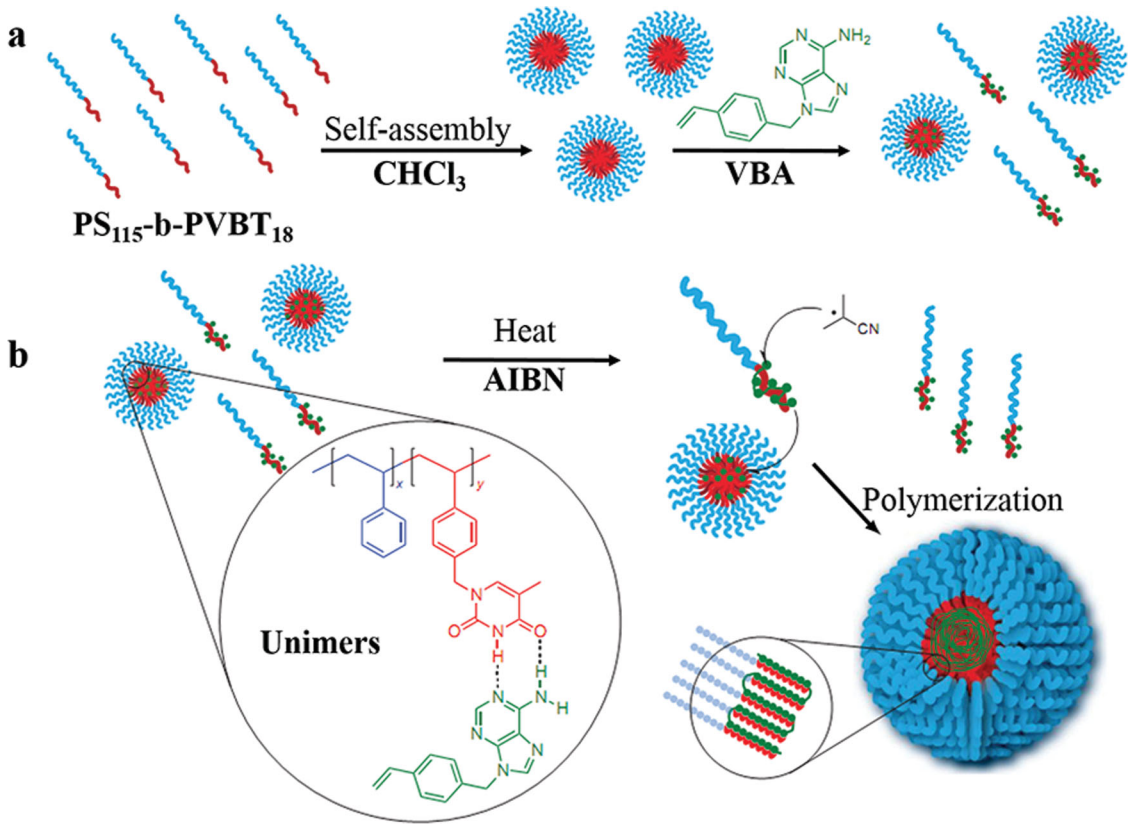

Figure 36. Dynamic exchange and cooperative assembly of templates. (a) Self-assembly of template block copolymer PS_{115}-*b*-$PVBT_{18}$ in $CHCl_3$ yields a stable monodisperse micellar system with PVBT cores. The addition of a complementary adenine monomer (VBA) induces dynamic exchange of VBA-loaded template unimers. (b) Upon the addition of AIBN and heating, VBA initiation occurs on an exchanging unimer before returning to a micelle for continued propagation. Further dynamic VBA-loaded unimers add to the initiated micelle, from a reservoir of non-initiated micelles, to yield a stable, non-dynamic larger micelle that contains the high MW, low PD.I PVBA daughter polymer. Reproduced with permission.[203] Copyright 2012 NPG.

daughter polymer with high molecular weight and extremely low PDI (Figure 36b).

In this case, the dynamic nature of the micelles, i.e., chain dissociation and re-insertion, as well as the segregation property of the micelle core, was the two crucial points to get high molecular weight daughter polymers. Differing from the homogeneous i.e., non-micellar systems or other segregated environments, under the help of MSA, current procedure provided high molecule weight polymers with extremely low PDI However, due to the micelle rearrangement, the molecule weight of the daughter polymer could not be precisely controlled. In other words, the information is not precisely translated. Even so, we are still confident that this combined segregation/template approach represents a significant step towards the fundamental goals in the biomimetic study of polymers, such as sequence-controlled polymerization and controlled polymer folding.

5.4. Nanoreactor

Polymersomes have been widely utilized as nanoreactors, which can accommodate either enzymes or organic/inorganic reactive sites, or even carry catalytic center on the polymer skeleton, allowing various reactions to occur inside the hollow sphere. This scenario, especially when a multicompartment polymersome is involved, is a typical biomimetic design of organelle inside the cell, which can be highlighted by site isolation (incompatible reactions happen cooperatively in one cell) and segregation (concentration changes in isolated place). For the polymersomes incorporating enzymes, these two features are more shining. For example, cascade reactions were successfully achieved by van Hest et al. in their polymersome, where three different enzymes were deliberately placed in different positions, i.e., Candida antarctica lipase B (CalB) in the membrane, glucose oxidase (GOx) in the inner aqueous compartment and horseradish peroxidase (HRP) on the surface of the polymersome.[204] CalB and GOx were incorporated to the vesicle during self-assembly where the former is hydrophobic and the latter is hydrophilic which directed their positions in the vesicle. HRP was attached on the vesicle surface via click chemistry (**Figure 37**). The efficiency of this nanoreactor was tested by the cascade reaction from glucose acetate, which could be converted to glucose by CalB, then oxidized to gluconolactone by GOx in the second step. The hydrogen peroxide produced in the second step was subsequently used by HRP as the substrate to convert 2,2′-azinobis(3-ethylbenzothiazoline-6-sulfonic acid) (ABTS) into $ABTS^+$. This field became quite hot in the past ten years, especially with extensive studies by the groups

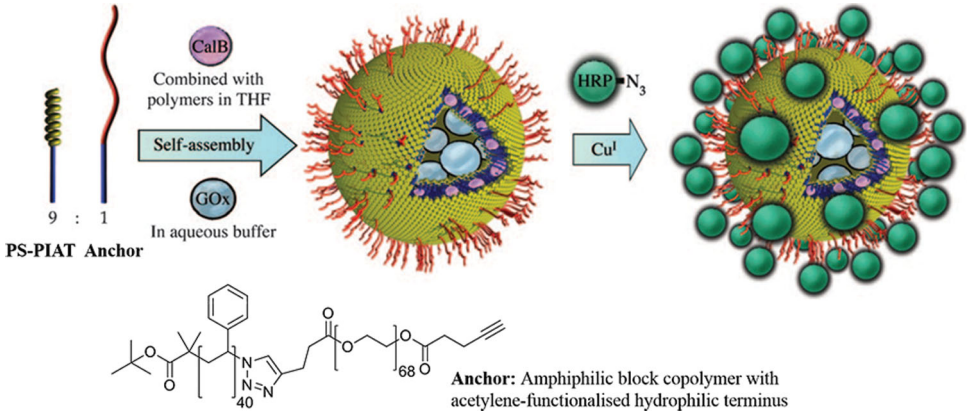

Figure 37. Self-assembly of polymersome for three-enzyme cascade reaction. CalB and GOx were first self-assembled into the membrane and inner cavity of the polymersome, respectively. And HRP was modified to vesicle surface via click chemistry. Reproduced with permission.[204] Copyright 2009 Wiley.

of Nolte,[205] van Hest[206] and Meier[159,207] etc., on which several reviews appeared in the past three years.[99,159,208,209]

In fact, the micelles constructed by MSA in water always supply an isolated hydrophobic pocket for organic reactions, where hydrophobic reactants can undergo chemical transformation.[210] As what the micelles provide is a segregated and confined reaction space, reaction rate there is expected to increase as a result of increasing the collision possibility between the reactants. Furthermore, water permeability of these micelles can be tuned as desired for accelerating the reaction by kinetically frozen nature of these micelles.[211]

Molecular catalyst has a quite long history and various high-molecular weight molecules have been proved to be effective as artificial catalysts, which include foldamers, dendrimers and star polymers. However, self-assembled macromolecules with molecular catalysis functions entered this field not so long ago. This is promoted by the development of the stimuli-responsive self-assembly of block copolymer resulting in catalysis-carrying micelles. An early work was contributed by Liu et al., by using micelles of PNIPAM-*b*-PVim (poly(*N*-vinylimidazole)) with catalytic ability of hydrolysis of p-nitrophenyl acetate.[212] Afterwards, by using MSA micelles as man-made reactors, various reactions, including aldol reaction, acylation, hydrogenation, hydrolytic kinetic resolution, have been achieved with higher efficiency in aqueous solution.[211,213] As the research in this field is quite fruitful, due to the length limitation, in this section, only a couple of recent examples with high stereoselectivity will be addressed.

L-Proline could efficiently catalyze aldol reaction, resulting in a good yield and high enantiomeric excess.[214] The reaction performs well in organic solvents (e.g., DMSO, DMF) but poorly in water. However, the presence of a small amount of water could accelerate the reaction rate and improve enantioselectivity.[215] Although the reaction has been performed in different nanoreactors,[216] O'Reilly et al. recently achieved very high stereo selectivity at elevated temperature in water by using a well-designed micelle as the nanoreactor, which was formed from the amphiphilic block copolymer $PDMA_{73}$-*b*-P($NIPAM_{63}$-*co*-BA_7-*co*-$ProlA_5$) containing L-proline in the hydrophobic segment (**Figure 38**).[217] The reaction between 4-nitrobenzaldehyde and cyclohexanone was studied as the model. When the temperature was above the LCST of PNIPAM, a micelle formed with the L-proline moieties located within the hydrophobic pocket where the controlled water content accelerated the reaction. In this case, very high enantioselectivity was achieved at the elevated temperature. This result was superior over that of using small molecular L-proline as catalyst at 50 °C. After the

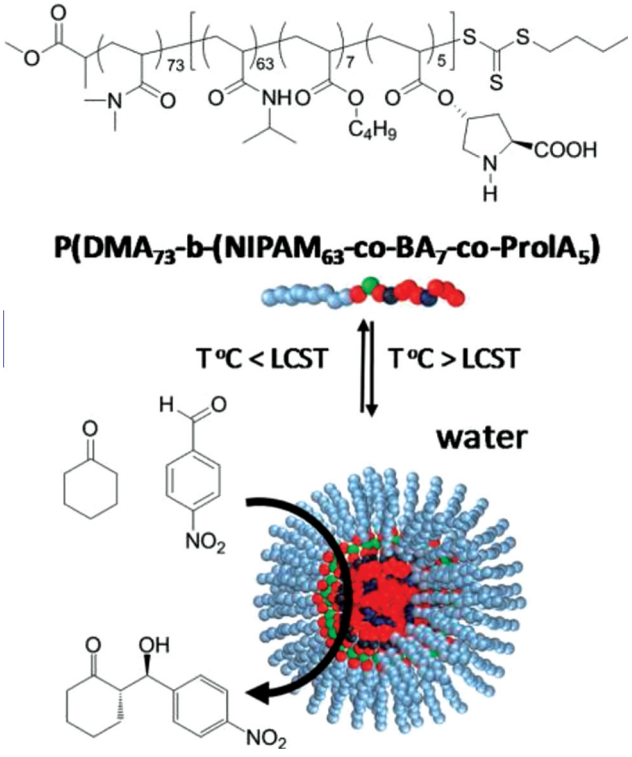

Figure 38. Aldol reaction performed inside micelles with high enantioselectivity and yield. Reproduced with permission.[217] Copyright 2013 ACS.

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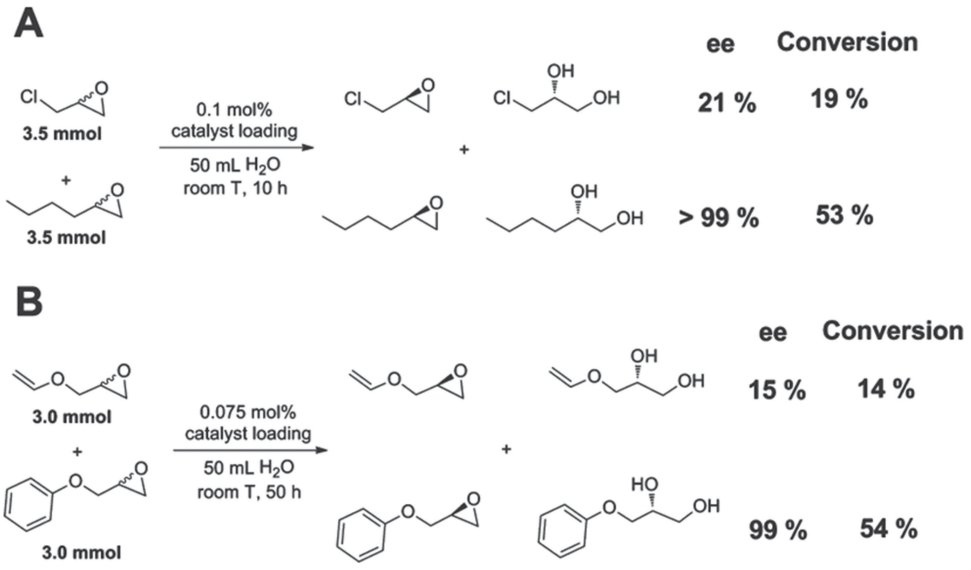

Figure 39. One-pot competitive HKR reactions to test the substrate selectivity of SCM using 1:1 ratios of (A) enantiomer pairs of epichlorohydrin and epoxyhexane and (B) enantiomer pairs of allyl glycidyl ether and phenyl glycidyl ether. Reproduced with permission.[219] Copyright 2011 ACS.

reaction was completed, the nanoreactors were disassembled to fully water-soluble polymers by decreasing the temperature below the LCST of PNIPAM, resulting in precipitation of the solid product in near pure form. The product was then isolated by centrifugation and the polymer/water solution was reused in additional catalytic cycles by heating the polymer above its LCST and, thus, reforming the nanoreactors. The excellent result shows a very bright perspective of using MSA micelles as nanoreactors for organic catalysis reaction. Meijer et al. constructed a single chain polymeric nanoparticles containing L-proline, which lead to an exceeding catalytic efficiency as well.[218] However, the stereoselectivity was not good enough and subtle optimization of the folded microstructure formed by stacking of the attached benzene-1,3,5-tricarboxamide around the catalytic site was needed.

Moreover, by using a shell-crosslinked-micelle (SCM) with 2-oxazoline as the polymer backbone and covalently immobilized Co(III)-salon as a catalytic center, hydrolytic kinetic resolution (HKR) of epoxides was successfully performed with high catalytic efficiency and substrate selectivity due to the hydrophobic nature of the micelle core.[219] The substrate selectivity of this SCM was highlighted by one-pot competitive experiment involving enantiomer pairs of epoxyhexane and epichlorohydrin (**Figure 39**A) or enantiomer pairs of phenyl glycidyl ether and allyl glycidyl ether (Figure 39B). High enantioselectivity was observed when only one of the starting enantiomer remained and the product of the other enantiomer was obtained at the end of reaction. It was found that high enantioselectivity was achieved to epoxyhexane and phenyl glycidyl ether over the other enantiomer pairs of reactant in their own one-pot reaction, proving the substrate selectivity of the micelle. This result clearly demonstrated the remarkable power of the hydrophobic core of micelle in substrate selectivity, showing the great potential of MSA micelles as nanoreactors to chemical transformations. Compared to the traditional catalysts in small molecular weight, the re-useable nature and easy-controllable separation ability might be the most attractive feature of this type of materials.

6. Conclusions and Perspective

In this review, recent achievements in MSA in biomimetic and bio-inspired research have been demonstrated. This research field has been quite vivid recently and some of the "hot" topics show a stormy increase. Although it is not possible for us to cover every research topic in this field, the examples included in this paper do show the large perspective and promising future, which are tightly associated with the inherent advantages of MSA for the biomimetic and bio-inspired investigation: (1) The successes in polymer chemistry, particularly in precise polymerization, provide a huge "warehouse" that stores a remarkably diverse and large variety of polymers to meet different requirements of self-assembly mimicking biological prototypes. (2) The long chain nature and the controllable multiple binding sites are benficial for to mimicking the multifunctionality of biological building blocks, such as proteins, including antibody and chaperon; (3) The stability of polymeric vesicles provides a stable platform to construct a variety of cell-inspired materials with a given specific structure or function, e.g., site segregation, fission/fusion, phase separated raft structure, glycocalyx, etc.; (4) Phase separation, probably the most common feature of MSA, provides another simple but powerful way to construct self-healing materials with attractive properties; (5) The hydrophobic and segregated micelle core is suitable for catalytic reactions using hydrophobic substrates. However, disadvantages compared to other relatively mature mimicking tools is also obvious: (1) For synthetic polymers it seems unachievable – at least in the near future – to obtain a strictly self-assembled structure such as protein; (2) The current state of cell-mimicking is in its infant stage compared to that of phospholipid bilayers; (3) Most of the self-healing and/

or self-sorting materials obtained at the moment might be too expensive to be commercialized.

As we have mentioned, it would not have been possible to start biomimetic studies and then to make it "vivid" in chemistry without the cooperation of organic chemistry and supramolecular chemistry. Later on, it was MSA that promoted the study to the current level featured by being capable of fabricating materials. Although the resultant objects are still in their infancy, some of the achievements are really encouraging, for example, the cascade reactions were successfully performed in polymersome, where three different enzymes located separately in their own compartments.[204] Polymers with exceedingly high molecular weight and extra low PDI were achieved inside polymeric micelles via template polymerization.[203] So one has reasons to keep confidence for the future of biomimetic and bioinspired studies based on MSA, which of course is an ongoing and hard task. Any further remarkable and substantial achievements will depend on the intense cooperation of scientists from different research fields.

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