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Amphiphilic Building Blocks for Self-Assembly: From Amphiphiles to Supra-amphiphiles

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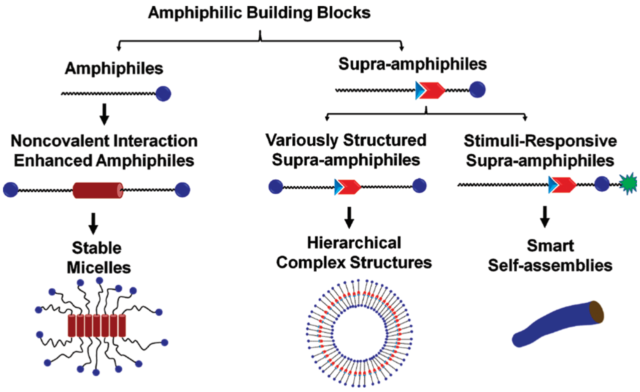

The process of self-assembly spontaneously creates well-defined structures from various chemical building blocks. Self-assembly can include different levels of complexity: it can be as simple as the dimerization of two small building blocks driven by hydrogen bonding or as complicated as a cell membrane, a remarkable supramolecular architecture created by a bilayer of phospholipids embedded with functional proteins. The study of self-assembly in simple systems provides a fundamental understanding of the driving forces and cooperativity behind these processes. Once the rules are understood, these guidelines can facilitate the research of highly complex self-assembly processes.

Among the various components for self-assembly, an amphiphilic molecule, which contains both hydrophilic and hydrophobic parts, forms one of the most powerful building blocks. When amphiphiles are dispersed in water, the hydrophilic component of the amphiphile preferentially interacts with the aqueous phase while the hydrophobic portion tends to reside in the air or in the nonpolar solvent. Therefore, the amphiphiles aggregate to form different molecular assemblies based on the repelling and coordinating forces between the hydrophilic and hydrophobic parts of the component molecules and the surrounding medium.

In contrast to conventional amphiphiles, supra-amphiphiles are constructed on the basis of noncovalent interactions or dynamic covalent bonds. In supra-amphiphiles, the functional groups can be attached to the amphiphiles by noncovalent synthesis, greatly speeding their construction. The building blocks for supra-amphiphiles can be either small organic molecules or polymers. Advances in the development of supra-amphiphiles will not only enrich the family of conventional amphiphiles that are based on covalent bonds but will also provide a new kind of building block for the preparation of complex self-assemblies. When polymers are used to construct supra-amphiphiles, the resulting molecules are known as superamphiphiles.

This Account will focus on the use of amphiphiles and supra-amphiphiles for self-assembly at different levels of complexity. We introduce strategies for the fabrication of robust assemblies through self-assembly of amphiphiles. We describe the supramolecular approach for the molecular design of amphiphiles through the enhancement of intermolecular interaction among the amphiphiles. In addition, we describe polymerization under mild conditions to stabilize the assemblies formed by self-assembly of amphiphiles. Finally, we highlight self-assembly methods driven by noncovalent interactions or dynamic covalent bonds for the fabrication of supra-amphiphiles with various topologies. Further self-assembly of supra-amphiphiles provides new building blocks for complex structures, and the dynamic nature of the supra-amphiphiles endows the assemblies with stimuli-responsive functions.

1. Introduction

Amphiphiles contain both hydrophilic and hydrophobic parts, and the two parts are linked on the basis of covalent bonds.[1] Amphiphiles are able to self-assemble in water to form various well-defined molecular assemblies, such as micelles and vesicles.[2] The structure and the properties of the assemblies are closely connected to the architecture of the amphiphiles.[3] For example, amphiphiles with a multitail

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topology favor forming bilayer structures.[4,5] Natural phospholipids are a typical kind of amphiphile, generally composed of one hydrophilic head and two hydrophobic tails. When phospholipids are dispersed in water, they tend to aggregate spontaneously to form bilayers, which resemble the types of structures they form in biological membranes. Synthetic amphiphiles possessing similar topology can also self-assemble into bilayers. Moreover, it is interesting to see that every topology corresponds to unique physical properties. For example, when two headgroups are linked to one alkyl chain, it was possible to produce a bolaform amphiphile.[6,7] Bolaform amphiphiles have high thermal resistance and are found in the cell membranes of thermophilic bacteria. Another example is the gemini-form amphiphile, in which two headgroups are in the middle of the alkyl chain.[8] Amphiphiles with the gemini-form topology can aggregate at very low concentrations and are very good candidates for use as carriers. Therefore, even two amphiphiles with similar molecular weight and chemical components can possess distinct physical properties if their topologies are different. Aiming at self-assemblies with different purposes, we can design amphiphiles with different topologies. Their rich topologies are one of the reasons that amphiphiles are widely chosen to fabricate functional materials.

The concept of amphiphiles has been extended to polymers.[9−12] Generally, a polymeric amphiphile is constructed by linking a hydrophilic segment and a hydrophobic segment through a covalent bond. Compared with low-molecular-weight amphiphiles, polymeric amphiphiles are endowed with structural diversity and stability. The self-assemblies fabricated using polymeric amphiphiles have a larger capacity for guest molecules and better thermal sustainability. The assemblies from low molecular weight amphiphiles are comparatively dynamic, due to the balance between the aggregated molecules and the dissociated nonaggregated molecules in the bulk solution. In the aggregates from polymeric amphiphiles, however, the stronger interactions as well as the entanglement between the polymer chains prevent quick molecular exchange. Moreover, the longer molecular chains also provide the aggregates with a larger capacity for guest molecules. The unique property of the polymeric topology has led to applications in drug delivery and templated synthesis of nanomaterials.

Despite the long history of amphiphiles, they still continue to attract the attention of scientists, inspiring them to design new types of amphiphiles. The hybrids of conventional building blocks with biomolecular and inorganic segments have led to unexpected structures and self-assembly properties. For example, the combination of an alkyl chain and a short peptide sequence leads to a new concept, the peptide amphiphile, which can self-assemble into various one-dimensional structures.[13] Other examples include giant amphiphiles from the hybrid with a protein,[14] polyhedral oligomeric silsesquioxanes[15] or polyoxometalates,[16] which self-assemble into new structures such as toroids and other complex architectures and display intriguing properties that are significantly different from conventional amphiphiles.

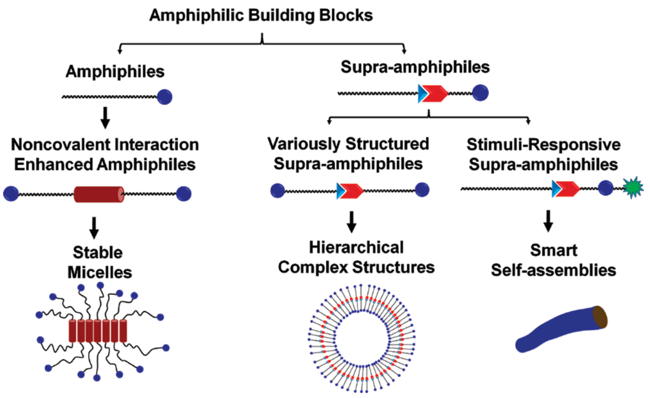

FIGURE 1. Diversified building blocks for self-assembly: toward fabrication of functional materials and surfaces.

It is interesting to witness that this line of research has progressed from regular amphiphiles toward giant amphiphiles and further on to supra-amphiphiles. In contrast to conventional amphiphiles based on covalent bonds, there emerges a new field of supra-amphiphiles that refer to amphiphiles constructed on the basis of noncovalent interactions or dynamic covalent bonds.[17−20] In supra-amphiphiles, functional moieties can be attached by noncovalent synthesis, greatly reducing the need for tedious chemical synthesis. The building blocks for supra-amphiphiles can be either small molecules or polymers. The advance of supra-amphiphiles will not only enrich the family of conventional amphiphiles but also provide a new kind of building blocks toward complex self-assemblies, including hierarchical self-assemblies and functional nanostructures.

As shown in Figure 1, this Account intends to discuss and summarize our recent efforts on how to design and prepare diversified amphiphiles to satisfy different requirements. Robust assemblies are required for studying the relationship between chemical structure of the building blocks and the self-assembling nanostructures, as well as for the application in the field of templated synthesis. To this end, we have proposed the concept of noncovalent-interaction-enhanced amphiphiles and discussed polymerizable amphiphiles. Considering the trend of complex nanostructures, we have further established the concept of supra-amphiphiles on the basis of noncovalent interactions. The dynamic nature of the noncovalent interactions facilitates the introduction of functional moieties into supra-amphiphiles, leading to the fabrication of molecular assemblies that are responsive to environmental stimulus. It is hoped that the study on self-assembly of amphiphiles and supra-amphiphiles can enrich the field of molecular engineering of functional supramolecular systems and provide new avenues for the construction of self-assembling soft materials and functional surfaces by rational design.

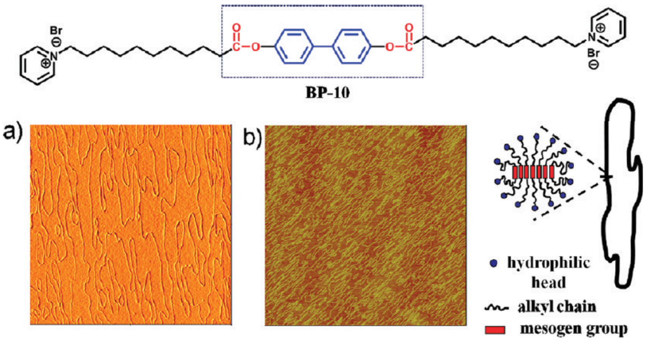

FIGURE 2. Cylindrical micelles of BP-10 on a mica sheet: (a) in situ AFM observation with a possible model picture; (b) ex situ AFM observation. Scan size is 5 × 5 μm^2. Reproduced from ref 27 with permission. Copyright 2003 Wiley Publishers.

2. Stable Self-Assemblies from Amphiphiles: A Noncovalent Approach

As mentioned, amphiphiles can self-assemble into micellar structures with defined sizes and shapes that may be used in applications such as templates for making nanostructured materials and mimicking biomineralization processes. Engineering robustness is required to make these applications practical. However, micellar assemblies are inherently dynamic and fluid. The most straightfoward method to stabilize self-assemblies is based on a covalent approach, mainly using polymerizable amphiphiles.[21,22] However, harsh treatments, such as UV irradiation, are required. In this Account, we conclude and put forward the noncovalent approach to stabilize the micellar structures. The micellar structures can be directly stabilized using noncovalent interactions without any harsh treatments.

2.1. Micellar Structures Stabilized by van der Waals Interactions: Introduction of Mesogenic Groups into Amphiphiles. Mesogenic groups refer to rigid segments endowed with sufficient anisotropy in both attractive and repulsive forces to contribute strongly to the mesophase or, in particular, liquid-crystal mesophase formation in low molar mass and polymeric substances. Upon the introduction of mesogenic groups, the van der Waals interactions between the amphiphiles can be enhanced, subsequently resulting in stable self-assembled nanostructures.

Take bolaform amphiphiles as an example. It is known that the bolaform amphiphiles have special physical properties compared with the conventional surfactants, such as high thermal stability and low critical micelle concentration (CMC).[23] Generally, cationic bolaform amphiphiles prefer to form irregular monolayers on negatively charged substrates since the interactions between the amphiphiles are not strong enough to establish a stable nanostructure on the surface.[22] We were wondering whether we could construct robust supramolecular nanostructures on surfaces from bolaform amphiphiles introducing mesogenic groups. In this regard, we have designed and synthesized a bolaform amphiphile bearing a biphenyl mesogenic group and two hydrophilic pyridinium heads, **BP-10**, as shown in Figure 2.[24−27] In situ AFM observation shows that the bolaform amphiphile **BP-10** forms cylindrical micelles, with a "spaghetti" morphology at the mica/liquid interface, as shown in Figure 2a. The average width of the structures is around 40 nm, and some of them reach as large as several micrometers in length. The ex situ AFM image shows the same structure as that of the in situ AFM image (Figure 2b), suggesting that **BP-10** can retain its structure formed in the solution. The stability of the dry-state surface micelles is further investigated by heating the substrate and monitoring changes by temperature-dependent AFM. The micellar structures of BP-10 are stable until the substrate was heated to 70 °C. That is to say, the noncovalent bonded self-assemblies not only can be stable against drying but also can withstand thermal treatment up to 70 °C.

2.2. Introduction of Strong $\pi-\pi$ Interactions into Amphiphiles. We were wondering whether a similar idea can be also applied to bolaform amphiphiles bearing a $\pi-\pi$ stacking moiety. To answer this question, we have introduced a strong $\pi-\pi$ stacking moiety of diaryldiketopyrrolopyrrole (DPP) dye into bolaform amphiphiles and have found that such a bolaform amphiphile with appropriate spacer lengths gives a stable micellar nanostructure.[28] As depicted in Figure 3, **DPP-11** forms disk-like micelles with diameters ranging from several hundreds of nanometers to 1 μm. The section analysis of Figure 3a shows that the disk-like micelles have an average thickness of about 3.7 nm. This value agrees well with the length of a single **DPP-11**

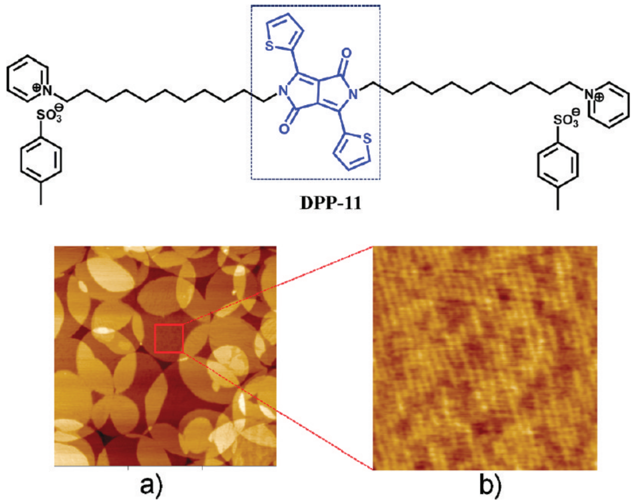

FIGURE 3. Ex situ AFM observation of **DPP-11** micellar structures adsorbed on a mica sheet: (a) large area image, 2 × 2 μm^2; (b) small area image, 400 × 400 nm^2. Reproduced from ref 28 with permission. Copyright 2005 Wiley Publishers.

molecule, suggesting that the disks are monolayer structures with the thickness of a single molecule. Detailed studies of the disk-like aggregate reveal that there are uniform stripes of about 10 nm wide within the disk (Figure 3b). Thus, the disk-like micelle is a combination of micro- and nanostructures, which can be explained in terms of a compromise between the different intermolecular interactions. The intermolecular $\pi-\pi$ stacking in the middle part of the aggregates forces the molecules to pack densely, while the repulsive interaction of the positively charged head groups has the reverse effect. Due to the strong $\pi-\pi$ interactions in the amphiphiles, the self-assembled disks can be still stable under temperature as high as 80 °C without any significant changes.

2.3. The Combination of Noncovalent Approach and Covalent Approach in Amphiphiles. The combination of noncovalent interactions and covalent interactions in amphiphiles can integrate the advantages of the both approaches, leading to new self-assembly structures. For example, the noncovalent interaction can serve as first level of "locking" and provide necessary packing or scaffold for polymerization; the packed structure is then further "locked" by covalent polymerization. As shown in Figure 4a, DPDA-10, an amphiphile containing $\pi-\pi$ interaction groups and polymerizable diacetylene, is designed and synthesized. DPDA-10 can self-assemble into nanofibers driven by the $\pi-\pi$ interactions.[29] At the same time, due to the close packing induced by $\pi-\pi$ interactions, the diacetylene bonds are tightly packed with each other. As a result, quick and efficient polymerization can be observed upon UV irradiation, leading to uniform and stable nanofibers. This concept can also be introduced into polymeric amphiphiles. As shown in Figure 4b, the triblock amphiphilic polymer α-norbornenyl polystyrene-*b*-poly(methylacrylate)-*b*-poly(*tert*-butylacrylate) (NB-PS-*b*-PMA-*b*-PtBA) can self-assemble into spherical structures in the mixing solvent of DMF and water.[30] However, after covalent polymerization, the combination of covalent bonds and noncovalent interactions ($\pi-\pi$ interactions of the polystyrene block) will lead to the formation of cylindrical structures. The combination of covalent and noncovalent approaches is expected to create soft materials with new structures and new functions.

3. Hierarchical Complex Structures and Smart Self-Assemblies from Amphiphiles: A Supra-amphiphile Approach

Nature has demonstrated the most elegant examples of self-assemblies from amphiphiles. In the perspective of self-assembly, natural cell is prefectly a hierarchical complex structure with segregated structures and functions. More importantly, the cellular structure is "smart". Once "feeling" some changes in the surrounding environment, the cells will automatically respond to the changes quickly. To mimic this perfect example, various artificial amphiphiphiles have been synthesized, mostly linked by covalent bonds. However, synthetic amphiphiles can suffer from tedious synthesis and low response speed, due to the irreversible nature of covalent bonds.

But if we look back to the components of the cell membranes, they are generallly not covalently linked amphiphiles. Instead, they are complexes of small lipids and proteins linked by noncovalent interactions. Therefore, the functional protein, such as sensing proteins, can be attached and dettached reversibly, maintaining the daily activities. Inspired by nature and toward the goal of constructing hierarchical structures and smart self-assemblies, the concept of the supra-amphiphile is proposed.

With supra-amphiphiles, the building blocks are linked by noncovalent interactions. They have the following advantages over conventional amphiphiles: (1) The noncovalent nature of supra-amphiphiles may simplify the procedures for chemical synthesis. (2) Incorporation of functional moieties can be easily achieved. (3) Supra-amphiphiles with various topologies can be formed. (4) Both low and high molecular weight supra-amphiphiles can be fabricated.

3.1. Supra-amphiphiles for Hierarchical Complex Self-Assemblies. If the formation of supra-amphiphiles is regarded as a primary self-assembly, it is likely that supra-amphiphiles

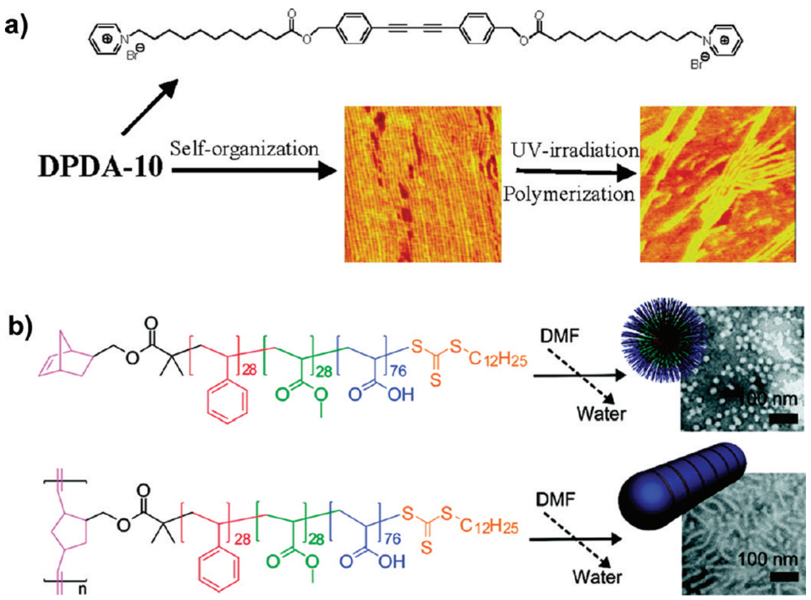

FIGURE 4. Schematic illustrations of the combination of covalent bonds and noncovalent interactions of (a) low-molecular-weight amphiphiles and (b) polymeric amphiphiles. Reproduced from refs 29 and 30 with permission. Copyright 2007 and 2011 American Chemical Society.

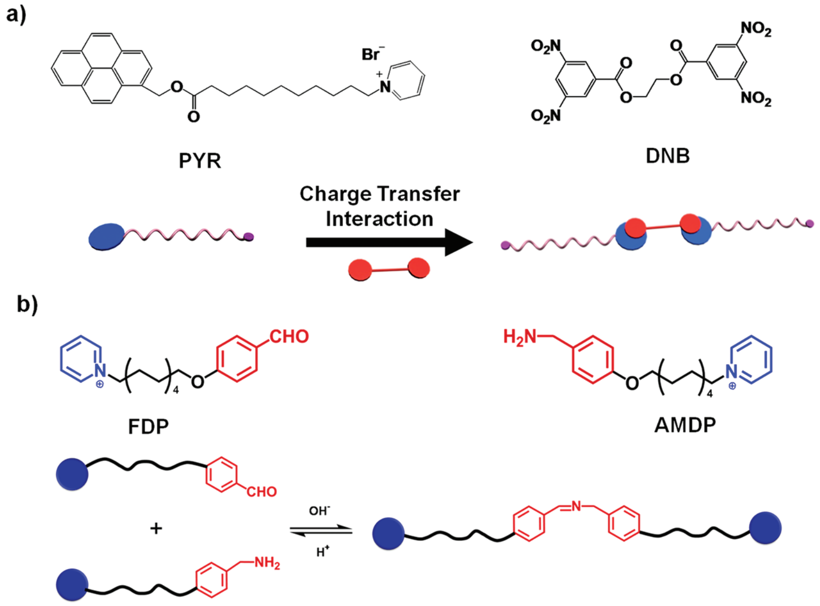

FIGURE 5. Bolaform supra-amphiphile on the basis of (a) charge-transfer interaction and (b) dynamic covalent bond. Reproduced from refs 31 and 40 with permission. Copyright 2008 Wiley Publishers and Copyright 2011 American Chemical Society.

can function as building blocks for constructing highly ordered assemblies by further or so-called secondary self-assembly. By a rational design of building blocks, we can construct supra-amphiphiles with various structures, which then can hierarchically self-assemble into complex architectures.

Just as their conventional counterparts, supra-amphiphiles can be of low-molecular weight or polymeric. Although some architectures created by supra-amphiphiles are similar to assemblies made by regular amphiphiles, some of them can never be realized using the latter. Examples of this are the hierarchical self-assemblies from bolaform supra-amphiphiles. For this purpose, we have designed and synthesized an amphiphile that contains an electron donor at the end (PYR) and a linker containing two electron acceptors (DNB), as shown in Figure 5a.[31] PYR and DNB can preassemble in THF to form a bolaform supra-amphiphile, driven by the charge transfer interactions between the electron donors and acceptors. An interesting finding is that

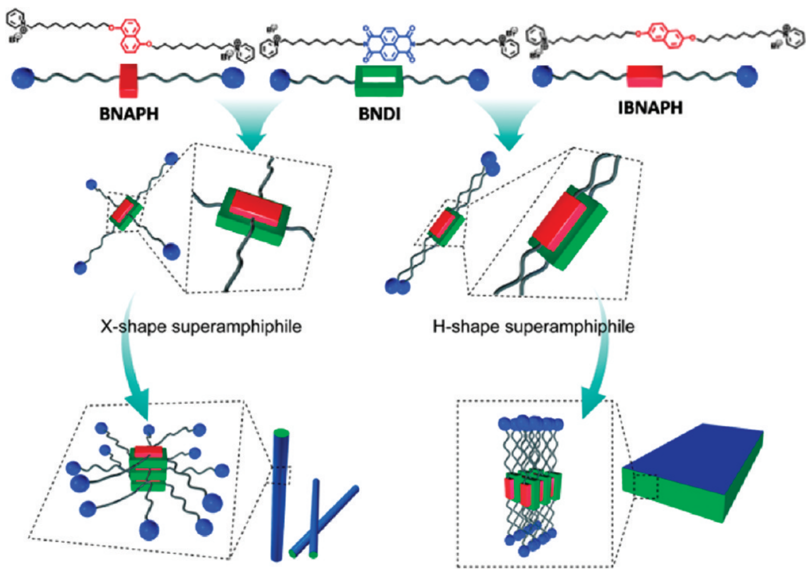

FIGURE 6. X-shaped and H-shaped supra-amphiphiles. Reproduced from ref 41 with permission. Copyright 2011 Wiley Publishers.

the formation of the bolaform supra-amphiphile results in a transformation from tube-like aggregates into vesicles. Due to its dynamic and reversible nature, a dynamic covalent bond (DCB) can also be used as a type of noncovalent bond.[32−39] The concept of bolaform amphiphiles can also be realized using DCBs. The imine bond, which is formed between amine and aldehyde, is a typical DCB. As shown in Figure5b, driven by the formation of imine bonds, 1-(10-(4-formylphenoxy)decyl)pyridinium (FDP) and 1-(10-(4--(ammoniomethyl)phenoxy)decyl)pyridinium (AMDP) can form a bolaform supra-amphiphile in basic conditions.[40] The supra-amphiphile possesses a lower critical micellar concentration (cmc), which is the typical feature of conventional bolaform amphiphiles.

Using the concept of supra-amphiphile, we can realize building blocks with the same topologies as conventional amphiphiles. Moreover, some topologies that are difficult or impossible realize with conventional amphiphiles can also be constructed based on the supramolecular engineering of supra-amphiphiles. For example, X-shaped and H-shaped supra-amphiphiles, which are very difficult to realize in conventional amphiphiles, have been successfully constructed on the basis of directional-charge-transfer complexes of naphthalene diimide and naphthalene.[41] The X-shaped supra-amphiphiles were prepared by mixing BNDI with 1,5-substitution on naphthalene and BNAPH in aqueous solution, resulting in the formation of one-dimensional nanorods (Figure 6). However, the complexation of IBNAPH with 2,6-substitution on naphthalene leads to the formation of H-shaped supra-amphiphiles, which can self-assemble into two-dimensional nanosheets. This means that a small change in the structure of the supra-amphiphile may cause a big change in the structure of the self-assemblies. This represents a nice example of supramolecular engineering for well-defined nanostructures.

Some of the architectures can never be realized in conventional amphiphiles, such as rotaxane-type supra-amphiphiles. To achieve this structure, an amphiphile bearing an azobenzene group and cyclodextrin are chosen as building blocks for the supra-amphiphiles.[42] In water, upon UV irradiation, the cyclodextrin can slip reversibly between the alkyl chains and azobenzene groups, functioning as a molecular shuttle. The amphiphilicity of the supra-amphiphile can be switched from more hydrophilic to more hydrophobic, leading to self-assembly and disassembly in a controlled manner.

3.2. "Smart" Self-Assemblies Based on Supra-amphiphiles. Mimicking nature, we can link functional moieties, such as stimuli-responsive groups, to the supra-amphiphiles by noncovalent interactions. Moreover, the noncovalent interactions or DCBs are sensitive to environmental stimulus. Therefore, supra-amphiphiles are perfect building blocks for the construction of smart soft materials.

3.2.1. Smart One-Dimensional Nanostructures. Generally, the fabrication of one-dimensional nanostructures requires tedious chemical synthesis due to the necessity of highly directional interactions, such as multiple hydrogen bonding and strong interactions. The construction of responsive amphiphiles is even more difficult. However, using the concept of supra-amphiphiles, we were able to realize a

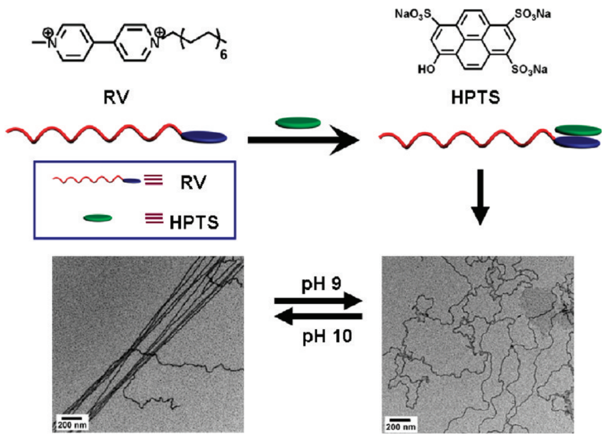

FIGURE 7. pH-responsive supra-amphiphiles with tunable straightness. Reproduced from ref 43 with permission. Copyright 2009 Wiley Publishers.

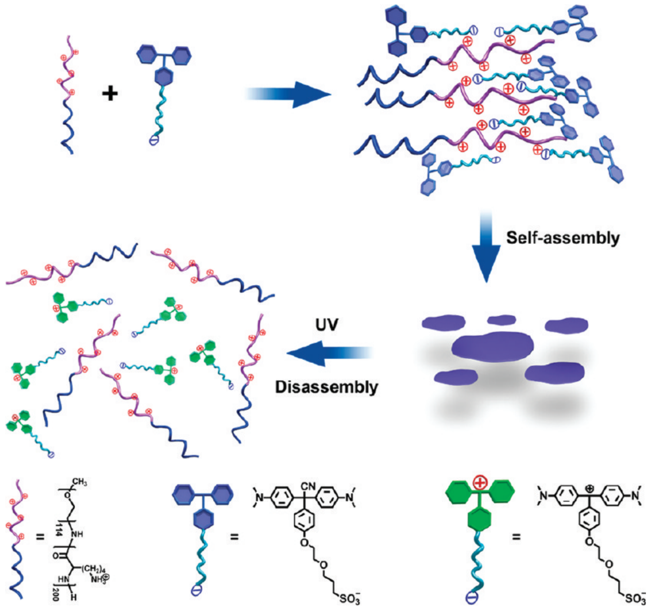

FIGURE 8. Photoresponsive supra-amphiphiles on the basis of malachite green-containing surfactants. Reproduced from ref 44 with permission. Copyright 2010 American Chemical Society.

straightforward fabrication of responsive one-dimensional nanostructures. A noteworthy example uses a water-soluble charge-transfer complex to fabricate supra-amphiphiles for assembling pH-responsive one-dimensional nanostructures (Figure 7). An amphiphile containing an electron-deficient viologen group (RV) is chosen as one building block.[43] The other building block is 8-hydroxypyrene-1,3,6-trisulfonic acid (HPTS), a pH-responsive electron-rich molecule. Driven by the charge-transfer interactions and electrostatic interactions between the viologen groups and the HPTS molecules, RV and HPTS are able to form a supra-amphiphile when mixed in water at a molar ratio of 1:1. The supra-amphiphile can then self-assemble into ultralong nanofibers. The diameter of the nanofibers is about 10 nm, while the length reaches as long as tens of micrometers. Interestingly, the straightness of the nanofibers can be reversibly tuned by pH changes. At the same time, the physical properties such as conductivity of the nanofibers changes accordingly.

3.2.2. Smart Nanocontainers. Supra-amphiphiles as building blocks for self-assemblies can be used for the incorporation of guest molecules. If the amphiphilicity of the supra-amphiphile can be weakened upon environmental stimulus, the self-assembled nanostructures will disassemble, and the loaded guest molecules can be released from the assemblies subsequently, providing new carriers for cargoes and drugs.

For example, we have designed and prepared a photoresponsive supra-amphiphile using a double hydrophilic block copolymer, poly(ethylene glycol)-*b*-poly(L-lysine hydrochloride) (PEG-*b*-PLKC), and a small organic amphiphile containing a positively charged headgroup and a malachite green at the end (MG).[44] PEG-*b*-PLKC and MG can be complexed into a superamphiphile (PEG-*b*-PLKC−MG) driven by electrostatic attractions (Figure 8). PEG-*b*-PLKC−MG can self-assemble in water to form sheetlike structures. Upon UV irradiation, the malachite green groups transfer from the neutral form into ionic form, inducing the disassembly of the vesicles and releasing the loaded guest molecules.

This idea of redox-responsive supra-amphiphiles can be realized by complexing a double hydrophilic polymer with a redox-responsive moiety. An oxidation-responsive polymeric supra-amphiphile is fabricated by means of the electrostatic interaction between the double hydrophilic block copolymer of PEG-*b*-PAA and a selenium-containing surfactant.[45] The polymeric supra-amphiphile self-assembles to form micelles in solution, which can disassemble under very mild oxidative conditions using 0.1% H_2O_2, because the selenium-containing surfactant is very sensitive to oxidation (Figure 9). Such micelles can be used as nanocontainers to load guest molecules, and the guest molecules can be released in a controlled way under mild oxidation. The advantages of such a system include the avoidance of organic solvents, a simple preparation procedure, and the decrement of surfactants.

Besides synthetic building blocks, many natural molecules are alternatives for fabricating responsive supra-amphiphiles. Take adenosine triphosphate (ATP) as an example, it can be hydrolyzed into neutral adenine and singly charged phosphoric acid upon treatment with alkaline

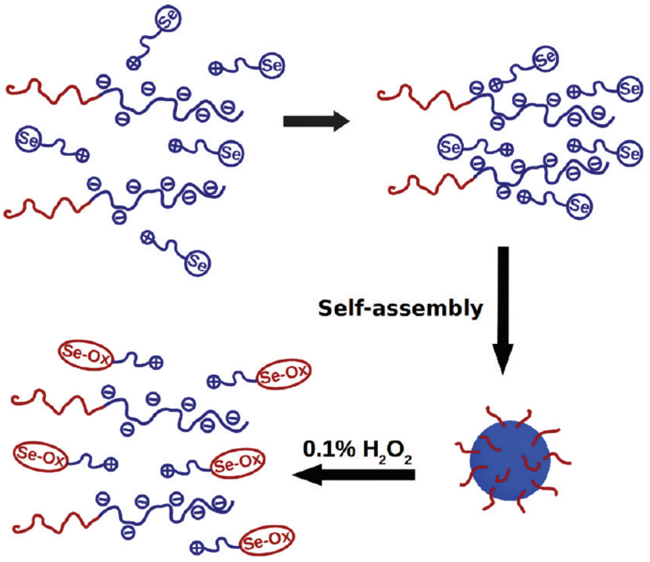

FIGURE 9. Redox-responsive supra-amphiphiles on the basis of selenium-containing surfactants. Reproduced from ref 45 with permission. Copyright 2010 American Chemical Society.

phosphatase (e.g., CIAP). Therefore, ATP is a natural multi-negatively charged enzyme-responsive molecule. Using this unique feature, ATP is complexed with polyglycol-*b*-polylysine (PEG-*b*-PLKC) to form a supra-amphiphile (PEG-*b*-PLKC−ATP) (Figure 10).[46] The supra-amphiphile can self-assemble in water to form spherical aggregates. Upon the treatment with CIAP, the spherical aggregates will disassemble and release the loaded guest molecules. The release process can be finished within 4 h, faster than conventional enzyme-responsive systems from amphiphilic polymers. The fast releasing speed could be attributed to the high enzymatic activity of the natural responsive sites on ATP molecules and the dynamic nature of the electrostatic interactions. The trends for the development of carriers for drugs will rely more and more on some important features, including low-cost, high releasing efficiency, good compatibility, etc. It is anticipated that supra-amphiphiles may be good candidates in the areas of drug delivery and nanoreactors.

Nanocontainers that are responsive to physiological pH are demonstrated using a polymeric supra-amphiphile based on imine bonds. In this regard, a double-hydrophilic block copolymer, ethoxy-poly(ethylene glycol)$_{114}$-*block*-poly(ʟ-lysine hydrochloride)$_{200}$ (PEG-*b*-PLKC), and 4-(decyloxy)benzaldehyde (DBA) are chosen as the two components of the polymeric supra-amphiphile (Figure 11).[47] At pH 7.4, the hydrophobic DBA molecules are attached to the PLKC blocks by the dynamic imine bonds formed between amine groups and benzaldehyde groups, leading to the formation of a brush-type supra-amphiphile. The supra-amphiphile can self-assemble into spherical aggregates. However, when pH changes to 6.5, which is about extracellular pH of tumor cells, the imine bonds are broken and the superamphiphilic spherical aggregates are disassembled, releasing the encapsulated guest molecules. The pH responsive supra-amphiphiles are expected to find applications in drug delivery and cancer therapy.

3.2.3. Responsive Surface. The properties of responsive supra-amphiphiles can also be introduced to surfaces, resulting in functional surfaces. For example, the rotaxane-like supra-amphiphile can be transferred to surfaces, displaying different properties from those in aqueous solution. For example, an azobenzene-containing building block with a mercapto group at the end is preassembled with α-CD in water based on the interaction between azobenzene and α-CD, forming a supra-amphiphile.[48] This supra-amphiphile can form a mixed SAM with n-butylthiol on a gold substrate. Before UV-light irradiation, α-CD stays on the top of the surface, and the SAM displays hydrophilic properties. After UV-light irradiation, α-CD moves down onto the alkyl chain and the SAMs become more hydrophobic. After visible light irradiation, the α-CD can move up, making the surface more hydrophilic once again. This great change in wettability can be cycled several times by alternating between UV- and visible-light irradiation.

The above examples have demonstrated several features, such as easy fabrication and quick response to stimulus, of supra-amphiphiles. However, this is only the beginning of the story. Apart from these features, supra-amphiphiles all show other prospective advantages over conventional amphiphiles toward applications. For examples, supra-amphiphiles are able to change between the amphiphilic state and nonamphiphilic small components, which are much easier to cleave. This means that, after use, the supra-amnphiphiles can be removed and recycled easily. This feature is extremely important in synthesizing nanoscystals or other electronic nanomaterials, where small amounts of impurities can significantly lower the performance. The easy cleavability is also important in the area of drug delivery, where the cargoes must be removed from human bodies after delivery. The concept of supra-amphiphiles is expected to find extensive applications in the areas of drug-delivery, electronic nanomaterials, oil extraction, etc. Due to the large variety of choices of noncovalent bonds, supra-amphiphiles are also expected to extend to hybrid supra-amphiphiles and bioconjugate supra-amphiphiles. Inorganic building blocks, such as polyoxometalates (POMs) and mesoporous silicas, could be linked as part of

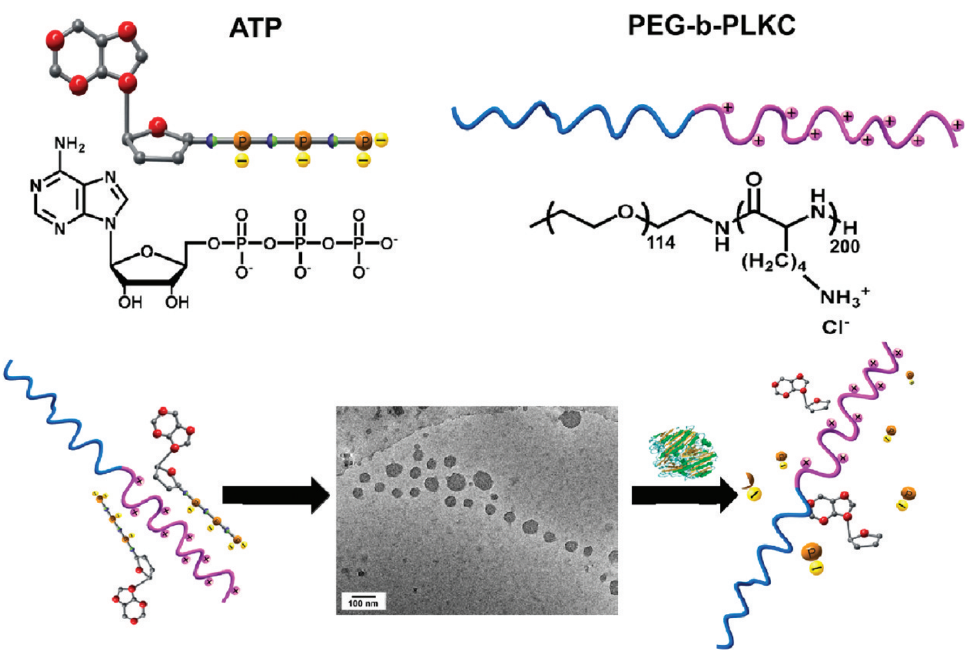

FIGURE 10. Enzyme-responsive supra-amphiphiles. Reproduced from ref 46 with permission. Copyright 2010 Wiley Publishers.

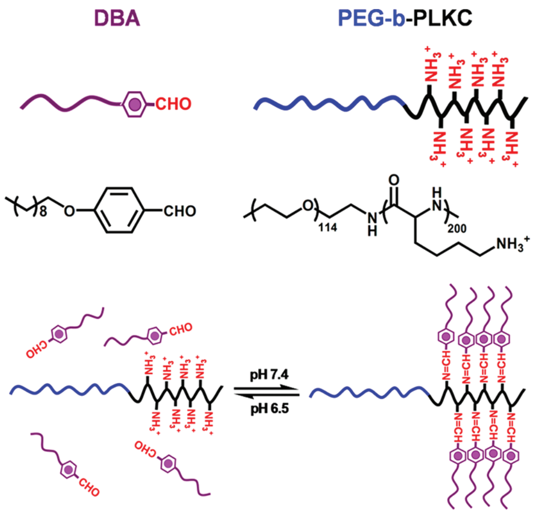

FIGURE 11. Polymeric supra-amphiphiles on the basis of dynamic convalent bonds. Reproduced from ref 47 with permission. Copyright 2011 Wiley Publishers.

supra-amphiphiles with noncovalent interactions. Biologic moieties, like protein and nucleic acid, may also be the building blocks for supra-amphiphiles. The easy fabrication and combination of different materials will lead to interesting properties and new applications.

4. Conclusion and Outlook

The development of new building blocks and creation of diversified supramolecular nanostructures have always been the most important parts in the area of self-assembly. Looking back to the history of supramolecular chemistry, every time a new type of building block is discovered and employed, it also represents a new milestone in the understanding and development of self-assembly. Herein this Account, we have summarized the line of research from amphiphiles to supra-amphiphiles. Basically, this line of research is regarded as development of supramolecular engineering, which utilizes noncovalent interactions, instead of covalent bonds, as a tool to tune the structure and the function of the building blocks. In the first part, nonvovalent interactions are used as an alternative force to stabilize the self-assembly structures, making the soft materials not that "soft" anymore. In the second part, inspired by nature, noncovalent interaction is used as a driving force to construct building blocks, named supra-amphiphiles. The supra-amphiphiles are then further self-assemble into hierarchical complex structures and smart self-assemblies.

With more and more building blocks developed for self-assembly, we should not forget that some basic challenges still remain unsolved. One challenge is how to control the process of self-assembly, which is a spontaneous process but should also be controllable.[49] In nature, the same building blocks, when different information is input, can experience different processes of self-assembly and form distinct structures with distinct functions. With the increasing understanding of self-assembly processes, self-assembly can be adjusted at start-up, in-process, and at termination. There is still plenty of room for research on the subject of complete control of the self-assembly process.

Another challenge is the relationships between functional building blocks and functional self-assemblies. The function of the building blocks can be brought into self-assemblies, and interestingly, the function can be improved by self-assembly. This means that functions of the self-assemblies rely not only on the properties of the building blocks, but also on the ordered arrangements of the building blocks in the self-assemblies. In this regard, theoretical computation and simulation should be interacted with experimental study more closely in order to establish the relationship among molecular structure, supramolecular structure and functions.

With the building blocks provided, we should not forget that in the field of self-assembly, the ultimate goal is to bridge the gap between material sciences and life sciences. However, we are still far away from this goal. It is hoped that self-assembly can proceed from a low to a high level and from nonliving to living. To this end, self-assembly remains a challenging field that can make full use of our power of imagination.

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FOOTNOTES

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