Supramolecular Amphiphiles

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Foreword

Since its emergence, supramolecular chemistry has been growing in importance in a wide range of fields, including organic, inorganic, physical and analytical chemistry, biology, materials science, medicinal chemistry and polymer chemistry. It has also affected the study of amphiphiles by extending the notion of molecular amphiphiles built on covalent bonding to supramolecular amphiphiles (supra-amphiphiles) fabricated on the basis of non-covalent interactions. As a result of these non-covalent interactions, supra-amphiphiles are easily tailored and have the ability to respond to physical stimuli or chemical effectors. They thus demonstrate adaptivity and can participate in the development of adaptive chemistry. Supra-amphiphiles build new bridges between colloid science and supramolecular chemistry, allowing the fabrication of supramolecular assemblies with controlled architectures and functions.

This book gives a detailed and systematic presentation of this topic, from an introduction of the history to the development and perspectives of the field of supra-amphiphiles. The many examples of supramolecular amphiphiles are presented in seven chapters according to the intermolecular interactions on which they are based, including host–guest interactions, electrostatic interactions, charge transfer interactions, hydrogen bonding and metal ion coordination. The introduction of reversible covalent bonding opens the field towards dynamic covalent chemistry. This book strives to combine molecular architecture and functional features. It aims to provide an open horizon and wide perspectives for the molecular engineering of supra-amphiphiles. The editor is to be congratulated for assembling such a remarkable roster of actors in the field, offering a set of presentations that will inspire researchers of various trades, from discovery to applications, extending further the frontiers of the chemistry of supramolecular matter.

Jean-Marie Lehn

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CHAPTER 1

Evolution of Supra-Amphiphiles from Amphiphiles

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1.1 Molecular Amphiphiles

Molecular amphiphiles are molecules that have both a hydrophilic part and a hydrophobic part linked by covalent bonds. With their ability to significantly decrease surface tension, amphiphiles can self-assemble at air–liquid or liquid–liquid interfaces, leading to the formation of organized molecular assemblies such as Langmuir monolayers, micelles, vesicles and emulsions. Amphiphiles are therefore used extensively as detergents, emulsifiers, solubilizers and foaming agents, and are essential in a number of modern industries, from mining and manufacturing to textiles and medicine. Amphiphiles such as phospholipids are crucial components of living organisms because they are the primary constituents of biological membranes, which are essential in the structure of cells. Membranes provide a compartmentalized microenvironment, ensuring that biochemical processes occur in a systematic rather than a chaotic manner, enabling the existence of life itself.

Molecular amphiphiles can be of different topologies (Figure 1.1) in terms of the different motifs acting as the linkage between the hydrophilic and hydrophobic parts.[1] A hydrophilic headgroup can be covalently linked to single, double or triple hydrophobic alkyl chains. The use of synthetic molecular

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amphiphiles to form vesicle-like structures dates back to the 1977 paper by Kunitake *et al.*[2] Two hydrophilic headgroups can be covalently linked by one or two hydrophobic alkyl chains, resulting in the so-called bola-form amphiphiles.[3,4] Two molecular amphiphiles covalently linked at their charged headgroups are classified as gemini amphiphiles.[5] The varied molecular amphiphiles have different properties, leading to different applications. For example, the critical micelle concentration of gemini amphiphiles is typically lower than that of conventional single-tailed amphiphiles, resulting in more stable micelles. The phase transition temperature of bola-form amphiphiles can be higher than that of conventional molecular amphiphiles. In other words, if a biological membrane contains a high percentage of bola-form amphiphiles, it remains stable at relatively high temperatures, which is essential for organisms that survive in harsh environments such as hot springs and submarine volcanoes.

Polymeric amphiphiles can self-assemble into structures with enhanced stability and structural diversity relative to the small molecular amphiphiles. The problem with polymeric amphiphiles is the two-dimensional (2D) orientation of the three-dimensional polymer coil. Ringsdorf *et al.*[6] introduced the concept of a flexible spacer into polymeric amphiphiles to overcome this problem. Figure 1.2 shows that there are three ways to introduce flexible spacers. Homopolymers with side-group spacers (Figure 1.2A) have been synthesized from lipids containing a hydrophilic spacer group between the membrane-forming amphiphilic part and the polymerizable unit. Hydrophilic comonomer amphiphilic copolymers with main-chain spacers (Figure 1.2B) can be prepared by the copolymerization of simple lipids. The combination of both spacer types (Figure 1.2C) can be realized by the copolymerization of spacer-containing lipids with hydrophilic comonomers.

Amphiphilic block copolymers are another kind of polymeric amphiphile. As reported by Eisenberg *et al.*,[7] amphiphilic block copolymers can self-assemble to form vesicle-like structures. By fine tuning the chain length, monomeric unit and structural topology of both the hydrophilic and hydrophobic

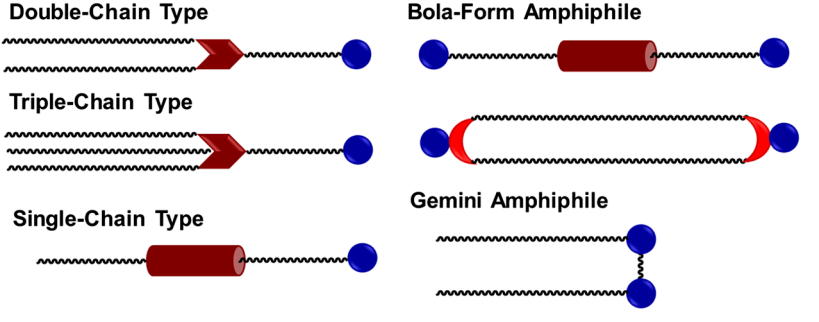

Figure 1.1 Different structures of molecular amphiphiles obtained by molecular engineering.

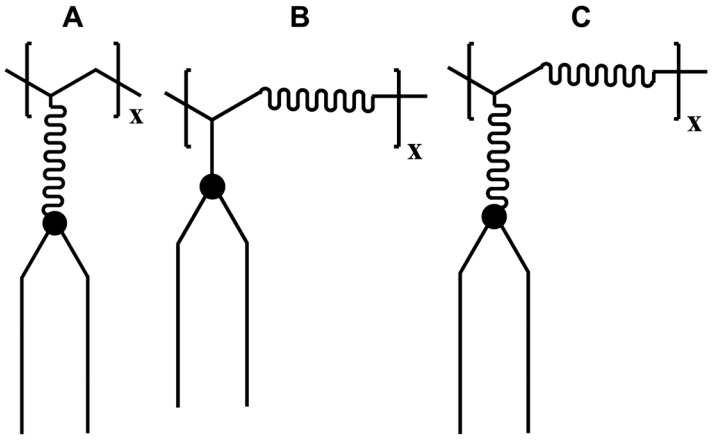

Figure 1.2 Three possible ways to introduce hydrophilic spacer groups into polymeric amphiphiles: (A) side-group spacer; (B) main-chain spacer; and (C) main-chain and side-group spacer.

segments of amphiphilic block copolymers, diverse organized structures can be achieved, such as spherical micelles, cylindrical micelles, bicontinuous rods, lamellae and vesicles.[8]

1.2 Molecular Amphiphiles for Self-Assembly

Self-assembly is a spontaneous process of forming ordered structures from a disordered initial state. Because the hydrophobic group carried by every amphiphile strongly avoids contact with water while the hydrophilic group favors contact with water, molecular amphiphiles tend to aggregate, although this does not usually result in macroscopic-scale phase separation. The unfavorable interaction between the hydrophobic group and water can be suppressed when amphiphiles self-assemble into micelles or onto low-energy surfaces, in which case the hydrophobic group aggregates in the core and the hydrophilic group is distributed on the interface with the bulk water. In this way, the net free energy of the whole system is reduced.

Amphiphiles can self-assemble to form well-defined organized structures, such as micelles and vesicles. The driving force behind the formation of such organized structures is the hydrophobic effect. The molecular basis for self-assembly is amphiphilicity. This means that controllable self-assembly can be realized by tuning the amphiphilicity of the building blocks. For example, molecular amphiphiles can form micelles by self-assembly. By relying on supramolecular chemistry to make the amphiphiles more hydrophilic, we can destroy the molecular basis for self-assembly, leading to the disassembly of micelles. When the amphiphilicity is recovered due to the noncovalent nature of supramolecular chemistry, the destroyed micelles can reform.[9]

1.2.1 One-Dimensional Assemblies from Molecular Amphiphiles

Micellar structures with a defined size and shape can 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 structures are inherently dynamic and fluid. The most straightforward method of stabilizing micellar structures is based on a covalent approach, mainly using polymerizable amphiphiles.[10]

There is a supramolecular approach to stabilizing micellar structures by noncovalent interactions. To this end, we need to use an appropriate molecular design to enhance the intermolecular interactions between the amphiphiles. As an example, we designed and synthesized a bola-form amphiphile bearing a biphenyl mesogenic group and two hydrophilic pyridinium heads (BP-10).[11] *In situ* atomic force microscopy (AFM) observations (Figure 1.3) showed that the bola-form amphiphile BP-10 formed cylindrical micelles with a spaghetti-like morphology at the mica–liquid interface. The average width of the structures was around 40 nm and some reached as long as several micrometers in length. The *ex situ* AFM image shows the same structure as the *in situ* AFM image, suggesting that BP-10 can retain the structure formed in solution. Therefore enhancing the noncovalent interactions between amphiphiles stabilizes the micellar structure against drying.

Combining various intermolecular interactions, including hydrogen bonding and π–π interactions, allows the fabrication of highly stable organized structures. For example, we designed and synthesized a bola-form amphiphile (DPP-11A) with two carboxylic acid headgroups and a diketopyrrolopyrrole (DPP) chromophore in the central part.[12] Figure 1.4 shows that DPP-11A

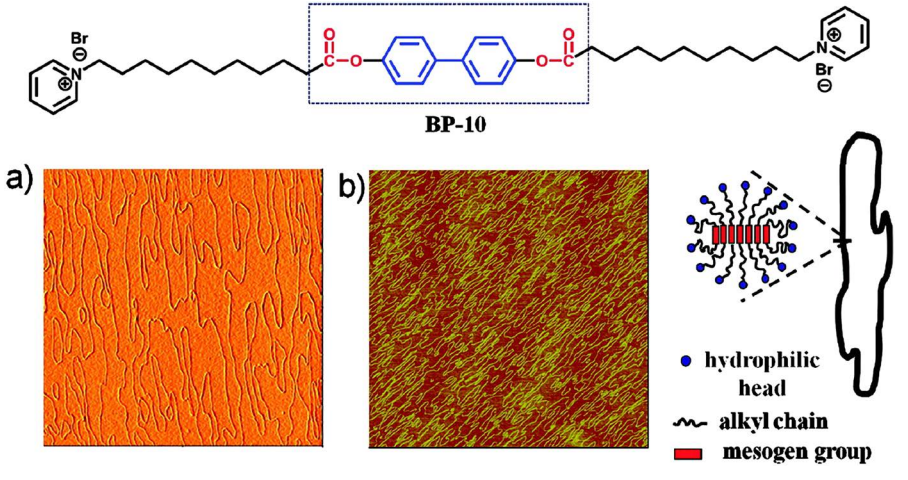

Figure 1.3 (a) *In situ* and (b) *ex situ* AFM observations of cylindrical micelles of BP-10 on a mica surface and proposed model picture. Reprinted with permission from Wang, C., Wang, Z. and Zhang, X., *Acc. Chem. Res.*, 2012, **45**, 608–618. Copyright (2012) American Chemical Society.

can self-assemble to form supramolecular nanofibers. We tested the thermal stability of these fibers by hot-stage AFM. When the temperature was increased from 28 to 130 °C, no obvious change in the contours of the fibers was observed. When the temperature was increased to 140 °C, several parts of the nanofibers melted together. Therefore these supramolecular nanofibers have good thermostability up to 130 °C.

1.2.2 Two-Dimensional Assemblies from Molecular Amphiphiles

Two-dimensional planar structures possess a low curvature in addition to a smaller thickness than their planar dimensions. Bola-form amphiphiles are usually able to self-assemble to form zero- or one-dimensional (1D) assemblies. However, we demonstrated that a cationic bola-form amphiphile (DPP-11-Ts), bearing DPP as the central chromophore, can form 2D planar aggregates. Different counter anions induced different properties in these cationic bola-

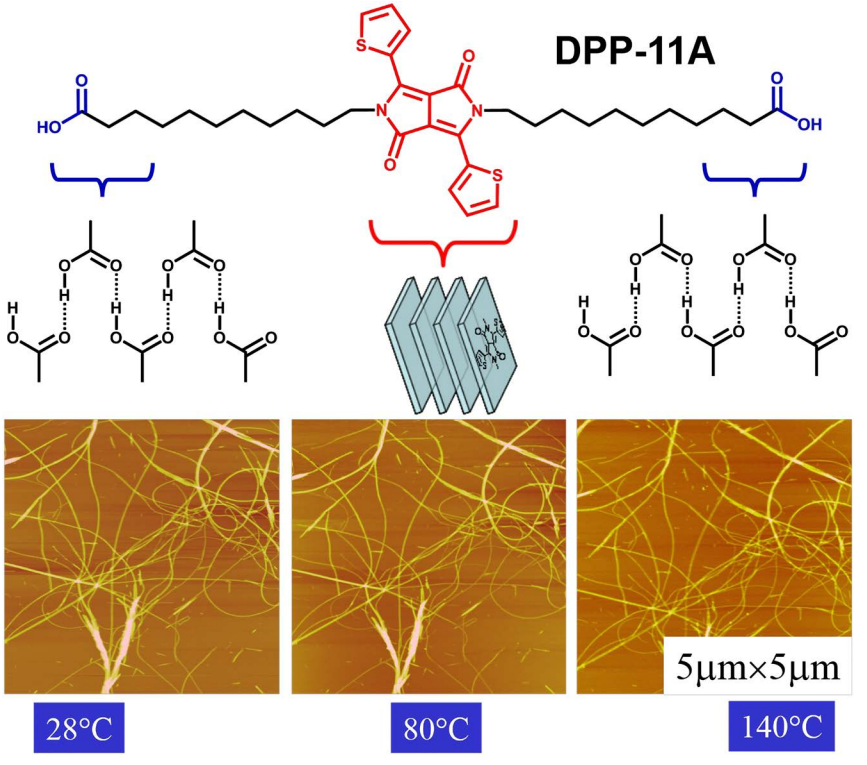

Figure 1.4 1D assemblies of DPP-11A showing high thermostability. Reproduced from B. Song, H. Wei, Z. Wang, X. Zhang, M. Smet and W. Dehaen, Supramolecular nanofibers by self-organiztion of bola-amphiphiles through a combination of hydrogen bonding and π–π stacking interactions, *Adv. Mater.*, 2007, **19**, 416–420. Copyright © 2007 Wiley-VCH.

amphiphiles.[13] To keep the same structural skeleton, the bola-amphiphiles form 1D assemblies when the counter ion is bromide, whereas they form 2D aggregates when the counter ion is tosylate. Therefore the counter ion can induce a transition from 1D to exclusively 2D planar structures (Figure 1.5).

To understand why the tosylate counter ion can induce a transition from 1D to 2D structures, we propose a simple model (Figure 1.6).[14] First, the counter ion significantly affects the average interfacial area occupied by each headgroup. If the counter ion, such as the bromide ion, prefers to dissolve as free ions in solution, then the electrostatic repulsion between adjacent headgroups gives rise to a relatively large average interfacial area occupied by each headgroup. As a result, the curvature of its interface is high, resulting in bent interfaces (Figure 1.6a). The bent interface leads to the formation of vesicles, spherical micelles or fibers. If, however, the counter ion, such as tosylate, exhibits strong binding with a cationic headgroup and prefers the insertion of the organic substructure into the hydrophobic interior of the assemblies, the average interfacial area occupied by each headgroup is small enough to generate planar interfaces of low or zero curvature (Figure 1.6b). Following these arguments, we suggest that these interfaces possess low curvature, which is responsible for the formation of 2D planar structures.

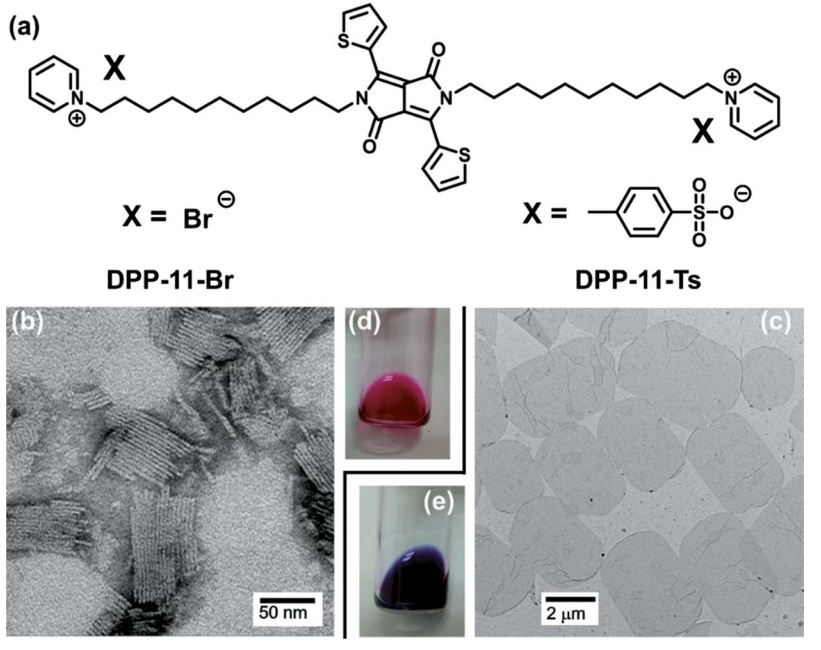

Figure 1.5 Tuning the assemblies from a 1D structure to a 2D planar structure by varying the counter anions. (a) Molecular structures of DPP-11-X. (b) The 1D rod-like structure of DPP-11-Br, and (c) the 2D planar structure of DPP-11-Ts observed by TEM. The colors of DPP-11-Br and DPP-11-Ts aqueous solutions are (d) light pink, and (e) dark blue, respectively. Reproduced from ref. 13 with permission from the Royal Society of Chemistry.

It is anticipated that crystal structure data will support this assumption. However, single crystals of DPP-11-Ts cannot be prepared due to its long alkyl chains containing 11 carbon atoms. Fortunately, by shortening the chain length to seven carbon atoms, single crystals of DPP-7-Ts can be obtained.[13] This crystal is crystallized directly from a concentrated aqueous solution and is therefore likely to reflect the molecular arrangement of its aggregates in solution. Figure 1.7 shows that the crystal is made up of numerous 2D planar

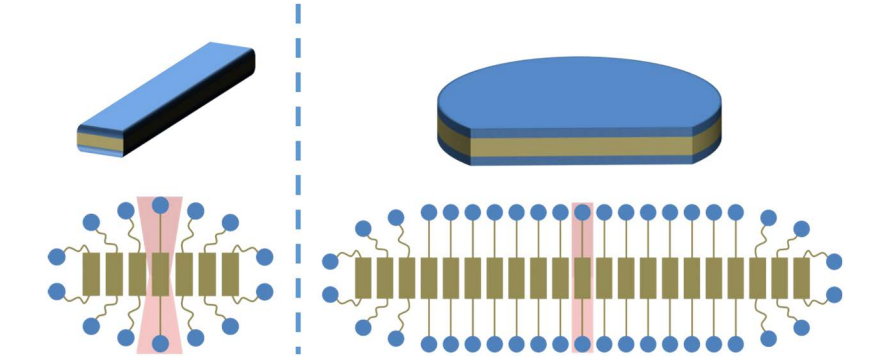

Figure 1.6 Simple model summarizing the self-assembled structures of mesogen-containing cationic bola-amphiphiles depending on different counter ions. Reproduced from ref. 14 with permission from the Royal Society of Chemistry.

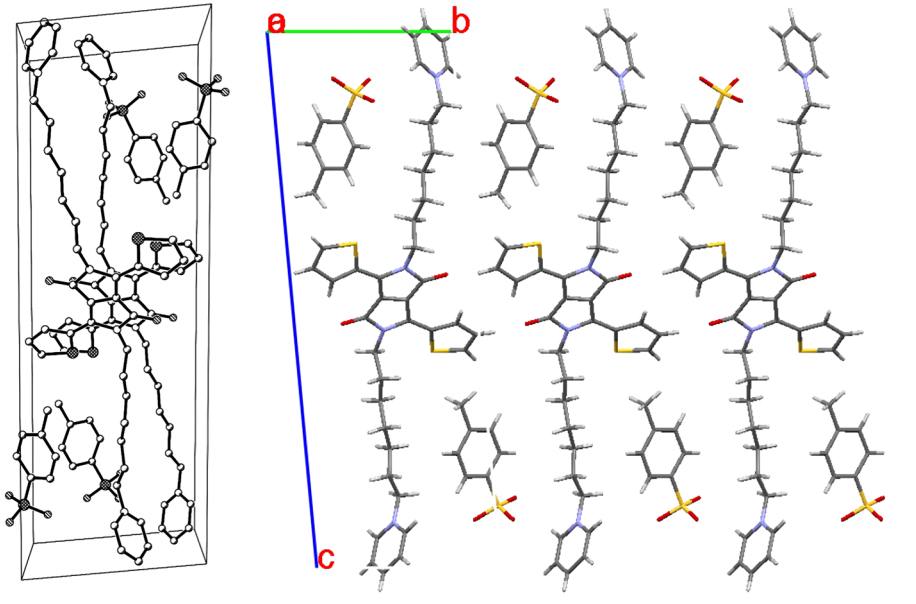

Figure 1.7 Crystal structure of DPP-7-Ts, directly crystallized from its concentrated aqueous solution, clearly showing the insertion of tosylate ions at the aggregate–water interface. Reproduced from ref. 13 with permission from the Royal Society of Chemistry.

monolayers (only one monolayer is shown here). In each monolayer, the DPP chromophores exhibit extended orientational stacking along the 2D plane. A favorable insertion of hydrotropic anions such as tosylate at the aggregate–water interface can be clearly observed from the crystal structure. Figure 1.6b shows that both sides of the 2D planar monolayers are hydrophilic surfaces consisting of cationic pyridinium groups and tosylate ions. The tosylate ion inserts its hydrophobic segment into the hydrophobic cavity of the aggregates, leaving its polar head pointing toward the water phase. This energy-favorable orientation means that tosylate prefers to stay at the aggregate–water interface. Compared with the example of the freely dissolved bromide ion, the inserted tosylate anion weakens the repulsive forces between the adjacent cationic head groups, favoring interfaces of low curvature and thus leading to the formation of 2D planar structures.

In addition to the tosylate counter ion, we used different hydrotropic anions to reveal how the size and substituent of the organic segments in hydrotropic anions determine their ability to induce the formation of 2D planar aggregates. We have demonstrated that the ability of a hydrotropic counter ion to induce the formation of 2D planar aggregates depends weakly on its polar head, but is strongly correlated with the size and substitution pattern of its organic portion. In addition, the shapes of the obtained 2D planar aggregates can be triangular, quadrangular or hexagonal and they can be modulated by both hydrotropic counter anions and the embedded conjugated moieties. Using this knowledge, it is possible to control the self-assembly of bola-amphiphiles by easily exchanging the counter ions, which provides a simple and feasible way of approaching functional supramolecular materials.

Lowering the dimensionality of intermolecular interactions is another effective strategy for fabricating 2D structures from amphiphiles.[15] Figure 1.8a shows that a 3D structure is formed from melamine protonated by various kinds of acid. In the direction perpendicular to the figure, π–π interactions drive the stacking of protonated triazine rings. In one of the directions parallel to the figure, counter ion bridging (including counter ion bridged multiple hydrogen bonds as well as electrostatic interactions) drives the assembly. In the other direction, adjacent protonated melamines are connected by multiple hydrogen bonds. As the interaction of multiple hydrogen bonds can be easily blocked by the introduction of alkyl chains, dialkylated melamine derivatives with different length alkyl chains (Mela-*n*) are synthesized as building blocks (Figure 1.8b), where *n* refers to the carbon number of the alkyl chain. In the assemblies of protonated melamine derivatives, alkyl chains are used to eliminate the interaction of multiple hydrogen bonds, while the interactions of counter ion bridging and π–π stacking can be preserved, thus generating 2D structures.

Self-assembly of the protonated melamine derivative (Mela-12·HCl) leads to the formation of 2D microsheets. As indicated by transmission electron microscopy (TEM) (Figure 1.9a), the 2D assemblies are planar sheets with elegant rectangular shapes, extending in size over the micrometer scale. The AFM image of Mela-12·HCl in Figure 1.9b shows microsheets with highly flat

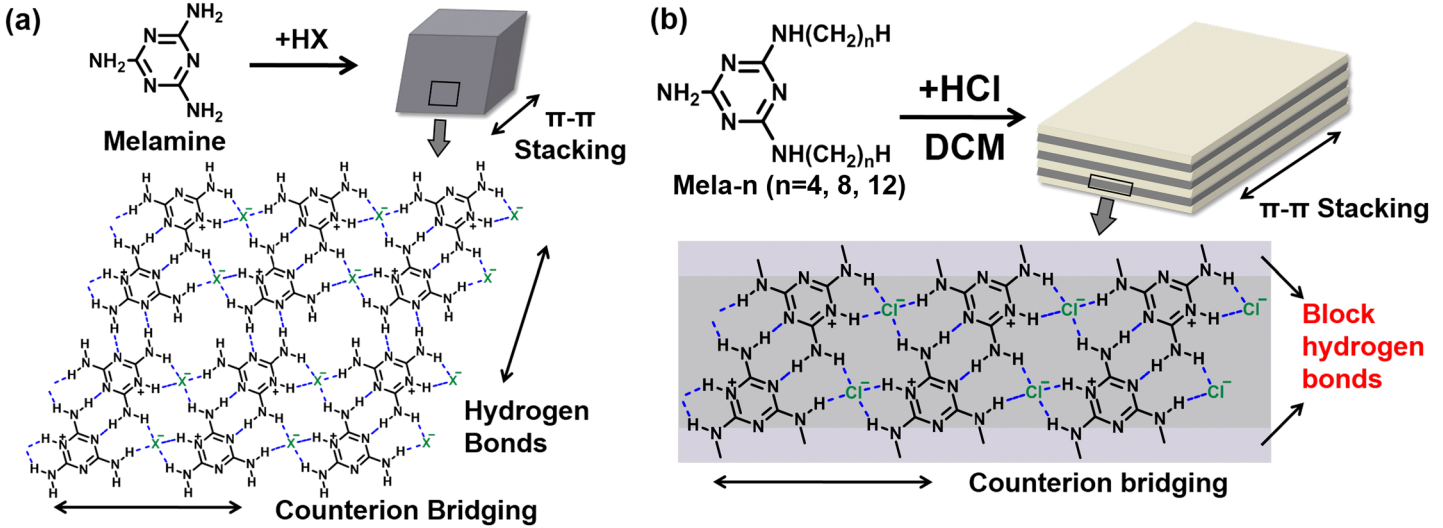

Figure 1.8 Schematic illustration of (a) the 3D network produced from protonated melamine through multiple hydrogen bonds, counter ion bridging and π–π stacking and (b) 2D microsheets produced from dialkylated melaminium derivatives through chloride ion bridged hydrogen bonds as well as electrostatic interactions and π–π stacking while alkyl chains are introduced to eliminate the interaction of multiple hydrogen bonds in the previous 3D network. Reproduced from ref. 15 with permission from the Royal Society of Chemistry.

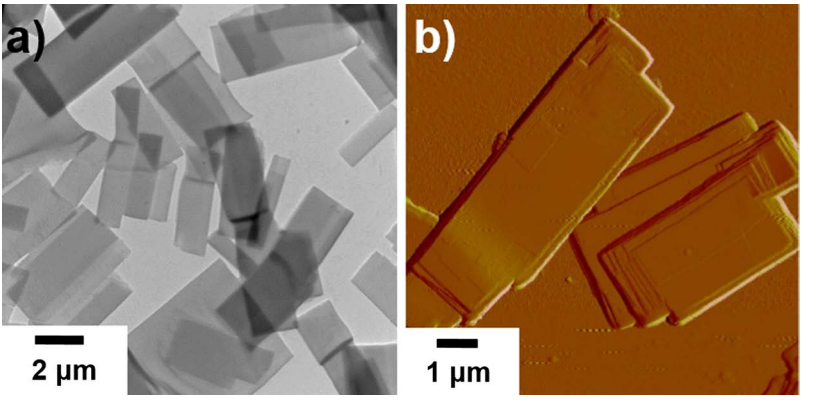

Figure 1.9 Rectangular microsheets of Mela-12·HCl with a lamellar structure observed from (a) TEM and (b) AFM. Reproduced from ref. 15 with permission from the Royal Society of Chemistry.

surfaces over a length scale of up to several micrometers and with stepped edges of height intervals on the nanometer scale, which suggests that the assemblies are 2D microsheets of lamellar structures. A similar strategy also works to further lower the dimensionality of the self-assemblies of melamine-derived amphiphiles from 2D to 1D structures.

1.2.3 Stimuli-Responsive Molecular Amphiphiles

Stimuli-responsiveness in an amphiphile system means that the physicochemical properties of the system can vary under specific external stimuli. Various factors can be designed and applied as external stimuli for stimuli-responsive amphiphiles, such as pH, redox conditions, heat and specific chemical substances. It is not possible to cover every aspect of this vastly developed area in this chapter, so we will briefly introduce amphiphile systems responsive to carbon dioxide (CO_2), enzymes and light.

1.2.3.1 CO_2-Responsive Amphiphiles

As a benign gas that is easily added to, and separated from, a system, CO_2 is a good stimulant to modulate the physicochemical properties of a surfactant system. Jessop *et al.*[16] designed an elegant CO_2-responsive amphiphile containing an amidine group as the polar head and a long alkyl chain as the hydrophobic part (Figure 1.10). This amphiphile is a poor surfactant before exposure to CO_2, but becomes an effective surfactant when exposed to CO_2 because the pristine amidine group can react with CO_2 to yield the amidinium bicarbonate salt, which is of higher polarity. The hexadecane–water mixture containing this amphiphile can be shaken to generate an emulsion.

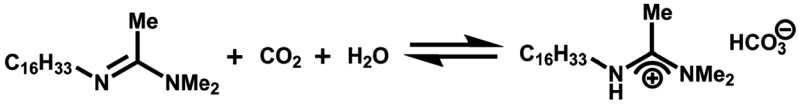

Figure 1.10 Molecular formulas of the CO_2-responsive amidine amphiphile.

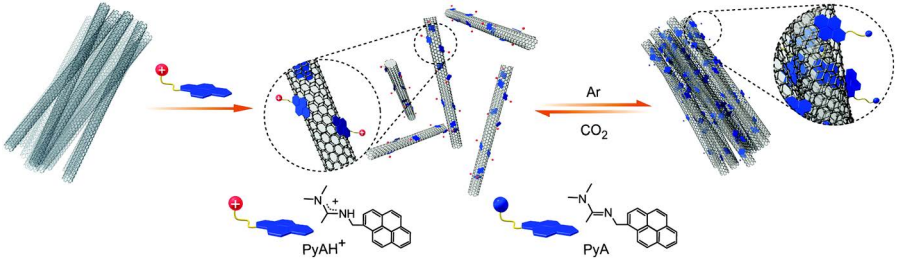

Figure 1.11 Controlled dispersion and aggregation of SWCNTs with a CO_2-responsive amphiphile. Reproduced with permission from Y. Ding, S. Chen, H. Xu, Z. Wang and X. Zhang, *Langmuir* 2010, **26**, 16667–16671. Copyright (2010) American Chemical Society.

If previously treated with CO_2, the emulsion is significantly stabilized, with no evidence of phase separation within 3 h, whereas the untreated emulsion clearly separates into two layers within 5 min of the end of shaking. The ability of the CO_2-treated amphiphile to form an emulsion can be decreased by bubbling argon or air into the solution; the ability to form an emulsion is recovered when CO_2 is bubbled through again. This process can be reversibly and facilely repeated, which is highly favorable in practical applications, such as enhanced oil recovery.

The same amidine moiety can be adopted in the design of functional molecular amphiphiles. For example, we synthesized a CO_2-responsive dispersant (PyAH) bearing a pyrene and an amidine moiety, which became an effective surfactant after exposure to CO_2. Figure 1.11 shows that, through strong π–π interactions between the pyrene moiety and single-walled carbon nanotubes (SWCNTs), we demonstrated that PyAH can be modified onto SWCNT surfaces to promote the dispersion of SWCNTs in water.[17] Taking advantage of the gas-triggered interconversions between the amidinium cation and amidine, reversible control of the solubility of SWCNTs has been achieved simply through the alternate bubbling of CO_2 and argon. This work demonstrates a new method for the controlled dispersion and aggregation of SWCNTs.

The amidine moiety can also be attached to the side-chains of block polymers for the development of CO_2-responsive polymeric amphiphiles. Figure 1.12 shows that amidine-containing block copolymers can spontaneously form vesicles in aqueous media on the basis of their amphiphilicity.[18]

CO_2 can tune the size of these vesicles over a wide range by controlling the degree of protonation of the amidine moieties. Alternating treatment with CO_2 and argon realizes a smart expansion and contraction cycle of these vesicles, which can be considered as "breathing" nanocapsules.

In addition to the amidine moiety, there are other functional groups that display CO_2-responsiveness, including tertiary amines, guanidines and imidazoles. They can also be used for the construction of CO_2-responsive small molecular amphiphiles and polymeric amphiphiles.[19] It will be particularly interesting to explore the use of CO_2-switchable amphiphiles in applications that currently require repeated on–off cycles through the addition of chemical species (*e.g.* acids, bases, redox agents, ions or molecules) that cannot be facilely separated and may suffer from an enhanced ionic strength after many cycles.

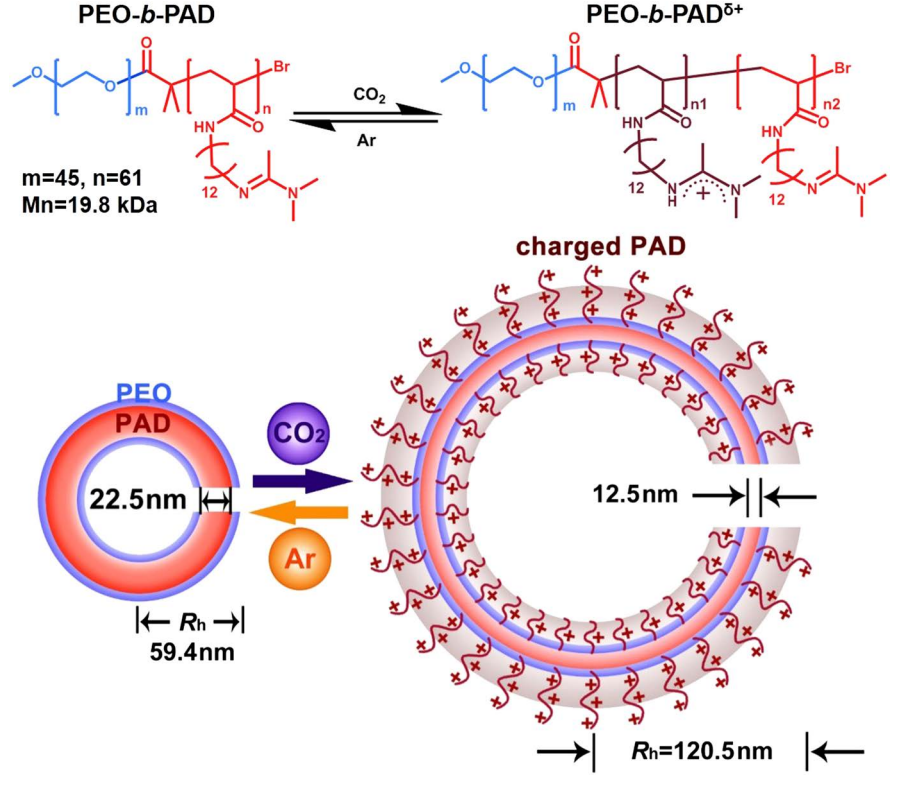

Figure 1.12 Molecular structure of the amidine-containing diblock copolymer (top); schematic representation of its self-assembly into vesicles and their reversible CO_2/argon-responsive "breathing" in aqueous solution (bottom). Reproduced from Q. Yan, R. Zhou, C. Fu, H. Zhang, Y. Yin and J. Yuan, CO_2-responsive polymeric vesicles that breathe, *Angew. Chem., Int. Ed*. 2011, **50**, 4923–4927. Copyright © 2011 Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim.

1.2.3.2 Enzyme-Responsive Amphiphiles

Enzymes are proteins that catalyze biochemical reactions with high selectivity and efficiency. As enzymes play a crucial part in metabolic processes, the concentration and activity of enzymes are closely related to the physiological and pathological conditions of organisms. Therefore enzymes are intriguing stimuli for smart molecular amphiphile systems, which may be used for biomedical applications such as diagnosis and drug delivery.[20]

Enzyme-responsiveness is generally realized by covalently incorporating the enzyme-responsive moiety into the molecular structure of amphiphiles. As every enzyme recognizes its own specific substrate structure, the design of enzyme-responsive amphiphiles is dependent on the specific enzyme assigned to act as the stimulus. For example, Figure 1.13 shows that acetylcholinesterase (AChE) can spontaneously hydrolyze alkylcholine into choline and alkyl carboxylic acid.[21] Myristoylcholine is a good substrate for AChE in addition to being a cationic amphiphile. Below its critical micelle concentration, myristoylcholine forms premicellar aggregates with an anionic aggregation-induced emissive compound (TPE-1) in aqueous solution due to electrostatic attraction. In the presence of AChE, cationic myristoylcholine is hydrolyzed into choline and myristic acid. Although the resultant myristic acid is still an amphiphile, the interaction between TPE-1 and myristic acid switches to electrostatic repulsion. As a result, the addition of AChE leads to the disassembly of the premicellar aggregates and a decrease in the fluorescence of TPE-1. In the presence of an AChE inhibitor, the hydrolysis process can be paused and the residual fluorescence of TPE-1 observed. Thus coupling the charge reversal of myristoylcholine hydrolyzed by AChE with the

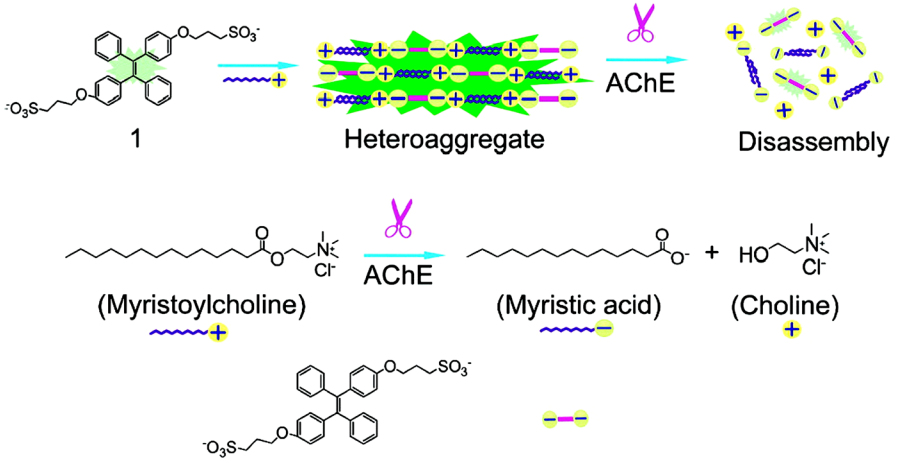

Figure 1.13 Schematic illustration of the formation of heteroaggregate between myristoylcholine and TPE-1 and its AChE-triggered disassembly. Reproduced with permission from Wang, M., Gu, X., Zhang, G., Zhang, D. and Zhu, D., *Anal. Chem.* 2009, **81**, 4444–4449. Copyright (2009) American Chemical Society.

aggregation-induced emissive properties of TPE-1, this amphiphile system can achieve AChE-responsiveness and could be used to screen AChE inhibitors.

Polymers are also good platforms for enzyme-responsive moieties. Amir *et al.*[22] synthesized a diblock copolymer with one segment formed from a hydrophilic polyethylene glycol chain and the other segment formed from a polyvinyl phenol part-chain modified with hydrophilic phosphate moieties (Figure 1.14). The diblock copolymer was hydrophilic and was freely dispersed in aqueous solution. However, when treated with acid phosphatase, the phosphate moieties were cleaved off, making the polyvinyl phenol segment hydrophobic. The block copolymer spontaneously became amphiphilic and self-assembled. Therefore phosphatase-triggered self-assembly was achieved by attaching phosphatase-responsive moieties onto the hydrophobic segment of a diblock copolymer. Branched polymers can also be designed as enzyme-responsive amphiphiles. Azagarsamy *et al.*[23] fabricated an amphiphilic dendrimer with hexyl ester functionalities on the hydrophobic parts (Figure 1.15). The amphiphilic dendrimers easily formed micellar assemblies at millimolar concentrations and were able to encapsulate hydrophobic cargo molecules inside the assemblies. When treated with porcine liver esterase, the hexyl ester functionalities were hydrolyzed, leaving the carboxylic acid groups on the dendrimer backbones and gradually changing the dendrimer from amphiphilic to hydrophilic, achieving esterase-induced disassembly and cargo release.

Other enzymes, such as proteases, nucleases and hyaluronidases, can also be used as stimuli for smart amphiphile systems. The general strategy for

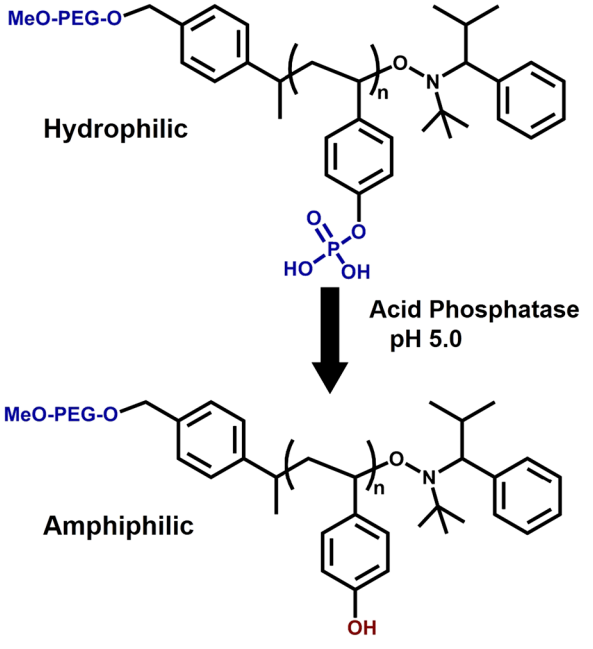

Figure 1.14 Molecular formulas of the phosphatase-responsive diblock copolymer.

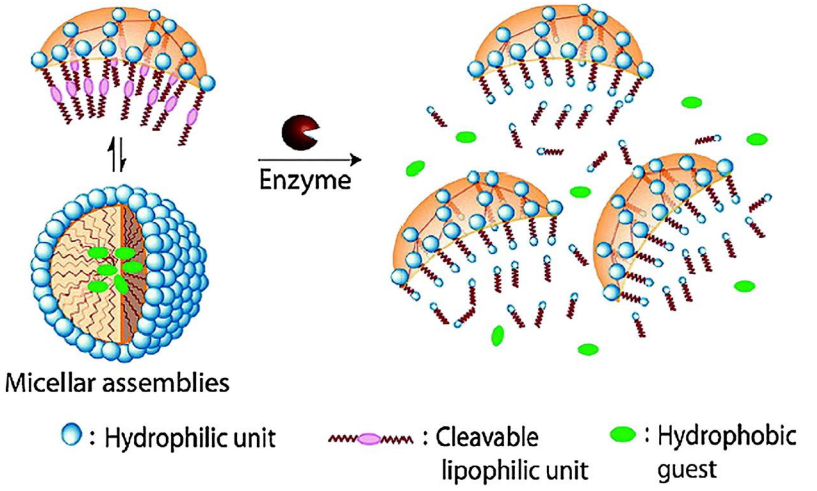

Figure 1.15 Schematic illustration of esterase-triggered disassembly of dendrimer-based micellar assemblies and guest release. Reproduced with permission from Azagarsamy, M. A., Sokkalingam, P. and Thayumanava, S., *J. Am. Chem. Soc.* 2009, **131**, 14184–14185. Copyright (2009) American Chemical Society.

the design of enzyme-responsive amphiphile systems relies on the reversal of amphiphilicity before and after enzyme treatment, which means that the substrate moiety and its product moiety are always significantly different in their solvophilicity. This may explain why there has so far been no report of isomerase-responsive amphiphile systems: the substrate and product are too similar.

1.2.3.3 Photo-Responsive Amphiphiles

Light energy can be spatiotemporally controlled with high precision in terms of both wavelength and intensity. In addition, as a mass-less reagent, light can be noninvasively applied to certain systems. Therefore light can be a good stimulus for stimuli-responsive amphiphile systems, modulating the self-assembly of the amphiphiles. For example, Haubs *et al.*[24] synthesized a photo-responsive lipid (Figure 1.16). The lipid contained two ester chains and a zwitterionic *N*-(1-pyridino)amidate headgroup, and self-assembled to form liposomes in water. Under UV irradiation (320 nm), the headgroup moieties mainly underwent ring expansion to yield 1,2-diazepine structures. As the hydrophilicity of the diazepine was much lower than that of the zwitterionic headgroup, the liposomes became metastable after UV irradiation. These diazepine liposomes could easily be destroyed by mechanical stress and did not recover. Thus the amphiphile system achieved photo-responsiveness based on the photochemical variation of the hydrophilic headgroups. In addition, photo-responsiveness can also be realized based on the light-triggered cleavage of hydrophilic headgroups. Figure 1.17 shows that the quaternary benzylammonium headgroup

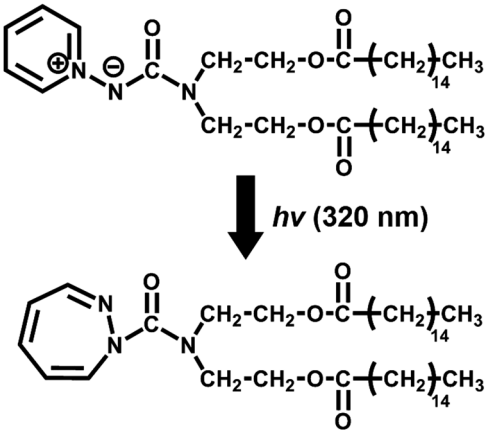

Figure 1.16 Molecular formulas of a photo-responsive lipid with a zwitterionic *N*-(1-pyridino)amidate headgroup.

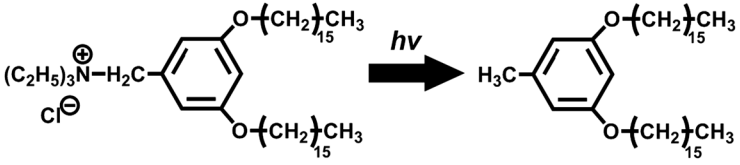

Figure 1.17 Molecular formulas of a photo-responsive lipid with a quaternary benzylammonium headgroup.

of the lipid could be detached by UV irradiation, leaving the lipid with a fully hydrophobic structure.[25] Consequently, the organized liposomes of the lipid collapsed and transformed into crystals of the photochemical products.

Photo-responsiveness can be extended from small molecules to polymers, as realized by the switch in amphiphilicity of polymers before and after irradiation with light. Jiang *et al.*[26] designed and prepared a diblock copolymer consisting of a hydrophilic polyethylene oxide segment and a hydrophobic polymethacrylate segment bearing pendant pyrene groups. This amphiphilic diblock copolymer self-assembled to form micellar aggregates in water. Upon UV irradiation, the pyrene moieties detached from the polymers and thus the hydrophobic polymeric segment was switched into a hydrophilic polymethacrylic acid segment, resulting in thorough dissociation of the micellar aggregates.

In these examples, the photo-responsiveness of amphiphile systems is irreversible. Once triggered, the photo-reactive moieties are not recovered. However, by the appropriate selection of photo-responsive moieties, reversible photo-responsiveness can also be achieved. For example, malachite green becomes cationic upon UV irradiation and reverts to a neutral, hydrophobic form after thermal treatment. Based on this reversible property, we synthesized a polymeric amphiphile bearing a polyethylene oxide backbone with a malachite green moiety on one end.[27] Figure 1.18 shows that the amphiphile self-assembled to form vesicles in aqueous solution. Upon UV irradiation, the malachite

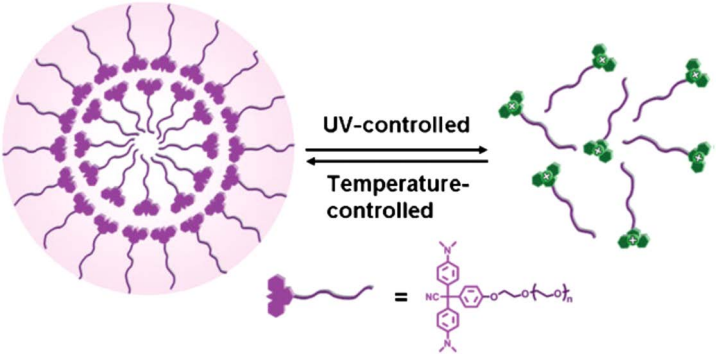

Figure 1.18 Schematic illustration of the reversible self-assembly of a light-responsive amphiphile bearing a malachite green moiety. (Reproduced from Wang, Y., Xu, H. and Zhang, X., Tuning the amphiphilicity of building blocks: controlled self-assembly and disassembly for functional supramolecular materials, *Adv. Mater.* 2009, **21**, 2849–2864. Copyright © 2009 Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim) .

green moiety was triggered to change to its cationic form and thus the amphiphile was transformed to a completely hydrophilic polymer, leading to the disassembly of the vesicles. When the UV irradiation was removed, the cationic malachite green moiety gradually returned to its hydrophobic form and the vesicles spontaneously reformed. A similar reversible photo-responsive moiety could be transplanted onto a solid surface to achieve a reversible transformation of the surface between superhydrophilicity and superhydrophobicity.[28]

In common with other stimuli-responsive amphiphile systems, the solvophilicity transformation of amphiphiles is the main mechanism involved in the design and operation of photo-responsive amphiphile systems. The influence of the light-induced variation in molecular structure can be amplified by its consequent variation of the self-assemblies, leading to stimuli-responsiveness of the whole system. Based on the energy matching of photons and the energy difference of frontier orbitals, UV radiation is the main stimulus for a large proportion of state-of-art photo-responsive amphiphile systems. As a result of developments in photochemistry and materials science, more amphiphile systems will be developed that are sensitive to visible and near-infrared radiation as long-wavelength radiation has better penetration and fewer destructive effects.

1.3 Molecular Engineering of Supra-Amphiphiles

In contrast with molecular amphiphiles, supramolecular amphiphiles (or supra-amphiphiles) are amphiphiles formed on the basis of noncovalent interactions.[29] This field of study serves as a bridge between colloid science[30] and supramolecular chemistry.[31] In principle, various noncovalent interactions can be used to drive the formation of supra-amphiphiles, including host–guest interactions, electrostatic interactions, hydrogen bonding and charge transfer interactions. Compared with molecular amphiphiles

fabricated on the basis of covalent bonds, this noncovalent approach may simplify the fabrication of supra-amphiphiles. Responsive and functional moieties can easily be incorporated into supra-amphiphiles, endowing supra-amphiphiles with stimuli-responsiveness, reversibility and adaptivity, which are not easily achieved by molecular amphiphiles.

Different topologies of covalently bonded amphiphiles can be realized in supra-amphiphiles on the basis of noncovalent interactions. Supra-amphiphiles can even construct topologies that are not easily accessible with conventional amphiphiles. The rich topologies of supra-amphiphiles are shown in Figure 1.19. For example, a hydrophobic building block bearing a hydrogen bonding donor can interact with a hydrophilic hydrogen bonding acceptor to form a single-chain supra-amphiphile on the basis of hydrogen bonding (**1**). Double-chain supra-amphiphiles can be fabricated in the same way (**2**). Two routes to the construction of a bola-form supra-amphiphile can be visualized: one is to combine two building blocks bearing two complementary interacting groups using either hydrogen bonding or metal coordination (**3**); the other is to introduce a bifunctional moiety to bridge the two building blocks (**4**). Based on electrostatic attraction, cationic surfactants can also be classified as a type of supra-amphiphile (**5**). A gemini amphiphile interacts with a suitable organic counter ion, leading to the formation of a gemini-type supra-amphiphile (**6**). Building blocks with a suitable molecular design can be used to fabricate gemini-type supra-amphiphiles with different structures on the basis of noncovalent interactions (**7**). Supramolecular host–guest systems can be intrinsically amphiphilic due to the opposing solvophilicity of the host and guest (**8**). Hydrophobic polymer segments can noncovalently link with hydrophobic polymer segments, leading to the formation of polymeric supra-amphiphiles (**9**, **10**).

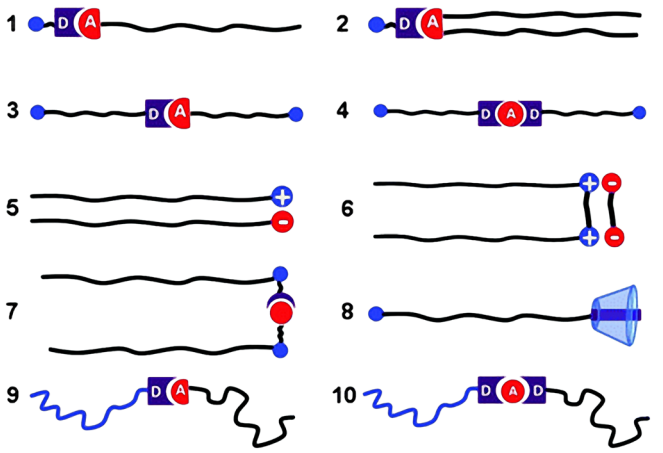

Figure 1.19 Different structures of supra-amphiphiles obtained by molecular engineering. Reproduced from ref. 29 with permission from the Royal Society of Chemistry.

The molecular design of the building blocks for the fabrication of supra-amphiphiles needs to fulfill the requirements of various noncovalent interactions. When hydrogen bonding is used, hydrogen bonding donors and acceptors need to be introduced into the building blocks. Considering that a single hydrogen bond is not strong enough to drive the formation of supra-amphiphiles with a well-defined composition, multiple hydrogen bonding is a sensible choice. Because water itself is a competitive donor and acceptor, it is usually necessary to locate the hydrogen bonding moieties within the hydrophobic parts of the supra-amphiphiles to ensure stability of the self-assemblies. Electrostatic interactions can conveniently be used to fabricate zero-dimensional assemblies because they are not directional interactions. To prepare 1D or 2D self-assemblies, it is usually necessary to lower the symmetry of the building blocks and to use directional noncovalent interactions, such as charge transfer and hydrogen bonding. Dynamic covalent bonds and coordination bonds are also able to cleave and reform reversibly under appropriate circumstances, which resemble the dynamic features of noncovalent interactions. Therefore they are used to fabricate dynamic supra-amphiphiles.

1.4 Nomenclature of Amphiphiles and Supra-Amphiphiles

Several terms have been used to describe supramolecular amphiphilic species—for example, the terms "superamphiphile" and "supra-amphiphile" have been used interchangeably.[32] To ensure clarity in this book, "supramolecular amphiphile" and its abbreviated form, "supra-amphiphile", are used to refer to the amphiphilic species in which some moieties are linked with each other *via* noncovalent interactions, dynamic covalent bonds or coordination bonds. "Amphiphile", "molecular amphiphile" and "conventional amphiphile" are used for amphiphilic molecules in which all the moieties are connected solely by covalent bonds.

Large, or giant, amphiphiles can be fabricated by either covalent or noncovalent bonds. When polymeric building blocks are used in the fabrication of amphiphiles on the basis of noncovalent interactions (*e.g.* **9** and **10** in Figure 1.19), the resultant supra-amphiphiles are giant amphiphiles as a result of their size. Single-molecule giant amphiphiles are not considered as supra-amphiphiles, however.

1.5 Characterization of Supra-Amphiphiles and Assemblies Formed by Self-Assembly of Supra-Amphiphiles

In terms of the building blocks, the formation of a supra-amphiphile is considered as primary self-assembly and the structures formed by supra-amphiphiles can be regarded as secondary self-assemblies. Consequently,

the characterization of supra-amphiphiles may be briefly categorized into two sections: one is the formation of supra-amphiphiles and the other is the further self-assembly of supra-amphiphiles. As the formation of supra-amphiphiles is, in essence, driven by noncovalent interactions, many of the characterization methods used in supramolecular chemistry can be applied, including nuclear magnetic resonance spectrometry, UV–visible spectrophotometry, fluorescence spectrometry and isothermal titration calorimetry. The characterization of the further self-assembly of supra-amphiphiles shares many methods with the self-assembly of molecular amphiphiles, such as dynamic laser scattering, AFM and TEM.

The formation of supra-amphiphiles and the self-assembly of supra-amphiphiles cannot be completely separated. In other words, the self-assembly of supra-amphiphiles occurs immediately after the formation of supra-amphiphiles. In addition, the self-assembly process of supra-amphiphiles may, in turn, enhance and stabilize the formation of supra-amphiphiles. For example, supra-amphiphiles formed by dynamic imine bonds can spontaneously self-assemble to form micelles as soon as the supra-amphiphiles are formed. Conversely, the hydrophobic environment of the micellar cores favors the formation of dynamic imine bonds, which further reinforces the stability of the supra-amphiphiles.

As a result of the dynamic nature of noncovalent interactions, the supra-amphiphiles themselves are mostly characterized by fast equilibria for complexation and decomplexation. Consequently, changes in the concentration of either building block affect the formation of supra-amphiphiles and their self-assembly, which is an important distinction from molecular amphiphile systems, in which the concentration of molecular amphiphiles influences their self-assembly, but has no influence on the intact structure of the covalently bonded amphiphiles. Therefore in supra-amphiphile systems where the desired properties rely on the formation–dissociation of supra-amphiphiles, it is crucial to keep the concentration constant throughout their characterization.

1.6 Supra-Amphiphiles: from Molecular Architecture to Functional Assembly

It is important to be able to fabricate supra-amphiphiles with various topologies, but this is not enough. Intricate structures may also induce specific properties and functions.[33] Noncovalent interactions endow supra-amphiphile systems with responsiveness to certain external stimuli. Therefore the surface activity of supra-amphiphiles can be easily and reversibly adjusted between strong and weak states. Supra-amphiphiles may show reversible functions such as foaming, wetting and emulsification. The hierarchical self-assemblies formed by supra-amphiphiles can be formed under one set of conditions and disassembled under another. Such self-assemblies can provide, for example, new micro- or nanocarriers, which may be useful for controlled drug delivery. When subtle changes in chemical composition cascade into a physical signal with considerable amplitude and clarity, such

supra-amphiphile systems can play a part in the analysis of chemicals of interest with outstanding sensitivity and selectivity.

Supra-amphiphiles provide a delicate platform for combining molecular architecture and functional assembly. For example, supra-amphiphiles bearing photosensitizer moieties may function as supramolecular photosensitizers with the enhanced generation of singlet oxygen, which can be effectively used to kill bacteria and pathogenic tissues, leading to a new horizon in supramolecular photodynamic therapy. Highly ordered assemblies of supra-amphiphiles can be used to locate and orient catalytic centers in a controlled manner, thus providing a new avenue for highly efficient enzyme mimics.

1.7 Outlook

The concept of supra-amphiphiles originates from molecular amphiphiles or surfactants, but research into supra-amphiphiles has now been extended much further, with a focus on the integration of structural motifs with various functions. Supra-amphiphiles function *via* their formation and disassociation under specific circumstances or by constructing certain structures as platforms integrating various functional components into one system. The applications of supra-amphiphiles are profoundly intertwined in the dynamic nature of noncovalent interactions, which is the foundation of their responsiveness, reversibility and adaptivity. It is well known that structure dictates properties, which further determine function, and therefore the promotion of this area can be reinforced by the discovery of new motifs, such as new molecular building blocks and interacting pairs. Detailed characterization of the structures and self-assembly processes is needed to investigate the correlation between structure and properties. Although there have been extensive studies on the utilization of supra-amphiphiles, real practical applications are still beyond the horizon. Strategies to prepare supra-amphiphiles need to be conducted more frequently in the condensed state rather than in solution, such as on surfaces, in liquid crystals or on other solids, because materials with fixed shapes and volumes are usually more convenient to apply and hybridize with other devices. The development of applicable supra-amphiphile systems will benefit from the interactive evolution between theoretical research and practical exploration. This field is far from over and is an area of research where we can make full use of our imagination.

References

1. C. Wang, Z. Wang and X. Zhang, *Acc. Chem. Res.*, 2012, **45**, 608–618.
2. T. Kunitake, Y. Okahata, K. Tamaki, F. Kumamaru and M. Takayanagi, *Chem. Lett.*, 1977, **6**, 387–390.
3. A. Gulik, V. Luzzati, M. De Rosa and A. Gambacorta, *J. Mol. Biol.*, 1985, **182**, 131–149.
4. J.-H. Fuhrhop and T. Wang, *Chem. Rev.*, 2004, **104**, 2901–2938.
5. F. M. Menger and C. A. Littau, *J. Am. Chem. Soc.*, 1991, **113**, 1451–1452.

6. H. Ringsdorf, B. Schlarb and J. Venzmer, *Angew. Chem., Int. Ed.*, 1988, **27**, 113–158.
7. Z. Lifeng and A. Eisenberg, *Science*, 1995, **268**, 1728–1731.
8. M. Jiang, A. Eisenberg, G. Liu and X. Zhang, *Macromolecular Self-Assembly*, Science Press, 2006.
9. Y. Wang, H. Xu and X. Zhang, *Adv. Mater.*, 2009, **21**, 2849–2864.
10. X. Zhang, M. Wang, W. Tao, S. Jiang and Z. Wang, *J. Am. Chem. Soc.*, 2004, **126**, 6572–6573.
11. B. Zou, M. Wang, D. Qiu, X. Zhang, L. Chi and H. Fuchs, *Chem. Commun.*, 2002, **9**, 1008–1009.
12. B. Song, H. Wei, Z. Wang, X. Zhang, M. Smet and W. Dehaen, *Adv. Mater.*, 2007, **19**, 416–420.
13. G. Wu, J. Thomas, M. Smet, Z. Wang and X. Zhang, *Chem. Sci.*, 2014, **5**, 3267.
14. G. Wu, P. Verwilst, K. Liu, M. Smet, C. F. J. Faul and X. Zhang, *Chem. Sci.*, 2013, **4**, 4486.
15. J. Xu, G. Wu, Z. Wang and X. Zhang, *Chem. Sci.*, 2012, **3**, 3227–3230.
16. Y. Liu, P. G. Jessop, M. Cunningham, C. A. Eckert and C. L. Liotta, *Science*, 2006, **313**, 958–960.
17. Y. Ding, S. Chen, H. Xu, Z. Wang, X. Zhang, T. H. Ngo and M. Smet, *Langmuir*, 2010, **26**, 16667–16671.
18. Q. Yan, R. Zhou, C. Fu, H. Zhang, Y. Yin and J. Yuan, *Angew. Chem., Int. Ed.*, 2011, **50**, 4923–4927.
19. Q. Yan and Y. Zhao, *Chem. Commun.*, 2014, **50**, 11631–11641.
20. Y. Ding, Y. Kang and X. Zhang, *Chem. Commun.*, 2015, **51**, 996–1003.
21. M. Wang, X. Gu, G. Zhang, D. Zhang and D. Zhu, *Anal. Chem.*, 2009, **81**, 4444–4449.
22. R. J. Amir, S. Zhong, D. J. Pochan and C. J. Hawker, *J. Am. Chem. Soc.*, 2009, **131**, 13949–13951.
23. M. A. Azagarsamy, P. Sokkalingam and S. Thayumanava, *J. Am. Chem. Soc.*, 2009, **131**, 14184–14185.
24. M. Haubs and H. Ringsdorf, *Angew. Chem., Int. Ed. Engl.*, 1985, **10**, 882–883.
25. M. Haubs and H. Ringsdorf, *Nouv. J. Chim.*, 1987, **11**, 151.
26. J. Jiang, X. Tong and Y. Zhao, *J. Am. Chem. Soc.*, 2005, **127**, 8290–8291.
27. Y. Jiang, Y. Wang, N. Ma, Z. Wang, M. Smet and X. Zhang, *Langmuir*, 2007, **23**, 4029–4034.
28. Y. Jiang, P. Wan, M. Smet, Z. Wang and X. Zhang, *Adv. Mater.*, 2008, **20**, 1972–1977.
29. X. Zhang and C. Wang, *Chem. Soc. Rev.*, 2011, **40**, 94–101.
30. G. Zhao, *Physical Chemistry of Surfactants*, Peking University Press, 1991.
31. J.-M. Lehn, *Supramolecular Chemistry: Concepts and Perspectives*, Wiley-VCH, 1995.
32. Y. Kang, K. Liu and X. Zhang, *Langmuir*, 2014, **30**, 5989–6001.
33. Y. Kang, X. Tang, Z. Cai and X. Zhang, *Adv. Funct. Mater.*, 2016, **26**, 8920–8931.

CHAPTER 2

Supra-Amphiphiles Based on Host–Guest Interactions

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2.1 Macrocyclic Molecules for Host–Guest Interactions

The study of host–guest interactions is inspired by molecular recognition in biology. In living organisms, molecules and other species can specifically recognize and non-covalently bind with each other if they are complementary in shape and interactions. The specific binding of enzymes and substrates, antigens and antibodies, hormones and acceptors can all be described as molecular recognition. In the field of supramolecular chemistry, when two or more molecules specifically recognize and bind together, a "host" is usually defined as an organic molecule or ion whose binding sites converge in the complex, whereas a "guest" is defined as any molecule or ion whose binding sites diverge in the complex. The host–guest interaction displays good selectivity, a high binding strength and stimuli responsiveness, making it an important driving force in the construction of functional supramolecular systems. Several types of synthetic macrocycles—such as crown ethers,

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cyclodextrins, calixarenes, pillararenes and cucurbiturils—have been developed as hosts to construct host–guest systems. We provide an introduction to the properties and features of these macrocycles before illustrating their use in the formation of supra-amphiphiles based on host–guest interactions.

2.1.1 Crown Ethers

Crown ethers are known as the first generation of macrocyclic host molecules[1–3] and are cyclic molecules consisting of several repeating $-CH_2-O-CH_2-$ units (Figure 2.1a). Crown ethers have a cavity in the center that can accommodate a suitable ion as a host due to the ion–dipole attraction between the O atoms on the crown ether and the guest ions. Inorganic or organic ions—such as metal, ammonium and pyridinium ions—can be accommodated in the cavity of a crown ether as a guest. Crown ethers are able to complex with alkali ions, which are difficult to complex with other organic ligands. For example, [18]-crown-6 can accommodate a K^+ ion in its cavity with an association constant as high as 1.2×10^6 mol^{-1} L (in methanol, 293 K). In this way, [18]-crown-6 enables some inorganic potassium salts to become soluble in nonpolar organic

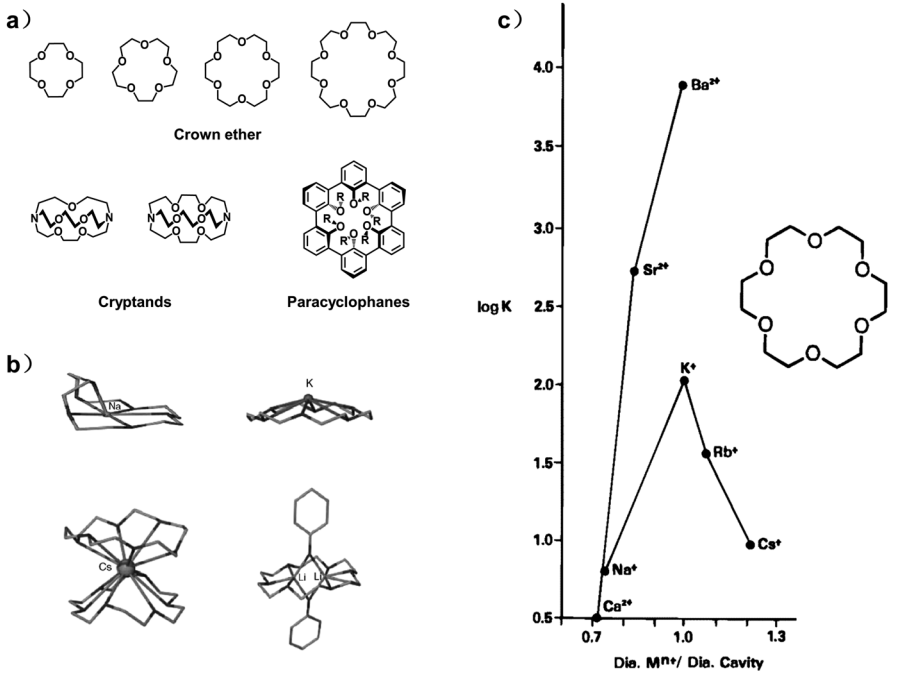

Figure 2.1 (a) Molecular structures of crown ethers, crytands and paracyclophanes. (b) Configuration of host–guest complexes based on [18]-crown-6. (c) Log *K* values at 25 °C for the interaction of [18]-crown-6 with alkali and alkaline earth ions *versus* the ratio of cation diameter to the [18]-crown-6 cavity diameter. Reproduced with permission from J. S. Bradshaw and R. M. Izatt, Crown ethers: the search for selective ion ligating agents, *Acc. Chem. Res.*, 1997, **30**, 338. Copyright (1997) American Chemical Society.

solvents. Figure 2.1b shows the configuration of host–guest complexes formed with [18]-crown-6 and different alkali metal ions; K^+ best matches the cavity size of [18]-crown-6 among these ions. The association constant of K^+ and [18]-crown-6 in water is higher than that for other alkali ions (Figure 2.1c).[4] Crown ethers usually prefer guest ions with a suitable size for their inner cavity, as indicated by the higher association constant. This means that the association of the crown ether and its guest is selective. This selectivity is a significant feature of host–guest interactions; in other words, a strong host–guest interaction requires that the host and guest molecules match each other in shape, size and even charge distribution. This observation is one of the basic principles of host–guest interactions for crown ethers and other macrocyclic hosts.

After the discovery of crown ether, two types of cyclic molecules with similar, but more complex, structures—cryptands and paracyclophanes—were successfully prepared and investigated as new "host" molecules. Three chemists, C. Pedersen, J.-M. Lehn and D. Cram, shared the 1987 Nobel Prize in Chemistry for the preparation and investigation of these extraordinary cyclic molecules, their development and the use of molecules with structure-specific interactions of high selectivity.[5–7]

2.1.2 Cyclodextrins

Cyclodextrins (CDs) are cyclic oligosaccharides composed of D-glucose units connected by α-1,4-glucosidic linkages. CDs were firstly obtained from natural products by Villiers in 1891,[8] and their structures were reported by Schardinger in 1903.[9] The CD ring has a bucket-like shape (Figure 2.2b). The exterior of CD molecules is hydrophilic because of the exposed hydroxyl groups, whereas the interior is a hydrophobic cavity and allows one or more hydrophobic molecules to be encapsulated as guests. CDs containing six, seven and eight repeating D-glucose units are most commonly used as host molecules and are called α-, β-, and γ-cyclodextrins (α-, β- and γ-CD), respectively, for convenience. Each CD has a hydrophobic cavity with a unique size (Figure 2.2; Table 2.1).[9] In a similar manner to crown ethers, CDs can also selectively accommodate guest molecules. In general, derivatives of benzene, cyclohexane and adamantane fit better with β-CD than with α-CD. One example is that the association constant of α-CD and benzene is only 32 mol^{-1} L because the cavity of α-CD is too small to accommodate benzene (Figure 2.2c). However, the association constant of β-CD and benzene can be five times larger because the hydrophobic cavity of β-CD is large enough to contain the whole benzene ring. Another remarkable example is the host–guest complexation of adamantane derivatives with β-CD, which is 100 times stronger than that for α-CD. Linear alkyl chains with smaller sizes usually prefer α-CD. For example, heptane has a larger association constant with α-CD (6.6×10^3 mol^{-1} L) than β-CD (2.6×10^3 mol^{-1} L). γ-CD is suitable for encapsulating polycyclic aromatic compounds—for example, pyrene—or two small hydrophobic molecules. More details about the association behavior of CDs and their guest molecules were discussed in a 1998 review by Rekharsky and Inoue.[10]

CDs are cheap, easily prepared, nontoxic and can encapsulate various liposoluble organic molecules in water.[11] These properties make CDs one of the most popular macrocyclic hosts in the field of supramolecular chemistry. They have been widely used for organic catalysis,[12] drug delivery,[13] molecular motors,[14] gels,[15] polyrotaxane,[16] self-healing materials[17] and as highly flexible elastomers.[18,19]

To fabricate supramolecular assemblies with the desired properties and functions, CDs often need to be conjugated with other organic molecules or

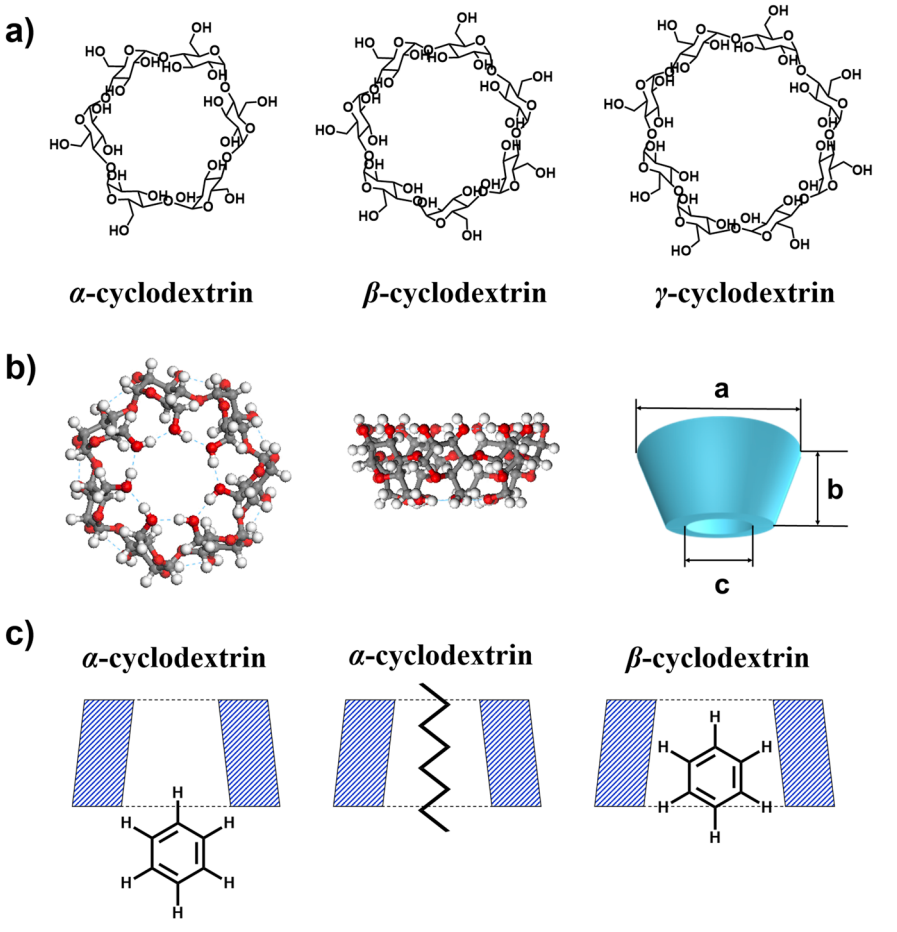

Figure 2.2 (a) Molecular structures of α-, β- and γ-cyclodextrin; (b) bucket-like shape of the β-cyclodextrin ring; and (c) the selective accommodation of cyclodextrins.

Table 2.1 Sizes of the α-, β- and γ-CD rings shown in Figure 2.2b.

Parameter	*a* (nm)	*b* (nm)	*c* (nm)
α-CD	1.37	0.78	0.57
β-CD	1.53	0.78	0.78
γ-CD	1.69	0.78	0.95

polymers, or are used to modify solid surfaces. Unfortunately, the modification of CDs is challenging because of the presence of the hydrophobic cavity and the large number of hydroxyl groups. Hydroxyl groups at the 2-, 3- and 6-positions of D-glucose have similar reactivities and make selective modification extremely difficult. In addition, the hydrophobic cavity often complexes with the reactant and directs it to react at an unexpected place. The modification of CDs is generally performed on the 6-position hydroxyl groups because the primary hydroxyl group is more nucleophilic and less sterically hindered. Even so, the synthetic conditions should be carefully controlled to avoid the participation of the hydroxyl groups on the 2- or 3-positions.[20]

2.1.3 Calixarenes and Pillararenes

Calixarene is a type of macrocyclic molecule synthesized by phenol–formaldehyde condensation, which is a famous reaction used to prepare the widely available commercial resin Bakelite. Research into the cyclic condensation of phenol and formaldehyde can be traced back to the 1940s. Zinke and coworkers obtained products with very high melting points when they treated various *p*-alkylphenols with aqueous formaldehyde and sodium hydroxide at elevated temperatures. The products were proved to be cyclic tetramers with a calix-shaped structure (Figure 2.3) and were termed calixarene.[21,22] In some cases, these moieties can also be described as calix[*n*]arene, according to the number of repeating units *n*.

From 1978, Gutsche published a series of papers reporting in detail the synthesis, modification and host–guest complexation of calixarenes.[21] Compared with CDs, calixarenes are much easier to modify. The lower rim of calixarenes can be simply modified by nucleophilic etherification as a result of the presence of hydroxyl groups. Calixarenes modified on the upper rim can be synthesized by the condensation of formaldehyde and *p*-substituted phenol. The upper rim can also be modified by strategies such as the Claisen rearrangement[23] and Mannich reaction.[24] Shinkai *et al.* were the first to obtain a water-soluble calixarene by sulfonation of the upper rim.[25] Because various calixarenes can be synthesized with different substituents, a wide range of molecules can be a guest in calixarenes, including metal or organic ions, neutral organic molecules, amino acids or even molecules as large as C_{60}. A remarkable example reported by Shinkai *et al.* showed that calix[5 or 6]arene modified with $-SO_3Na$ on the upper rim and $-CH_2COOH$ on the lower rim

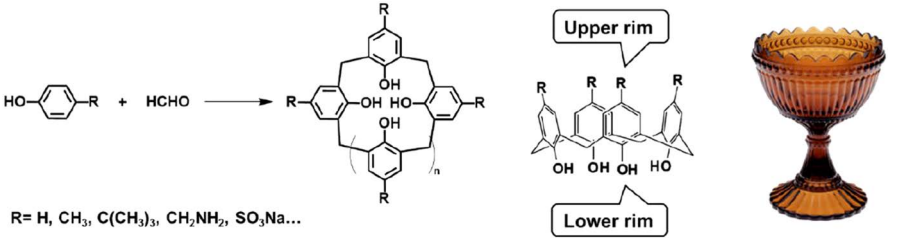

Figure 2.3 Molecular structure of calixarene.

was able to selectively accommodate UO_2^{2+}.[26] This showed that calixarenes have great potential utility in the enrichment of uranium from seawater.

Pillararene or pillar[*n*]arene refers to another class of macrocyclic molecules with a similar structure to calixarenes (Figure 2.4a). Pillararene was first reported in 2008 by Ogoshi and coworkers as a product of the condensation of 1,4-dimethoxybenzene and paraformaldehyde in the presence of the Lewis acid $BF_3O(C_2H_5)_2$.[27,28] Pillararene consists of several hydroquinone units linked by methylene groups at the *p*-positions. This linkage makes the macrocyclic molecule pillar-shaped, with the cross-section of the pillar as an equilateral polygon (Figure 2.4b and c). The cavity of pillararenes is rigid and electron-rich, thus electron-deficient guests with a suitable size—such as quaternary ammonium, pyridinium, imidazodium and viologen derivatives—are preferred. Similar to calixarenes, pillararenes are easily modified or functionalized by virtue of the existence of the two –OH groups on both rims.[29]

2.1.4 Cucurbiturils

The molecular structure of cucurbituril (CB) is shown in Figure 2.5a. Cucurbituril can be described in more detail as cucurbit[*n*]uril (CB[*n*]) according to the number *n* of repeating glycol units (Figure 2.5a). The earliest report of CBs dates back to 1905 by Behrend *et al.*[30] and the molecular structure of CBs was characterized in 1981 by Freeman *et al.*[31] However, the CBs could not be studied in detail until the 2000s because of difficulties in isolating the CB homologues containing different numbers of glycol units from the crude product. From 2000 to 2002, Kim and coworkers successfully synthesized

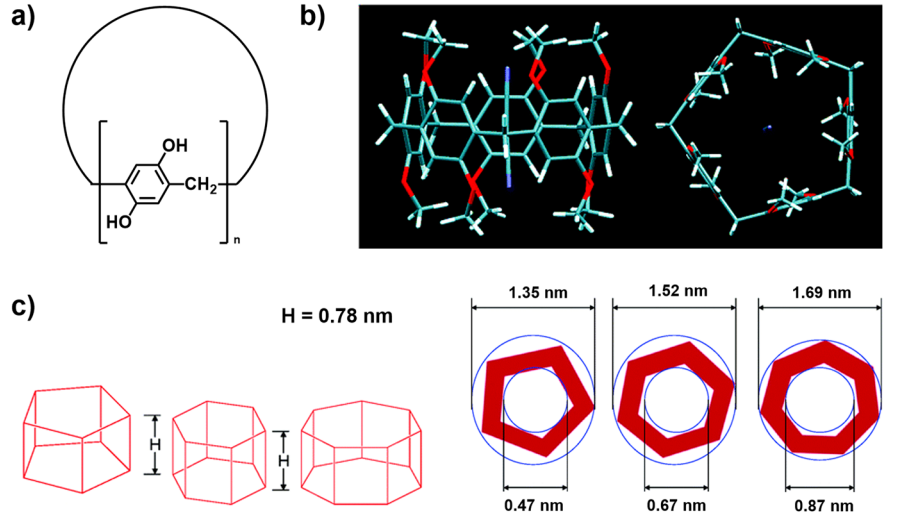

Figure 2.4 (a) Molecular structure of pillar[*n*]arene. (b) Crystal structure of methyl-modified pillar[5]arene from the side (left) and upper view (right). (c) Molecular size of pillar[*n*]arene, $n = 5$, 6 and 7. Reproduced with permission from M. Xue, Y. Yang, X. D. Chi, Z. B. Zhang and F. H. Huang, Pillararenes, a new class of macrocycles for supramolecular chemistry. *Acc. Chem. Res.*, 2012, **45**, 1294. Copyright (2012) American Chemical Society.

and isolated CB[5], CB[6], CB[7], CB[8] and CB[10], which significantly progressed research into CBs.[32–34]

Among the different types of cucurbiturils, CB[6], CB[7] and CB[8] are most commonly used as host molecules. Similar to the macrocyclic hosts mentioned earlier, CBs also have a hydrophobic cavity whose size is determined by the number of repeating units (Figure 2.5c and Table 2.2), so that each kind of CB has its own suitable guest. CB[7] is suitable for accommodating one aromatic molecule such as benzene, naphthalene, anthracene, adamantane and their derivatives. However, CB[6] is only suitable for encapsulating a short alkyl chain. The cavity of CB[8] is large enough to contain two stacked aromatic rings. Along with this line of study, more and more host–guest complexation properties of CBs and their corresponding guest molecules were studied.[35,36] In general, the association constant of CBs toward guest molecules in water is much higher than that of CDs. The rims of the cavity of CBs are negatively charged (Figure 2.5b) due to the carbonyl groups of the repeating units. This

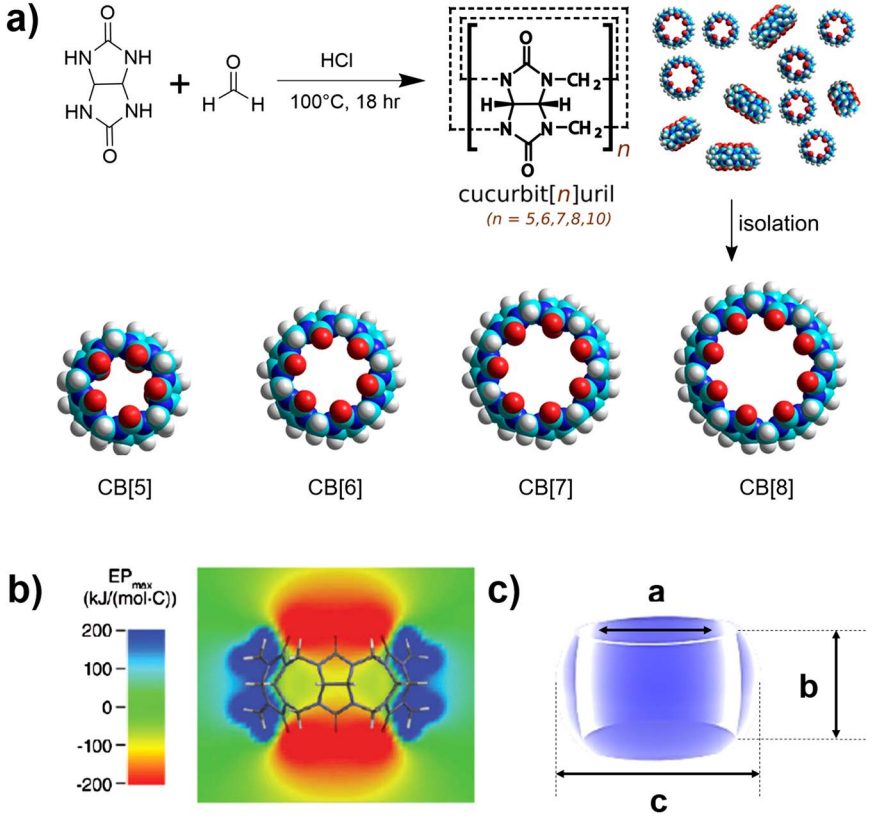

Figure 2.5 (a) Synthesis and molecular structure of CBs; (b) calculated electrostatic potential for CB[6]; and (c) the barrel-like shape of the CB ring. Reproduced with permission from S. J. Barrow, S. Kasera, M. J. Rowland, J. del Barrio and O. A. Scherman, Cucurbituril-based molecular recognition, *Chem. Rev.*, 2015, **115**, 12320. Copyright (2015) American Chemical Society.

Table 2.2 Parameters of the CB[5], CB[6], CB[7] and CB[8] rings shown in Figure 2.5c.

Parameter	Portal diameter (*a*) (nm)	Height (*b*) (nm)	Outer diameter (*c*) (nm)
CB[5]	0.24	0.91	1.31
CB[6]	0.39	0.91	1.44
CB[7]	0.54	0.91	1.60
CB[8]	0.69	0.91	1.75

means that CBs always prefer guest molecules with positive charges. The association constant of CB[7] and *N*,*N*,*N*-trimethyl-1-ammonium adamantane is as high as 1.7×10^{12} mol^{-1} L, whereas the association constant of CB[7] with 1-adamantane carboxylate sodium is only 2.0×10^{5} mol^{-1} L.

As CBs usually have a much stronger affinity with guest molecules than CDs, CBs have been used to catalyze chemical reactions,[37] protect sensitive bonds[38] and to fabricate functional surfaces,[39–41] supramolecular polymers[42] and soft materials.[43] Functional CB-based self-assembly is now a very active field of supramolecular chemistry. However, compared with CDs, a serious disadvantage of CBs is their poor solubility in water. Even CB[7], which has the highest aqueous solubility of all CBs, has a solubility <20 mmol L^{-1}, far lower than that of β-CD. This poor solubility may limit the application of CBs in materials science. To overcome this shortcoming, a highly soluble guest molecule with a positive charge is usually used to improve the solubility of the host–guest complex. Another effective strategy to enhance the solubility of CBs is to add an appropriate group onto the CB ring. The modification of CBs may open up possibilities for preparing CB-based materials with interesting properties and practical functions. Therefore new strategies to prepare appropriately modified CBs are urgently required.

2.2 Supra-Amphiphiles Based on Crown Ethers

Although crown ethers were the first generation of macrocyclic host molecules, reports of supra-amphiphiles based on crown ethers are rare. This may be attributed to the limited choice of guest molecules. Except for organic ammonium salts and viologen derivatives, no guest molecule is suitable for fabricating supra-amphiphiles. Also, the interaction between crown ethers and organic ammonium salts or viologen derivatives are usually not sufficiently strong, especially in water.[44] The association constants are of the order of 10^{1}–10^{3} mol^{-1} L, which indicates difficulties for the fabrication of robust supra-amphiphiles driven by host–guest interactions based on crown ethers.

One example of a supra-amphiphile based on crown ether was reported by Huang and coworkers.[45] They used a hydrophilic polyethylene glycol (PEG)-terminated bis(*m*-phenylene)-32-crown-10 with two –COO^{-} groups and a viologen dication derivative containing a long hydrophobic alkyl chain to fabricate a crown ether based supra-amphiphile (Figure 2.6). The two additional –COO^{-} groups were introduced to enhance the host–guest interaction by electrostatic attraction, but the association constant was only 1.5×10^{3} mol^{-1} L. This meant that the supra-amphiphile could not be prepared at

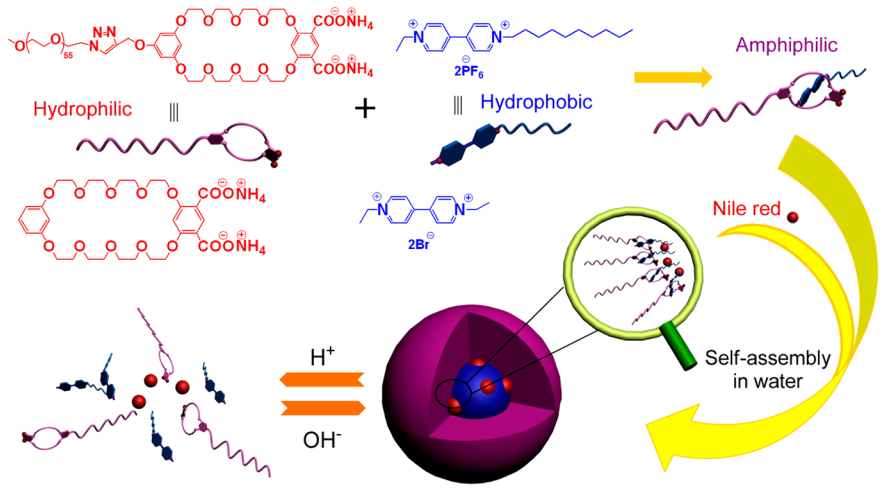

Figure 2.6 A supra-amphiphile based on crown ether and its pH-responsive self-assembly. Reproduced with permission from X. F. Ji, J. Y. Li, J. Z. Chen, X. D. Chi, K. L. Zhu, X. Z. Yan, M. M. Zhang and F. H. Huang, *Macromolecules*, 2012, **45**, 6457. Copyright (2012) American Chemical Society.

very low concentrations. At a concentration of 0.5 mmol L^{-1}, it was observed that the supra-amphiphile formed and self-assembled as dispersed micelles with a diameter of 50 nm in water. The introduction of the two –COO^- groups introduced pH-responsiveness to the supra-amphiphile. The –COO^- groups could be converted into neutral –COOH groups by tuning the pH to 3.0. This lowering of the pH weakened the complexation between the crown ether unit and the viologen moiety, resulting in the destruction of the supra-amphiphile and the micelles. When the pH was tuned back to 7.0, the supra-amphiphile and the micelles formed again. Nile Red, a hydrophobic dye, could be encapsulated in the hydrophobic core of the micelles formed by the supra-amphiphile. When the pH was adjusted to 3.0, the destruction of the supra-amphiphile and the micelles released the Nile Red. These results indicated that the supra-amphiphiles were not only applicable for the solubilization of hydrophobic molecules, but could also realize the controlled release of the encapsulated molecules as a result of their stimuli-responsive properties.

A similar strategy can be used to fabricate a pH-responsive polymeric supra-amphiphile (Figure 2.7a).[46] It should be pointed out that the morphology of the aggregates formed by the polymeric supra-amphiphiles can be easily tuned by the molar ratio of the two building blocks (Figure 2.7b). The length ratio of the hydrophilic and hydrophobic segments, which can determine the packing parameter, can be adjusted by tuning the molar ratio. When the hydrophilic block is longer than the hydrophobic block, the supra-amphiphile self-assembles into spherical micelles. Conversely, its aggregates would be vesicles. If the lengths of the two blocks are approximately equal, disk-like micelles are obtained. This shows that the self-assembly of the supra-amphiphile is more controllable than that of covalently synthesized amphiphiles.

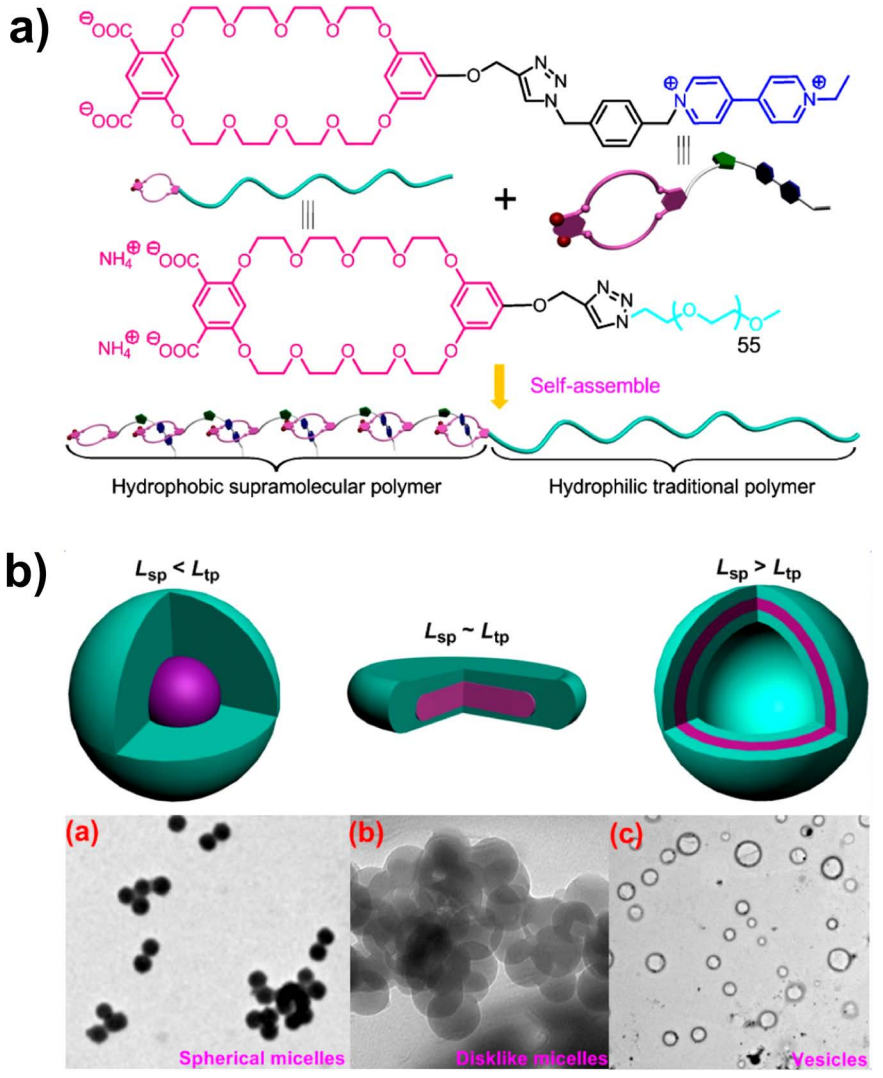

Figure 2.7 (a) Polymeric supra-amphiphile based on crown ether; and (b) self-assembly of the supra-amphiphile. Reproduced with permission from X. F. Ji, S. Y. Dong, P. F. Wei, D. F. Xia and F. H. Huang, A novel diblock copolymer with a supramolecular polymer block and a traditional polymer block: preparation, controllable self-assembly in water, and application in controlled release, *Adv. Mater.*, 2013, **25**, 5725. Copyright © 2013 Wiley-VCH Verlag GmbH & Co. KGaA.

2.3 Supra-Amphiphiles Based on Cyclodextrin

To fabricate a robust supra-amphiphile, the driving force should be sufficiently strong. The adamantyl group is hydrophobic and of a suitable size for encapsulation in β-CD. The association constant is of the order of about

10^3–10^5 mol^{-1} L. Therefore the host–guest interaction between the adamantyl group and *β*-CD is an appropriate driving force for fabricating supra-amphiphiles.

An early example was reported in 2004 by Craig and coworkers.[47] The hydrophobic building block was a *β*-CD modified by two *n*-$C_{16}H_{33}$ chains and the hydrophilic building block was a PEG-terminated adamantane (Figure 2.8a). The supra-amphiphile self-assembled into rectangular aggregates. Similarly, in 2009 Cho and Allcock fabricated a polymeric supra-amphiphile by host–guest complexation between *β*-CD and a hydrophobic di-copolymer containing adamantyl groups (Figure 2.8b).[48] The supra-amphiphile formed and self-assembled into micelles when the ratio of *β*-CD to adamantyl groups reached 0.3.

Supra-amphiphiles can be used to combine molecular architecture with functional assembly. A typical example was reported by Liu and coworkers.[49] Figure 2.9a shows that the supra-amphiphile could self-assemble into unusual giant nanotubes with a diameter of about 0.5 μm as a result of its bulky hydrophobic tail. As a result of the dynamic nature of the host–guest interaction, the giant nanotubes could easily be functionalized by adding *β*-CDs modified with selenium groups as active sites and guanidine groups as recognizing units (Figure 2.9b). The functionalized nanotubes exhibited catalytic properties similar to glutathione peroxidase. They showed good activity in catalyzing the reduction of H_2O_2 by glutathione and demonstrated potential applications in biosensors and biomedicine. Considering that the structure of the functionalized nanotubes is similar to that of cell membranes, this work provides a new strategy for building biomimetic functional nanomaterials and devices.

In addition to modifying CDs with functional groups, another strategy for introducing special properties and functions to CD-based supra-amphiphiles is

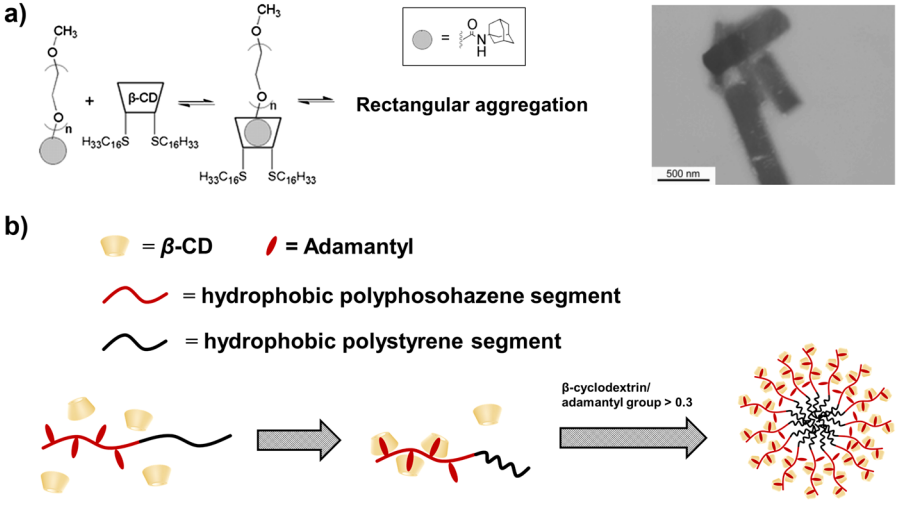

Figure 2.8 (a) Polymeric supra-amphiphile based on *β*-CD; and (b) self-assembly of the supra-amphiphile. Reproduced with permission from S. Y. Cho and H. R. Allcock, Synthesis of adamantyl polyphosphazene–polystyrene block copolymers, and *β*-cyclodextrin-adamantyl side group complexation, *Macromolecules*, 2009, **42**, 4484. Copyright (2009) American Chemical Society.

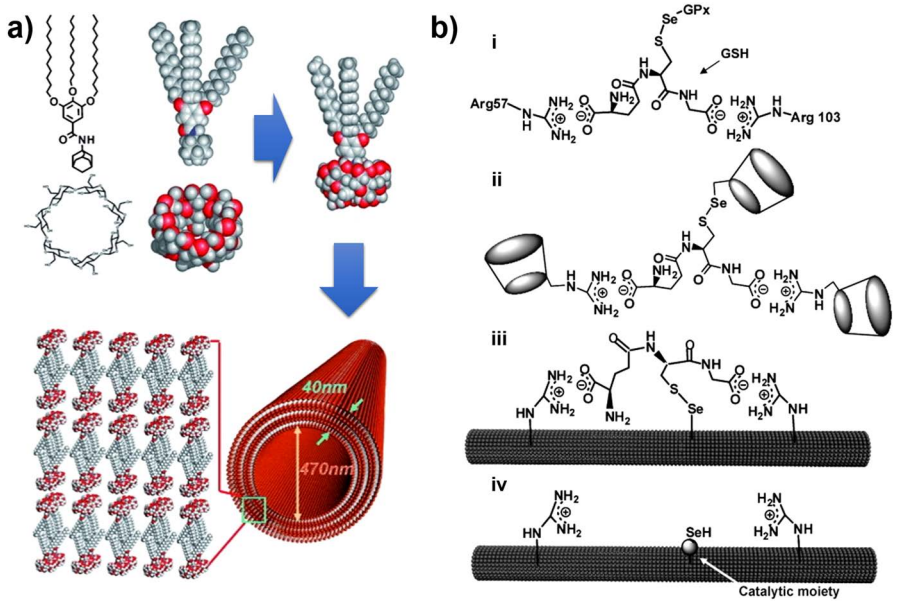

Figure 2.9 (a) The supra-amphiphile self-assembled into unusual giant nanotubes; and (b) the giant nanotubes were functionalized by adding β-CDs modified with selenium groups as active sites and guanidine groups as recognizing units. Reproduced with permission from Y. Tang, L. Zhou, J. Li, Q. Luo, X. Huang, P. Wu, Y. Wang, J. Xu, J. Shen and J. Liu, Giant nanotubes loaded with artificial peroxidase centers: self-assembly of supramolecular amphiphiles as a tool to functionalize nanotubes, *Angew. Chem., Int. Ed.*, 2010, **49**, 3920. Copyright © 2010 Wiley-VCH Verlag GmbH & Co. KGaA.

to use a stimuli-responsive guest. Azobenzene derivatives and ferrocene derivatives are two popular choices (Figure 2.10). Under UV irradiation (λ = 365 nm), the *trans* isomer of azobenzene, which is more thermodynamically stable, will isomerize to the *cis* configuration, while the *cis* isomer will change back to the *trans* form when the azobenzene is irradiated with visible light (λ = 425 nm) or heated. Unlike *trans*-azobenzene, which can be encapsulated in α- or β-CD, *cis*-azobenzene cannot be incorporated into the cavity of CDs due to its bent configuration. Hence the photo-controlled *cis–trans* isomerization can lead to the association and dissociation of the host–guest complex. Ferrocene is a neutral, hydrophobic molecule that can be accommodated in β-CD with an association constant of 10^3–10^4 mol^{-1} L. Once the Fe^{II} core is oxidized to Fe^{III}, the ferrocene is positively charged and water soluble, leading to dissociation of the complex.

The introduction of stimuli-responsive guests makes CD-based supra-amphiphiles very powerful tools for realizing controlled self-assembly and disassembly. By introducing an azobenzene group, Wang *et al.* prepared a rotaxane-like supra-amphiphile with α-CD for photo-controlled self-assembly (Figure 2.11).[50] The supra-amphiphile became hydrophilic when the azobenzene headgroup was included in the cavity of α-CD. Under UV irradiation, the *trans*-azobenzene converted to the *cis* form, forcing the α-CD to slide along the alkyl chain. The complex became amphiphilic and self-assembled into

micellar aggregates. After irradiation with visible light, the α-CD moved back to encapsulate the azobenzene, resulting in disassembly of the aggregates.

Another supra-amphiphile based on photo-controlled azobenzene/CD inclusion was reported by Wu and coworkers.[51] They functionalized a polyoxometalate with azobenzene groups on both sides to form a dumb-bell-shaped building block (Azo-POM). A bola-form supra-amphiphile was obtained when the two azobenzene groups of Azo-POM were encapsulated by a β-CD bearing a pyridine cation (β-CD-Py) (Figure 2.12a). It was shown that the supra-amphiphile self-assembled into very large right-hand twisted aggregates with

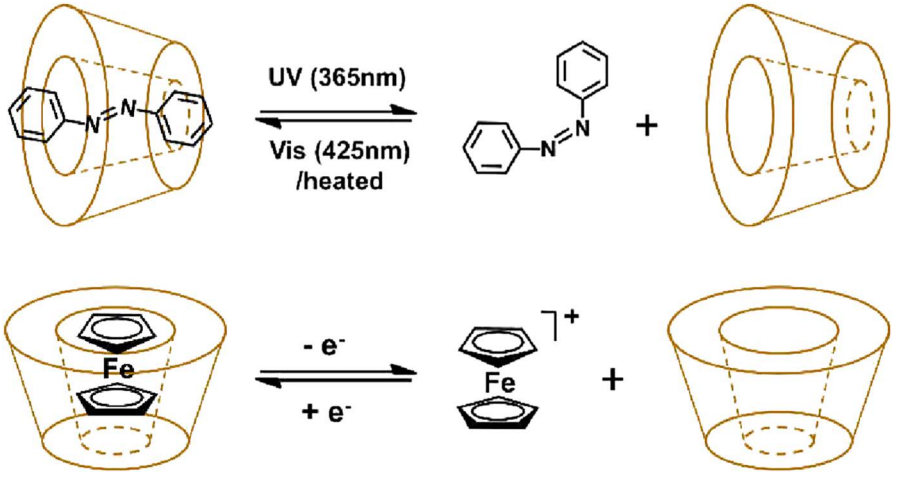

Figure 2.10 Photo-controlled host–guest interaction of azobenzene and α- or β-cyclodextrin and the redox-controlled host–guest interaction of ferrocene and β-cyclodextrin.

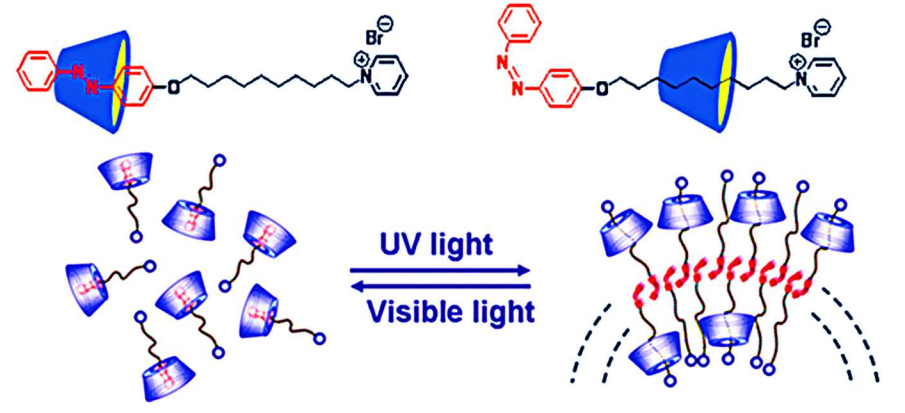

Figure 2.11 Photo-controlled rotaxane-like supra-amphiphile. Reproduced with permission from Y. Wang, N. Ma, Z. Wang and X. Zhang., Photo-controlled reversible supramolecular assemblies of an azobenzene-containing surfactant, *Angew. Chem., Int. Ed.*, 2007, **46**, 2823. Copyright © 2007 Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim.

a clear lamellar structure (Figure 2.12c). The size of the aggregates could be as large as about 10 μm. Interestingly, on UV irradiation for 2 h, the right-handed twisted assemblies converted to irregular nanofibers (Figure 2.12b), which were similar to the morphology of aggregates formed by *β*-CD-Py alone. After aging in the dark for 1 week, the right-handed twisted aggregates reformed as the *cis*-azobenzene isomerized to the thermodynamically stable *trans* form. Thus a photo-controlled self-assembly and disassembly process was achieved.

Similarly, the host–guest interaction between *β*-CD and ferrocene could be applied to fabricate voltage-responsive or redox-responsive supra-amphiphiles. As reported by Yuan and coworkers, a supra-amphiphile formed by *β*-CD-terminated polystyrene and ferrocene-terminated PEG could self-assemble into vesicles (Figure 2.13a).[52] After a +1.5 V stimulus for 5 h, the vesicles completely disassembled into small fragments (Figure 2.13c) because the neutral ferrocene group was oxidized to positively charged ferrocene and the host–guest complex dissociated. The vesicles could be approximately reformed to their original state by exerting a reductive voltage of −1.5 V. If Rhodamine B dye was encapsulated into the voltage-responsive vesicles, the controlled release of Rhodamine B could be realized. When the external potential was held at 1.0 V,

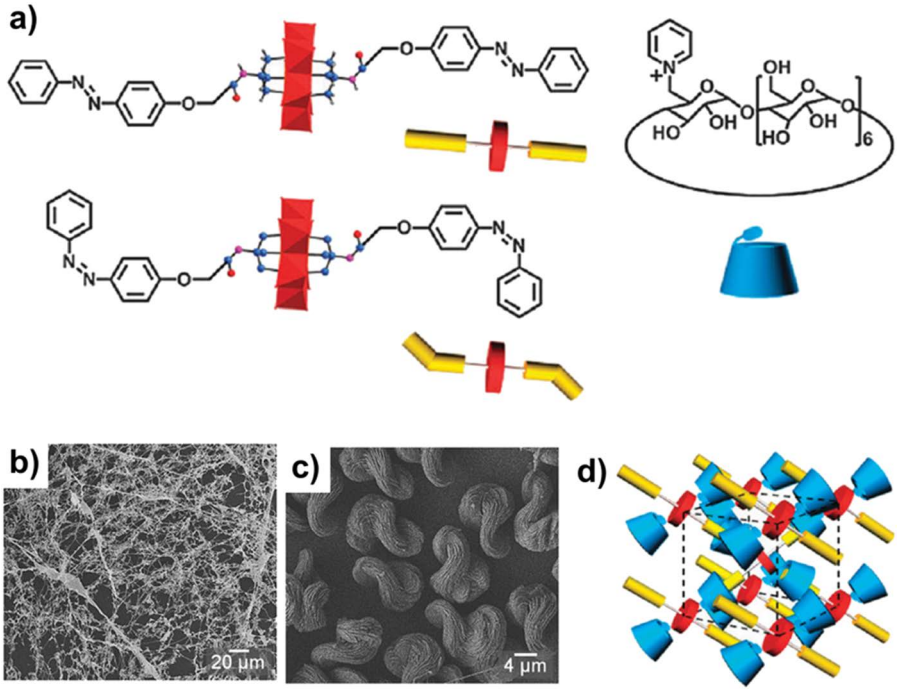

Figure 2.12 (a) Schematic chemical structures and representations of the azo-modified POM anion in its *trans* and *cis* state and the *β*-CD cation in the CD-Azo-POM complex; (b) irregular nanofibers; (c) right-handed twisted aggregates; and (d) possible packing model indexed from the X-ray diffraction pattern. Reproduced from ref. 51 with permission from the Royal Society of Chemistry.

the release lasted as long as 450 min; however, the release was complete within 32 min if the external potential was increased to 4.0 V. These results indicate that the kinetics of the controlled release realized by supra-amphiphiles may be tuned by the strength of the external stimulation.

In addition to azobenzene derivatives and ferrocene derivatives, other groups of a stimuli-responsive nature were also utilized in the fabrication of

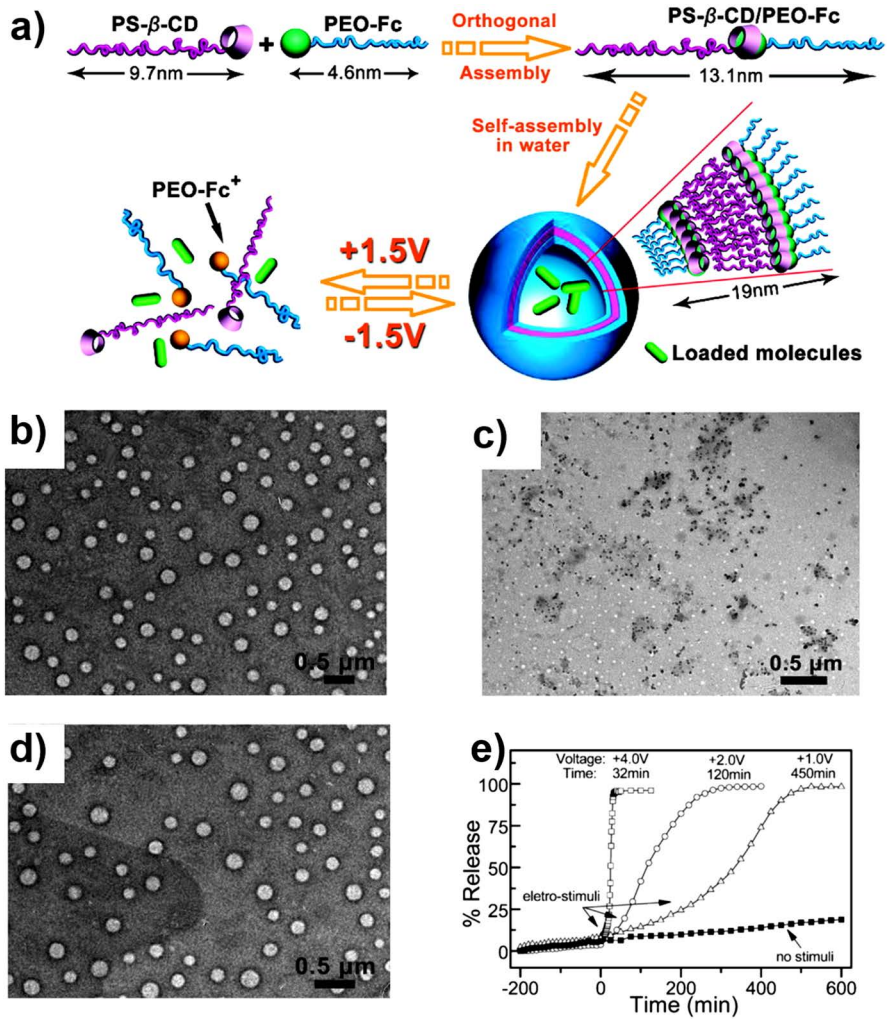

Figure 2.13 (a) Voltage-responsive supra-amphiphile based on CD; (b) vesicles formed by the supra-amphiphile; (c) dissociation of the vesicles with the +1.5 V stimulus for 5 h; (d) reformation of the vesicles; and (e) the variation in the release speed with external potential. Reproduced with permission from Q. Yan, J. Yuan, Z. Cai, Y. Xin, Y. Kang and J. Yin, Voltage-responsive vesicles based on orthogonal assembly of two homopolymers, *J. Am. Chem. Soc.*, 2010, **132**, 9268. Copyright (2010) American Chemical Society.

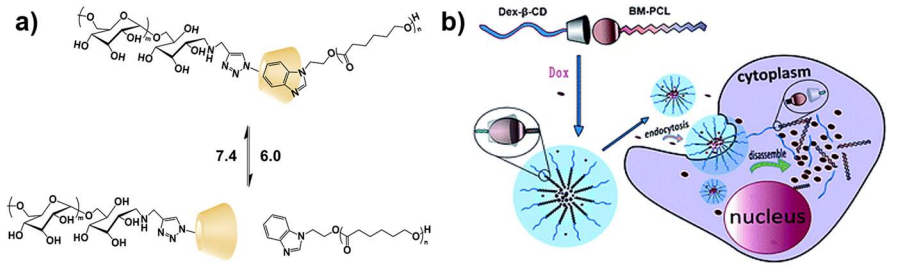

Figure 2.14 (a) pH-responsive supra-amphiphile based on benzimidazole and β-CD; and (b) the controlled release of doxorubicin. Reproduced from ref. 53 with permission from the Royal Society of Chemistry.

supra-amphiphiles for controlled self-assembly and controlled release. For instance, a neutral benzimidazole is hydrophobic and can be accommodated in the cavity of β-CD and then separated from β-CD and dissolved in water after being protonated by an acid (Figure 2.14). Therefore the host–guest interaction between benzimidazole and β-CD exhibits pH-responsiveness in aqueous solution. Chen and coworkers prepared a pH-responsive supra-amphiphile based on this interaction using benzimidazole-functionalized poly(ε-caprolactone) and β-CD-modified dextran.[53] At pH = 7.4 (physiological pH), the supra-amphiphile self-assembled into micelles with an average diameter of about 90 nm. These micelles can be used as nanocarriers for doxorubicin, a hydrophobic anticancer drug. The doxorubicin loaded into the micelles can be released rapidly into HepG2 cells as the intracellular pH of the tumor cells is as low as 5.5. A high cellular proliferation inhibition efficacy was achieved. These features of the micelles formed by the supra-amphiphile based on the host–guest interaction of benzimidazole and β-CD display promising applications in targeted drug delivery.

2.4 Supra-Amphiphiles Based on Calixarene or Pillararene

As supra-amphiphiles are usually studied in aqueous solution, water-soluble calixarenes and pillararenes are often adopted as the building block for fabricating supra-amphiphiles. For example, a typical supra-amphiphile reported by Basilio and García-Río was fabricated using dodecyltrimethylammonium bromide and sulfonated calix[6]arene.[54] It was observed that the supra-amphiphile had a more complicated self-assembly behavior than dodecyltrimethylammonium bromide itself, with two critical micelle concentrations.

Similar to the supra-amphiphiles based on CDs, the controlled assembly and disassembly of supra-amphiphiles based on calixarenes or pillararenes can also be realized by introducing guest moieties with stimuli-responsive properties, including photo-,[55] pH-,[56] redox-,[57] thermal,[58] enzyme[60] and even multi-stimuli responsiveness.[59] For example, Liu and coworkers fabricated an enzyme-responsive supra-amphiphile using a sulfonated calix[4]arene and natural enzyme-cleavable myristoylcholine as the guest molecule (Figure 2.15).[60] Myristoylcholine can be hydrolyzed to myristic acid and choline under catalysis with

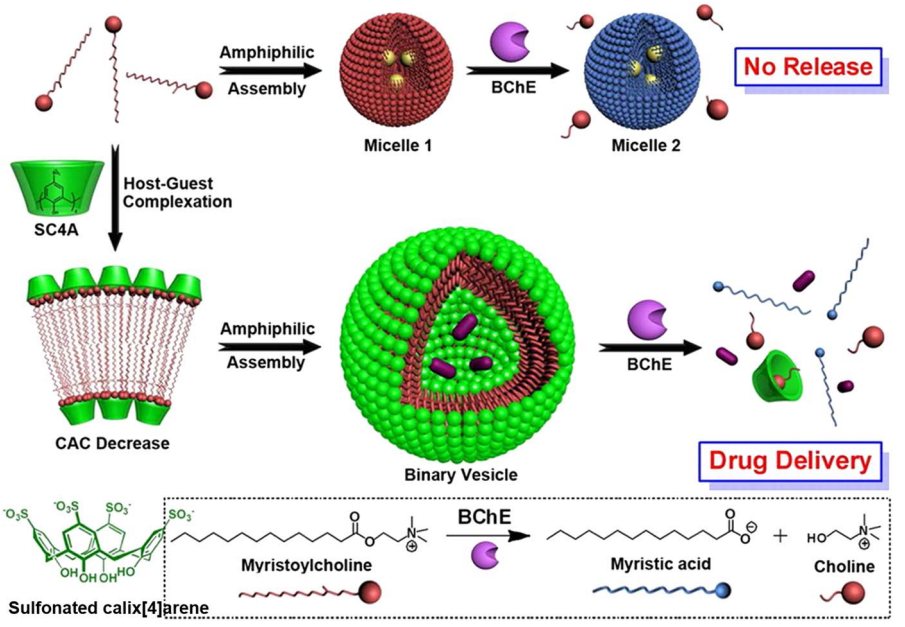

Figure 2.15 Enzyme-responsive supra-amphiphile based on calixarene and its controlled self-assembly and controlled drug delivery. Reproduced with permission from D. S. Guo, K. Wang, Y. X. Wang and Y. Liu., Cholinesterases-responsive supramolecular vesicle, *J. Am. Chem. Soc.*, 2012, **134**, 10244. Copyright (2012) American Chemical Society.

butyrylcholinesterase. Both myristoylcholine and myristic acid formed micelles with critical micelle concentrations of 2.5 and 4.5 mmol L^{-1}, respectively. However, on complexation with sulfonated calix[4]-arene, the supra-amphiphiles self-assembled into binary vesicles and the critical aggregation concentration (CAC) dramatically decreased to 0.02–0.03 mmol L^{-1}. These changes indicated that the supra-amphiphile had a better ability to self-assemble. Thus controlled self-assembly and delivery could be realized when the concentration of myristoylcholine was 0.10 mmol L^{-1}, which was in the range between the CAC of the supra-amphiphile and the building blocks. After adding cholinesterase, the supra-amphiphiles were cleaved into myristic acid and choline, which was encapsulated by calixarene, resulting in the dissociation of the vesicles and the release of the drugs loaded in the vesicular interior. Supra-amphiphiles with enzyme responsiveness may have potential applications in biotechnology.

Pillararenes can be used to prepare enzyme-responsive supra-amphiphiles in a similar way. Figure 2.16 shows a choline derivative guest (PyCh) encapsulated in a water-soluble pillar[5]arene to form a supra-amphiphile.[61] The PyCh itself could self-assemble into bilayered sheet-like aggregates driven by the π–π stacking of the pyrene groups, whereas the aggregates of the supra-amphiphile were spherical with an average diameter of about 250 nm. The CAC of the supra-amphiphile was measured as 1.25 μmol L^{-1}, much lower than the CAC of PyCh, which was 152 μmol L^{-1}. After adding acetylcholinesterase

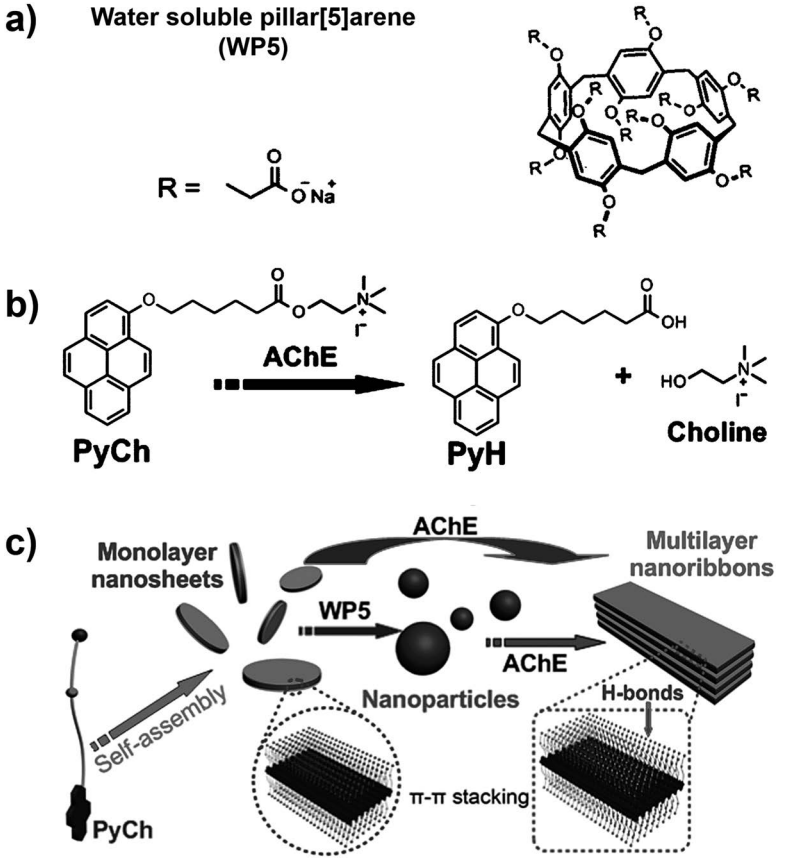

Figure 2.16 (a) Molecular structure of the water-soluble pillar[5]arene; (b) hydrolysis of PyCh catalyzed by AChE; and (c) enzyme-responsive self-assembly of the supra-amphiphile. Reproduced from ref. 61 with permission from the Royal Society of Chemistry.

(AChE), the supra-amphiphile dissociated and the residue (PyH) formed multilayered nanoribbons facilitated by the π–π stacking of the pyrene groups and hydrogen bonds of the carboxyl groups.

In addition to controlled self-assembly and controlled drug delivery, supra-amphiphiles can also be used to disperse carbon nanomaterials, including carbon nanotubes, graphene, C_{60} and C_{70}. Carbon nanomaterials have a range of attractive functions due to their large specific surface area, good photoelectric properties and thermal conductivity. However, carbon nanomaterials have a strong tendency to aggregate due to π–π stacking. Such aggregation significantly weakens their extraordinary functions. One strategy for preventing aggregation is modification of the surface of the carbon nanomaterials using amphiphiles with ionic headgroups and aromatic hydrophobic parts. The aromatic unit is able to associate onto the carbon nanomaterials by π–π interactions and the electrostatic repulsions of the ionic headgroups prevent the nanomaterials from aggregating, thus

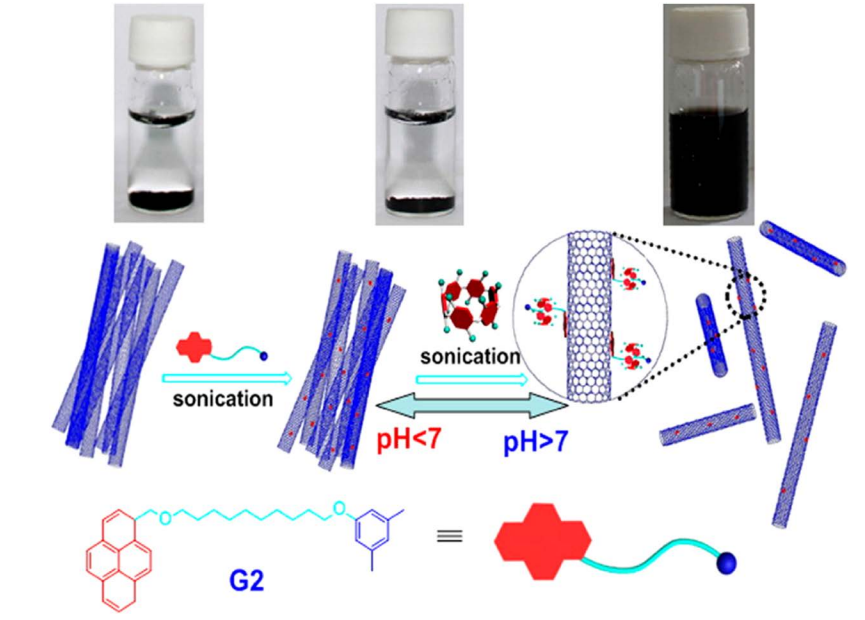

Figure 2.17 pH-responsive dispersion of carbon nanotubes in the presence of a supra-amphiphile. Reproduced with permission from G. Yu, M. Xue, Z. Zhang, J. Li, C. Han and F. Huang, A water-soluble pillar[6]arene: synthesis, host–guest chemistry, and its application in dispersion of multiwalled carbon nanotubes in water, *J. Am. Chem. Soc.*, 2012, **134**, 13248. Copyright (2012) American Chemical Society.

enhancing the solubility of the carbon nanomaterials. If a supra-amphiphile is used to replace the covalently synthesized amphiphile, a controllable dispersion and aggregation process can be realized. To this end, a building block terminated with a pyrene group was designed for contacting a carbon nanotube (Figure 2.17). The headgroup was accommodated in a pH-responsive water-soluble pillar[6]arene. At pH values >7, the pillar[6]arene was negatively charged, preventing the nanotube from aggregating. However, at pH values <7, the pillar[6]arene was neutral, leading to the aggregation and precipitation of the carbon nanotubes from solution.[62]

2.5 Supra-Amphiphiles Based on Cucurbiturils

Complexes of CBs and their guests are usually very stable and robust. For example, the association constant of CB[7] and 1-adamantanamine hydrochloride can be $>10^{12}$ mol^{-1} L. Although CBs have a disadvantage of unsatisfactory solubility, most of the guests preferred by CBs are positively charged and sufficiently water soluble; therefore the whole complex has good solubility. These considerations make CB-based host–guest interactions suitable for fabricating supra-amphiphiles.

Early in 2002, as soon as the successful isolation of the cucurbituril homologues was achieved, Kim and coworkers fabricated a supra-amphiphile by

mixing equimolar CB[8], 2,6-naphthalenediol and a viologen with a C_{12} or C_{16} alkyl chain.[63] The 2,6-naphthalenediol and viologen were bound together by the charge transfer interaction in CB[8] to form a hydrophilic headgroup. The hydrophobic tail was the C_{12} or C_{16} alkyl chain. The supra-amphiphile self-assembled into vesicles in water. The vesicles could be destroyed by oxidizing the 2,6-naphthalenediol to naphthoquinone with cerium(IV) ammonium nitrate because the naphthoquinone was not sufficiently electron-rich to bind the viologen moiety with charge transfer interactions for encapsulation. As well as destroying the electron-rich moieties, such as 2,6-naphthalenediol, the reduction of viologen can also weaken the charge transfer interactions and even destroy the whole complex. A typical example was reported by Zhang and coworkers.[64] A viologen with a C_8 alkyl chain ($RV8^{2+}$) and a naphthalene modified by a glucosamine (GlcNap) were encapsulated in CB[8] to form a supra-amphiphile. The supra-amphiphiles could self-assemble into vesicles 200–400 nm in diameter. When 1 equivalent of $RV8^{2+}$ was added and further reduced by $Na_2S_2O_4$, it was found that the free radical cation $RV8^{\bullet+}$ dimerized in the cavity of CB[8], driving the GlcNap out of the CB[8] and decomposing the supra-amphiphiles. When the mixture was exposed to air, $RV8^{\bullet+}$ was oxidized back to the original dicationic state ($RV8^{2+}$), which then interacted with free GlcNap to produce the supra-amphiphile again. Therefore the formation and decomposition of the supra-amphiphile was carried out in a reversible manner.

Using a stimuli-responsive guest is a feasible strategy for fabricating supra-amphiphiles for controlled assembly and disassembly. Adding one or more competitive guests is another strategy to control these processes. Scherman and coworkers fabricated a vesicle-forming supra-amphiphile using a pyrene imidazolium-labeled peptide and a viologen with a C_{16} alkyl chain (Figure 2.18).[65] The introduction of the peptide enabled the facile uptake of the vesicles by HeLa cells. The fluorescence of pyrene was significantly quenched due to the charge transfer interaction with the viologen and the cytotoxicity of viologen was significantly decreased because of the encapsulation by CB[8]. Interestingly, by adding different competitive guests, the disassembly of the supra-amphiphile could be triggered in different ways (Figure 2.18). When 1-adamantylamine was added, both the viologen moiety and the pyrene imidazolium-labeled peptide were driven out of the CB[8], leading to dissociation of the supra-amphiphile. The fluorescence of the pyrene partly recovered and the cytotoxicity of viologen increased significantly. About 60% of the HeLa cells were killed, as measured by the MTT assay. However, when 12 equivalents of 2,6-naphthalenediol were added, only the pyrene imidazolium-labeled peptide was displaced from the CB[8]. The fluorescence of the pyrene recovered and the residue was not cytotoxic because the viologen moiety was still encapsulated.

The π–π stacking of large aromatic moieties is unfavorable because their luminescent, photoelectric or catalytic properties can be significantly hindered by severe stacking. An effective strategy for avoiding stacking is covalently modifying the aromatic moieties by using bulky groups with significant steric hindrance on the edge, which can be called a covalent strategy. To avoid complicated synthetic procedures and to introduce controllability, a noncovalent or supramolecular strategy was developed to prevent π–π stacking. The

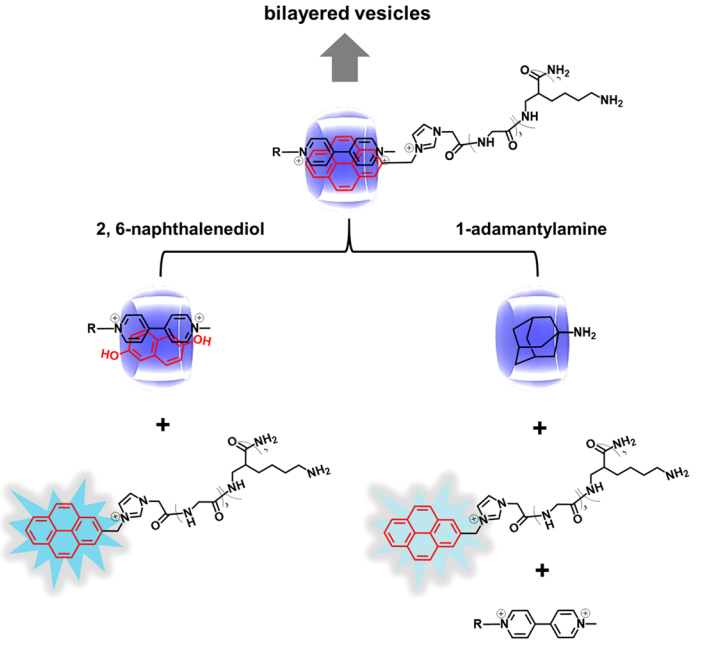

Figure 2.18 Peptide supra-amphiphile triggered by competitive guest.

aromatic moieties themselves or their side groups were encapsulated in macrocyclic hosts so that they were unable to stack. It is also possible to tune the stacking by the association and dissociation of the host–guest complexes. The strategy can thus be used to fabricate functional supra-amphiphiles. For example, Zhang *et al.* fabricated a supra-amphiphile by using a CB[7] host and a four-armed modified porphyrin (TPOR), which could catalyze the formation of $^1O_2$ as a supramolecular photosensitizer under irradiation with white light (Figure 2.19a). The efficiency of the $^1O_2$ generation of TPOR itself was unsatisfactory as a consequence of the π–π stacking of the porphyrin core. However, the $^1O_2$ generation was significantly improved by encapsulation in CB[7] because the bulky CB[7] weakened the close stacking of porphyrins through host–guest interactions. Very high $^1O_2$ generation and antibacterial efficiency could be achieved using this method. When 1-adamantanamine was added as a competitive guest, the TPOR was displaced, leading again to the low $^1O_2$ generation. The $^1O_2$ generation efficiency could be reversibly tuned by adding 1-adamantanamine and CB[7] alternately (Figure 2.19b). Other supra-amphiphiles with tunable fluorescence,[66] aggregation-induced emission,[67] surface activity[68] and free radical stability[69] have been explored using this supramolecular strategy.

2.6 Summary and Outlook

We have discussed the use of various macrocyclic hosts to fabricate supra-amphiphiles with controlled architecture and properties. The host–guest interaction can be different in terms of the structures of the hosts and guests,

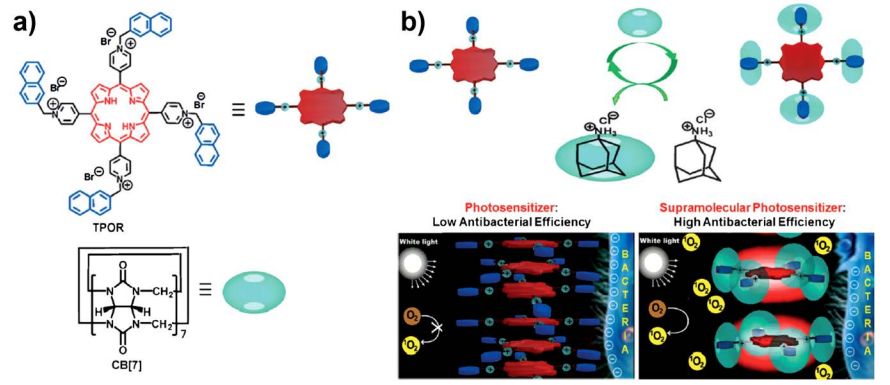

Figure 2.19 (a) Chemical structures of the TPOR (photosensitizers) and CB[7]; and (b) construction of the supra-amphiphile and the mechanism for the enhanced antibacterial efficiency of supra-amphiphile compared with that of TPOR. Reproduced with permission from K. Liu, Y. Liu, Y. Yao, H. Yuan, S. Wang, Z. Wang and X. Zhang, Supramolecular photosensitizers with enhanced antibacterial efficiency, *Angew. Chem. Int. Ed.*, 2013, **52**, 8285. Copyright © 2013 Wiley-VCH Verlag GmbH & Co. KGaA.

however, the host–guest interaction should be strong enough to fabricate supra-amphiphiles with well-defined compositions. The host–guest interaction is dynamic and reversible, which can endow the assemblies formed by supra-amphiphiles with controllable self-assembly and disassembly capabilities, thus enabling various potential functional applications, such as drug delivery, biomimics and optoelectronic materials.

References

1. C. J. Pedersen, *J. Am. Chem. Soc.*, 1967, **89**, 7017.
2. D. J. Cram and J. M. Cram, *Acc. Chem. Res.*, 1978, **11**, 8.
3. J.-M. Lehn, *Struct. Bonding (Berlin)*, 1973, **16**, 1.
4. J. S. Bradshaw and R. M. Izatt, *Acc. Chem. Res.*, 1997, **30**, 338.
5. C. J. Pedersen, *J. Inclusion Phenom.*, 1988, **6**, 337.
6. J.-M. Lehn, *J. Inclusion Phenom.*, 1988, **6**, 351.
7. D. J. Cram, *J. Inclusion Phenom.*, 1988, **6**, 397.
8. A. Villiers, *Compt. Rend.*, 1891, **112**, 536.
9. J. Szejtli, *Chem. Rev.*, 1998, **98**, 1743.
10. M. V. Rekharsky and Y. Inoue, *Chem. Rev.*, 1998, **98**, 1875.
11. G. Gattuso, S. A. Nepogodiev and J. F. Stoddart, *Chem. Rev.*, 1998, **98**, 1919.
12. B. L. Zhang and R. Breslow, *J. Am. Chem. Soc.*, 1997, **119**, 1676.
13. J. Li and X. J. Loh, *Adv. Drug Delivery Rev.*, 2008, **60**, 1000.
14. A. Harada, *Acc. Chem. Res.*, 2001, **34**, 456.
15. J. Li, A. Harada and M. Kamachi, *Polym. J.*, 1994, **26**, 1019.
16. F. Cacialli, J. S. Wilson, J. J. Michels, C. Daniel, C. Silva, R. H. Friend, N. Severin, P. Samorì, J. P. Rabe, M. J. O'Connell, P. N. Taylor and H. L. Anderson, *Nat. Mater.*, 2002, **1**, 160.

17. A. Harada, Y. Takashima and M. Nakahata, *Acc. Chem. Res.*, 2014, **47**, 2128.
18. M. Inutsuka, K. Inoue, Y. Hayashi, A. Inomata, Y. Sakai, H. Yokoyama and K. Ito, *Polymer*, 2015, **59**, 10.
19. Y. Kondo, K. Urayama, M. Kidowaki, K. Mayumi, T. Takigawa and K. Ito, *J. Chem. Phys.*, 2014, **141**, 134906.
20. A. R. Khan, P. Forgo, K. J. Stine and V. T. D'Souza, *Chem. Rev.*, 1998, **98**, 1977.
21. C. D. Gutsche, *J. Org. Chem.*, 1978, **43**, 4905.
22. C. D. Gutsche, *Acc. Chem. Res.*, 1983, **16**, 161.
23. C. D. Gutsche, J. A. Levine and P. K. Sujeeth, *J. Org. Chem.*, 1985, **50**, 5802.
24. C. D. Gutsche and K. C. Nam, *J. Am. Chem. Soc.*, 1988, **110**, 6153.
25. S. Shinkai, S. Mori, T. Tsubaki, T. Sone and O. Manabe, *Tetrahedron Lett.*, 1984, **25**, 5315.
26. S. Shinkai, H. Koreishi, K. Ueda, T. Arimura and O. Manabe, *J. Am. Chem. Soc.*, 1987, **109**, 6371.
27. T. Ogoshi and T. Yamagishi, *Eur. J. Org. Chem.*, 2013, 2961–2975.
28. T. Ogoshi, S. Kanai, S. Fujinami, T. A. Yamagishi and Y. Nakamoto, *J. Am. Chem. Soc.*, 2008, **130**, 5022.
29. M. Xue, Y. Yang, X. D. Chi, Z. B. Zhang and F. H. Huang, *Acc. Chem. Res.*, 2012, **45**, 1294.
30. R. Behrend, E. Meyer and F. I. Rusche, *Liebigs Ann. Chem.*, 1905, **339**, 1.
31. W. A. Freeman, W. L. Mock and N. Y. Shih, *J. Am. Chem. Soc.*, 1981, **103**, 7367.
32. J. Kim, I.-S. Jung, S.-Y. Kim, E. Lee, J.-K. Kang, S. Sakamoto, K. Yamaguchi and K. Kim, *J. Am. Chem. Soc.*, 2000, **122**, 540.
33. A. Day, A. P. Arnold, R. J. Blanch and B. Snushall, *J. Org. Chem.*, 2001, **66**, 8094.
34. A. I. Day, R. J. Blanch, A. P. Arnold, S. Lorenzo, G. R. Lewis and I. Dance, *Angew. Chem., Int. Ed.*, 2002, **41**, 275.
35. S. M. Liu, C. Ruspic, P. Mukhopadhyay, S. Chakrabarti, P. Y. Zavalij and L. Isaacs, *J. Am. Chem. Soc.*, 2005, **127**, 15959.
36. S. J. Barrow, S. Kasera, M. J. Rowland, J. del Barrio and O. A. Scherman, *Chem. Rev.*, 2015, **115**, 12320.
37. H. C. Kolb, M. G. Finn and K. B. Sharpless, *Angew. Chem., Int. Ed.*, 2001, **40**, 2004.
38. H. Cong, C.-R. Li, S.-F. Xue, Z. Tao, Q.-J. Zhu and G. Wei, *Org. Biomol. Chem.*, 2011, **9**, 1041.
39. F. Tian, M. Cziferszky, D. Z. Jiao, K. Wahlstrom, J. Geng and O. A. Scherman, *Langmuir*, 2011, **27**, 1387.
40. Y. Ahn, Y. Jang, N. Selvapalam, G. Yun and K. Kim, *Angew. Chem., Int. Ed.*, 2013, **52**, 3140.
41. C. Hu, Y. Lan, F. Tian, K. R. West and O. A. Scherman, *Langmuir*, 2014, **30**, 10926.
42. Y. L. Liu, Y. Yu, J. Gao, Z. Q. Wang and X. Zhang, *Angew. Chem., Int. Ed.*, 2010, **49**, 6576.

43. C. Li, M. J. Rowland, Y. Shao, T. Y. Cao, C. Chen, H. Y. Jia, X. Zhou, Z. Q. Yang, O. A. Scherman and D. S. Liu, *Adv. Mater.*, 2015, **27**, 3298.
44. H.-J. Buschmann, L. Mutihac and K. Jansen, *J. Inclusion Phenom. Macrocyclic Chem.*, 2001, **39**, 1.
45. X. F. Ji, J. Y. Li, J. Z. Chen, X. D. Chi, K. L. Zhu, X. Z. Yan, M. M. Zhang and F. H. Huang, *Macromolecules*, 2012, **45**, 6457.
46. X. F. Ji, S. Y. Dong, P. F. Wei, D. F. Xia and F. H. Huang, *Adv. Mater.*, 2013, **25**, 5725.
47. Y. Liu, J. Xu and S. L. Craig, *Chem. Commun.*, 2004, 1864.
48. S. Y. Cho and H. R. Allcock, *Macromolecules*, 2009, **42**, 4484.
49. Y. Tang, L. Zhou, J. Li, Q. Luo, X. Huang, P. Wu, Y. Wang, J. Xu, J. Shen and J. Liu, *Angew. Chem., Int. Ed.*, 2010, **49**, 3920.
50. Y. Wang, N. Ma, Z. Wang and X. Zhang, *Angew. Chem., Int. Ed.*, 2007, **46**, 2823.
51. L. Yue, H. Ai, Y. Yang, W. J. Lu and L. X. Wu, *Chem. Commun.*, 2013, **49**, 9770.
52. Q. Yan, J. Yuan, Z. Cai, Y. Xin, Y. Kang and J. Yin, *J. Am. Chem. Soc.*, 2010, **132**, 9268.
53. Z. Zhang, J. X. Ding, X. F. Chen, C. S. Xiao, C. L. He, X. L. Zhuang, L. Chen and X. S. Chen, *Polym. Chem.*, 2013, **4**, 3265.
54. N. Basilio and L. García-Río, *Chem.–Eur. J.*, 2009, **15**, 9315.
55. D. Y. Xia, G. C. Yu, J. Y. Li and F. H. Huang, *Chem. Commun.*, 2014, **50**, 3606.
56. Q. P. Duan, Y. Cao, Y. Li, X. Y. Hu, T. X. Xiao, C. Lin, Y. Pan and L. Y. Wang, *J. Am. Chem. Soc.*, 2013, **135**, 10542.
57. K. Wang, D.-S. Guo, X. Wang and Y. Liu, *ACS Nano*, 2011, **5**, 2880.
58. X. D. Chi, G. C. Yu, L. Shao, J. Z. Chen and F. H. Huang, *J. Am. Chem. Soc.*, 2016, **138**, 3168.
59. Y. Cao, X.-Y. Hu, Y. Li, X. C. Zou, S. H. Xiong, C. Lin, Y.-Z. Shen and L. Y. Wang, *J. Am. Chem. Soc.*, 2014, **136**, 10762.
60. D. S. Guo, K. Wang, Y. X. Wang and Y. Liu, *J. Am. Chem. Soc.*, 2012, **134**, 10244.
61. G. C. Yu, J. Yang, D. Y. Xia and Y. Yao, *RSC Adv.*, 2014, **4**, 18763.
62. G. Yu, M. Xue, Z. Zhang, J. Li, C. Han and F. Huang, *J. Am. Chem. Soc.*, 2012, **134**, 13248.
63. Y. J. Jeon, P. K. Bharadwaj, S. W. Choi, J. W. Lee and K. Kim, *Angew. Chem., Int. Ed.*, 2002, **41**, 4474.
64. L. L. Yang, H. Yang, F. Li and X. Zhang, *Langmuir*, 2013, **29**, 12375.
65. D. Z. Jiao, J. Geng, X. J. Loh, D. Das, T.-C. Lee and O. A. Scherman, *Angew. Chem., Int. Ed.*, 2012, **51**, 9633.
66. K. Liu, Y. Liu, Y. Yao, H. Yuan, S. Wang, Z. Wang and X. Zhang, *Angew. Chem., Int. Ed.*, 2013, **52**, 8285.
67. P. Wang, X. Z. Yan and F. H. Huang, *Chem. Commun.*, 2014, **50**, 5017.
68. G. T. Wang, Y. T. Kang, B. T. Tang and X. Zhang, *Langmuir*, 2015, **31**, 120.
69. Y. Jiao, K. Liu, G. T. Wang, Y. P. Wang and X. Zhang, *Chem. Sci.*, 2015, **6**, 3975.

CHAPTER 3

Supramolecular Amphiphiles Based on Multiple Hydrogen Bonds

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3.1 Introduction

Biomolecular systems are replete with well-defined secondary, ternary and supramolecular structures formed by ingeniously employing multiple non-covalent interactions, including electrostatic interactions, hydrogen bonding, dipole–dipole interactions and hydrophobic associations. The formation of these unique nano-architectures is directed by the surrounding water molecules, as exemplified by protein folding and nucleic acid hybridization. Biomolecular information, which holds the key to cellular functions, is stored in these self-organized structures and they are stabilized and maintained in water through the formation of amphiphilic architectures.

Inspired by these fascinating biological nano-architectures, chemists have long endeavored to develop artificial molecular assemblies utilizing secondary interactions and other directional forces such as coordination bonding.[1–5] This chapter focuses on supramolecular amphiphiles mediated by multiple

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hydrogen bonding and their recent developments. It also complements earlier reviews.[6–9] Although it is well established that intermolecular hydrogen bonding promotes the self-assembly of identical molecules and enhances their thermal stability, the supramolecular amphiphiles discussed here are composed of molecular pairs designed to acquire enhanced amphiphilicity, *i.e.* the ability to form ordered molecular assemblies on the formation of multiple, when more appropriate, complementary hydrogen bonds.[8] These hydrogen bonding pairs cooperatively form amphiphilic superstructures, which further hierarchically self-assemble in a given environment. Their secondary and higher assembly architectures are greatly influenced by the dispersion media *via* solvophilic–solvophobic interactions. It is essential to clearly distinguish these hydrogen bond mediated supramolecular amphiphiles from the ordinary single-component self-assemblies reinforced by multiple hydrogen bonding, which are beyond the scope of this chapter.[10–12] To provide a trajectory and lay out the road toward the future of this field, the basic design developed for bilayer membrane-forming amphiphiles and related self-assembly phenomena will also be discussed.

3.2 Amphiphilic Self-Assembly in Aqueous, Organic and Ionic Media

Self-assemblies such as surfactant micelles and surface monolayers were a subject of colloid chemistry decades before the coining of the term supramolecular chemistry.[13] The studies on Langmuir–Blodgett films by Kuhn and Möbius[14] opened a door to manipulate photofunctional molecular assemblies at the monomolecular layer level, although it is since the discovery of synthetic bilayer membranes by Kunitake and Okahata[15] that a general means for developing ordered molecular self-assemblies based on chemical design and the synthesis of unit molecules has been recognized as a field of chemistry. In the following decades, bilayer membranes with morphologies in the mesoscopic range (*ca.* 10–1000 nm)—such as vesicles, tubes, disks, lamellas and helical nanoarchitectures—were obtained from a great variety of synthetic amphiphiles in aqueous media,[1,6–9,16–18] which enabled chemists to examine and comprehend how supramolecular architectures and their functions can be predicted on self-assembly. The formation of ordered bilayer-based self-assemblies has naturally further extended to organic media[19,20] and ionic liquids[21–24] (Figure 3.1).

Bilayer membranes are a universal basis for cell membrane structures, which are spontaneously self-assembled from amphiphilic molecules under the conditions required to satisfy the intermolecular interactions for the formation of two-dimensional molecular arrays and the hydrophilic interface that secures their stable dispersion in water. The relationship between amphiphilic molecular structures and their self-assembly properties has been systematically investigated in synthetic bilayers and the requirements are typically fulfilled by double-chained amphiphiles (Figure 3.2A).[1,6,8]

Stable bilayers are also formed from triple-chained (Figure 3.2B)[25] or quadruple-chained amphiphiles (Figure 3.2C).[26] Single-chained amphiphiles

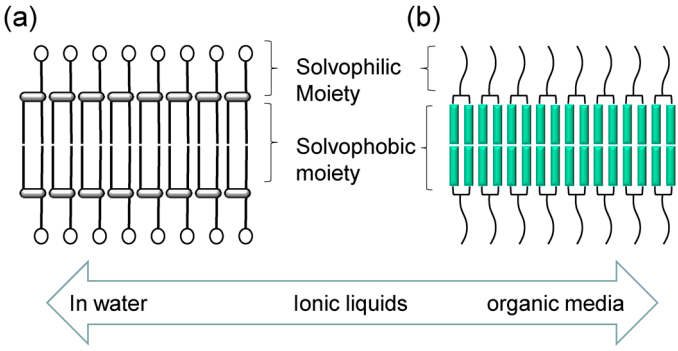


Figure 3.1 Schematic illustration of bilayer membranes formed in various solvents ranging from water (a) to organic media (b).

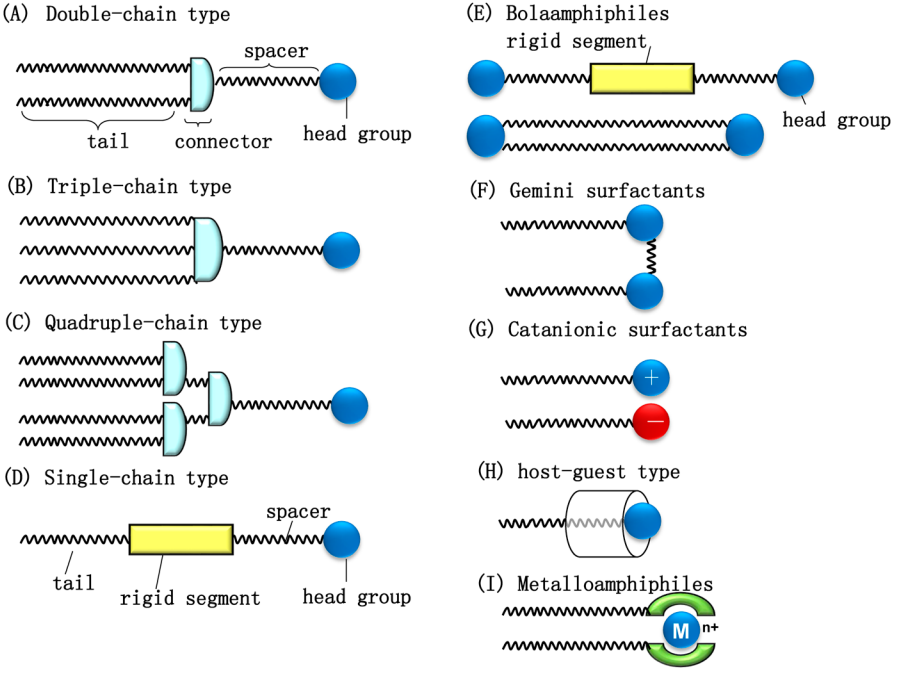


Figure 3.2 Schematic illustrations of the structures of amphiphiles forming aqueous bilayer membranes. Double-chain (A), triple-chain (B), quadruple-chain (C) and single-chain type amphiphiles, bolaamphiphiles (E), gemini surfactants (F), catanionic surfactants (G), host-guest type surfactants (H), and metalloamphiphiles (I).

also form bilayers when the intermolecular interactions are enhanced by the introduction of rigid segments such as aromatic chromophores (Figure 3.2D)[27,28] or extremely long alkyl chains.[29] Single- or double-chained amphiphiles that have a headgroup at each end form single-layered membranes (Figure 3.2E),[30] which were later popularized as bola-amphiphiles.[31]

Amphiphiles with two ionic groups covalently connected by a spacer (Figure 3.2F) are called gemini surfactants.[32,33]

In general, bilayer-forming amphiphiles are designed from single molecules in which the hydrophilic and hydrophobic groups are covalently connected. However, they can be also designed from molecular components put together *via* noncovalent interactions. Typical examples of such hybrid amphiphiles are catanionic surfactants (Figure 3.2G).[34,35] Mixtures of anionic and cationic surfactants display varied aggregate structures—such as globular and rod-like micelles, vesicles and lamellar phases—under the appropriate conditions. These catanionic vesicles are formed spontaneously without an external input of energy (equilibrium vesicles), in contrast with vesicular systems that usually require mechanical energy. Host–guest inclusion phenomena have been also employed to form vesicles (Figure 3.2H).[36–38] A stable ternary inclusion complex consisting of a host (cucurbit[8]uril), an electron donor and an electron acceptor (viologen) with a long alkyl tail triggered the spontaneous formation of giant vesicles.[36] A water-insoluble pillar[5]arene with 10 tertiary amine units on the rim acquired solubility in water on protonation by CO_2 and showed a host–guest interaction with sodium dodecyl sulfonate to produce vesicles.[39]

In contrast with these hybrid bilayer systems, when two molecular components are specifically assembled to form regularly aligned bilayer membrane structures by employing multiple intermolecular interactions, they are referred to as "supramolecular membranes" (see Section 3.4.1).[6,8] Amphiphilic metal complexes (metalloamphiphiles) formed from metal ions and lipophilic ligand molecules provide another class of supramolecular amphiphile (Figure 3.2H),[40–43] where metal complexes can be incorporated as hydrophilic groups[41–43] or in the hydrophobic interior.[40]

The concept of amphiphilic self-assembly can be extended to nonpolar[19,20,44] and polar[45] organic media and further to ionic liquids.[21–24,46] Kunitake and coworkers[19,20] have shown that a series of double-chain fluorocarbon amphiphiles containing flexible alkyl chains (solvophilic units) and fluorocarbon chains (solvophobic units) show spontaneous bilayer formation in nonpolar organic solvents (Figure 3.1b). In these non-structuring solvents, the self-assembly of the fluorocarbon amphiphiles is driven by enthalpic change, in contrast with the general perception of entropically driven hydrophobic self-assembly in water. The major enthalpic driving force for molecular association in organic media is caused by the limited miscibility between the fluorocarbon chains and hydrocarbon solvents; hydrogen bonding and van der Waals forces between the solute molecules provide secondary driving forces. The common driving force of bilayer self-assembly is the solute–solvent immiscibility that arises from the differences in cohesive energy between the solute (amphiphile) and the solvent.[20] This concept is equally applicable to the formation of organogels by the self-assembly of low molecular weight gelators.[47,48] It is natural that the physical properties of solvents and their interaction with solute molecules are essential features in directing solvophobic self-assembly, where

the degree of solvation at the supramolecular interface is the key to maintaining their stable dispersibility without the formation of a bulk gel or bulk crystalline materials.

The formation of hydrogen bond mediated supramolecular assemblies has been largely investigated in nonpolar organic media or in molecular crystals as a result of the highly deteriorating action of water molecules against hydrogen bonding. Accordingly, the front line of hydrogen bond mediated supramolecular amphiphiles will be the sophisticated control of the solvophilic–solvophobic interactions, which lead to (1) the *in situ* formation of hydrogen bonded pairs in water; (2) the folding of complementary hydrogen bond pairs into specific secondary and higher order structures in aqueous or organic media; and (3) specific functions unique to these hydrogen bond mediated systems.

3.3 Lessons from Complementary Hydrogen Bonding of DNA

Biological supramolecular assemblies are formed by ingeniously employing multiple noncovalent interactions, such as electrostatic interactions, hydrogen bonding, dipole–dipole interactions and hydrophobic associations. Among these intermolecular forces, hydrogen bonding is unique because of its directional feature, which plays a pivotal part in determining the association or folding structures of DNA, RNA, peptides, proteins and polysaccharides. DNA is a copolymer of four types of nucleotide, which are covalently linked into polynucleotide chains with a sugar–phosphate backbone. The nitrogen-containing bases [adenine (A), cytosine (C), guanine (G) and thymine (T)] are attached to each deoxyribose unit. The two ends of the chain are the 3′ hydroxyl group and 5′ phosphate at the termini and the DNA duplex is formed from a pair of strands with a complementary sequence of nucleobases in an antiparallel manner.[49]

Complementary DNA chains self-assemble in water below their melting temperatures by overcoming the electrostatic repulsion and hydration of nucleobases. The enthalpic gain from the formation of hydrogen bonds in water is generally canceled by the enthalpy needed to break the hydrogen bonds formed between these molecules and water.[50] Accordingly, the formation of hydrogen bonds in aqueous media requires the integration of other noncovalent interactions, such as hydrophobic interactions or aromatic stacking, to compensate for this entropic disadvantage, as can be learned from the structure of the DNA duplex.

In double helical DNA, all the bases are on the inside of the double helix and the sugar–phosphate backbones are on the outside (Figure 3.3). This amphiphilic superstructure allows complementary base pairs to be packed in the energetically most favorable arrangement in the hydrophobic interior of the double helix. In this arrangement, each base pair consists of a pair of purine and pyrimidine bases and the resultant similar width allows the

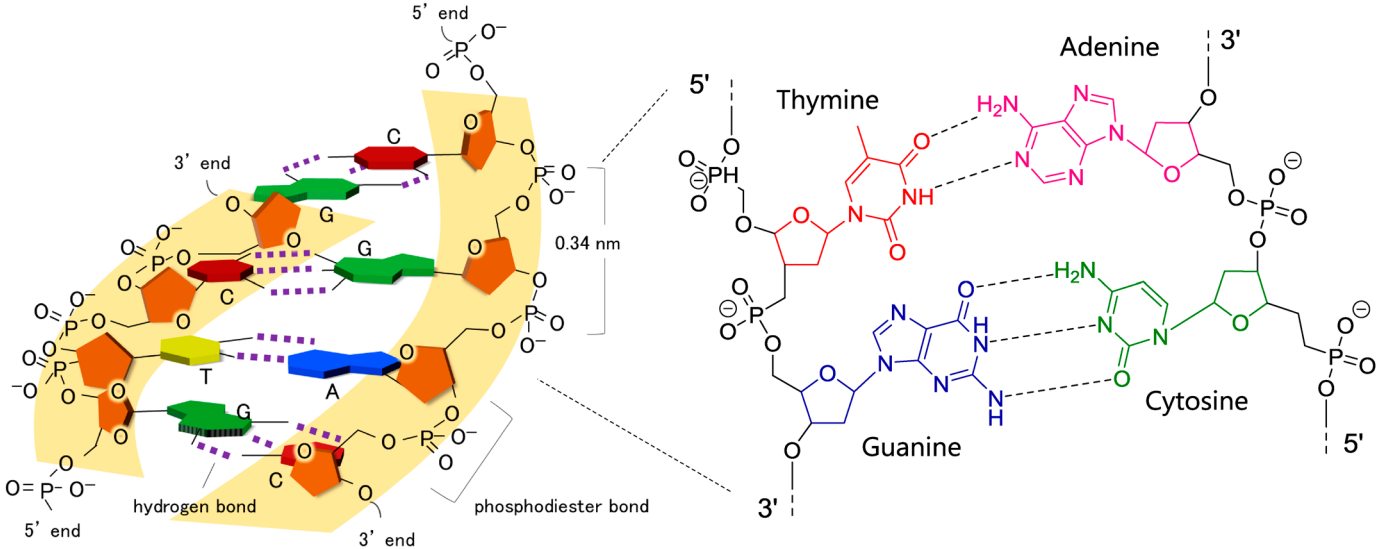


Figure 3.3 Structure of DNA duplex inspired by ref. 49.

sugar–phosphate backbones to be aligned at an equal distance apart along the DNA molecule. To maximize the efficiency of base pair packing, the two sugar–phosphate backbones wind around each other to form an amphiphilic double helix, with one complete turn every 10 base pairs.[49]

The emergence of such hydrophobic domains in an aqueous environment promotes and stabilizes the complementary hydrogen bonding. The effective accumulation of these multiple interactions in a controlled microenvironment has been realized in biological architectures, which also provides a basis to design hydrogen bond mediated supramolecular systems in the aqueous environment. Monomeric nucleotides have less ability to form hydrogen bonded dimers in dilute aqueous solution and the hybridization between oligomeric or polymeric DNA strands apparently mitigates the entropic disadvantage in self-assembly.

3.4 Multiple Hydrogen Bond Mediated Aqueous Supramolecular Amphiphiles

3.4.1 Supramolecular Membranes

Because of the highly deteriorating action of water against hydrogen bonding, artificial supramolecular systems with complementary hydrogen bonding have been studied in either nonpolar organic media or in crystalline solids,[51–55] avoiding aqueous environments. The early efforts to produce complementary hydrogen bonding in water took advantage of the hydrophobic microenvironments provided by aromatic surfaces[56] or by the interior of aqueous micelles.[50] Meijer and coworkers reported the formation of hydrogen bond mediated polymers in water from bifunctional, self-complementary ureido-*s*-triazines.[57] Kunitake and coworkers showed that complementary hydrogen bonding is facilitated at the air–water interface compared with that observed at the surface of aqueous micelles or bilayers.[58–60] More recently, a cationic supramolecular host was used for the G–C base pairing in water.[61] However, the formation of complementary hydrogen bond mediated regular molecular assembly was not achieved before the development of supramolecular membranes.[62–66]

Based on the principle of nucleic acid hybridization, we designed a complementary hydrogen bond mediated bilayer membrane from quaternary ammonium-derivatized cyanuric acid (**A**, hydrophilic subunit) and alkylated melamine (**B**, hydrophobic subunit), as illustrated schematically in Figure 3.4.

A pair of cyanuric acid melamine subunits was selected because they form polymeric complementary hydrogen bond networks in organic solvents[53,67] and in the solid state.[54,68] As described in the preceding section, hydrogen bonding in aqueous media requires the ingenious integration of other noncovalent interactions to compensate for the entropic disadvantage. The self-assembly of such monomeric subunits in water—unlike the hybridization of DNA, which occurs between nucleobases covalently attached to oligonucleotides—suffers from significant entropic disadvantages. To circumvent

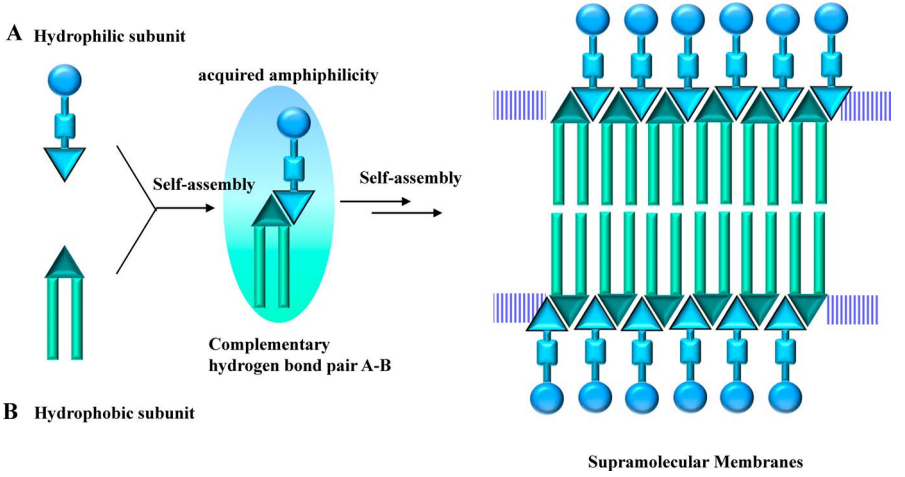


Figure 3.4 A supramolecular amphiphile formed by complementary hydrogen bonding between (A) hydrophilic and (B) hydrophobic subunits and its hierarchical self-assembly into a supramolecular membrane.

this issue, polymeric complementary hydrogen bonding was thought to be indispensable in achieving the cooperative self-assembly of each subunit in water. The introduction of alkyl chains in these subunits may promote their pre-organization into each micellar aggregate in water, which allows the formation of complementary hydrogen bonds in a hydrophobic molecular environment. Whitesides and coworkers reported that co-crystals of melamine and barbituric acid derivatives display polymorphism of hydrogen bonded motifs[54,68] and the pair of alkylated cyanuric acids and melamines can form linear hydrogen bond networks (Figure 3.5a), crinkled tapes (Figure 3.5b) and cyclic hexamer (rosette) structures (Figure 3.5c) in the solid state.

Upon the formation of complementary hydrogen bonding in water, each subunit will self-assemble to acquire amphiphilicity—that is, they will form the most stable nano-architecture in the aqueous environment. Linear complementary hydrogen bond networks were successfully formed from these subunits, giving the supramolecular amphiphiles **B**–**A**, which hierarchically self-assembled into supramolecular membranes in an aqueous environment (Figure 3.4, right-hand panel).

The structure of supramolecular membranes was first systematically investigated for pre-formed amphiphilic hydrogen bond pairs.[62–65] An equimolar pair of dialkylated melamine **1** and quaternary ammonium-derivatized cyanuric acid **2** formed complementary hydrogen bond pairs on the mixing of ethanolic solutions followed by evaporation of the solvent. The complex **1**–**2** was stably dispersed in water (*ca.* 30 mM) on ultrasonication. Electron microscopy showed that the pair **1**–**2** formed disk-like aggregates with a minimum thickness of *ca.* 90 Å (Figure 3.6), which is consistent with the long period of the supramolecular membrane structure confirmed by X-ray

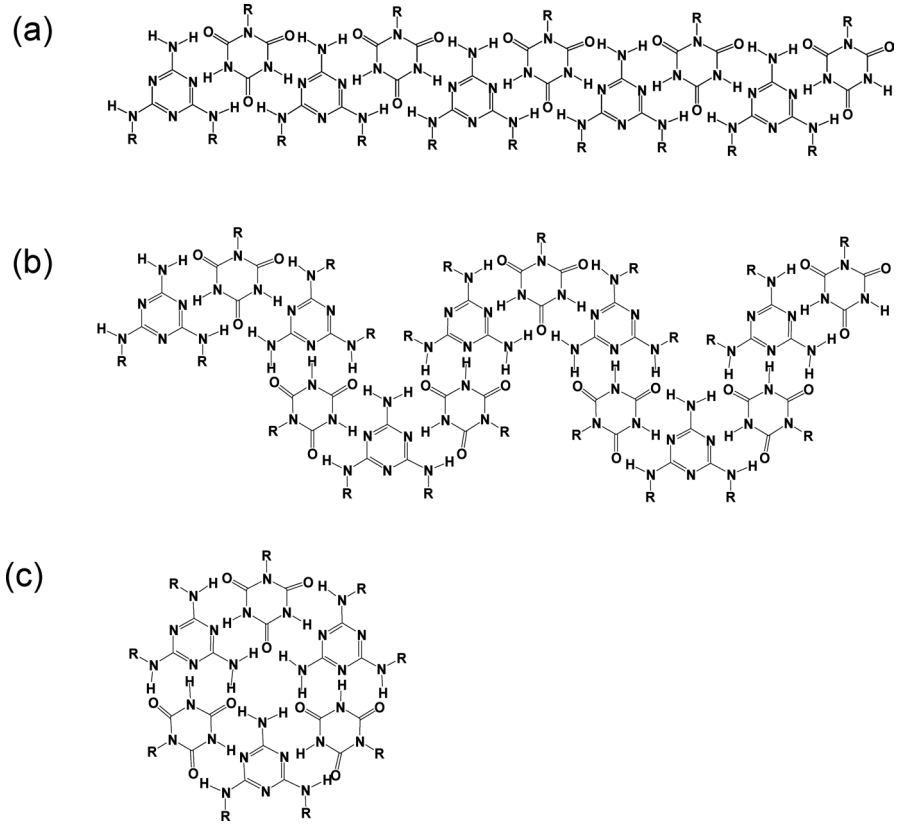


Figure 3.5 Structures of complementary hydrogen bond networks formed from alkylated cyanuric acid and melamine: (a) linear networks; (b) crinkled tapes; and (c) a cyclic hexamer (rosette).

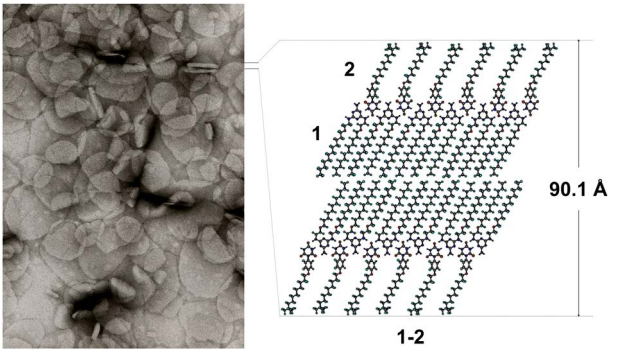
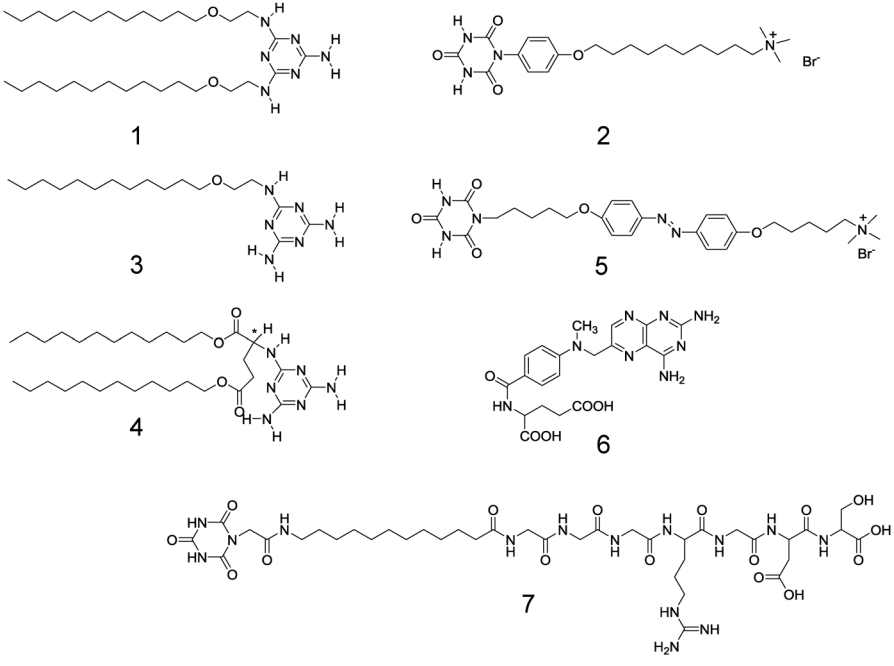


Figure 3.6 Transmission electron microscopy image of **1**–**2** and schematic illustration of the supramolecular membrane structure. Adapted with permission from N. Kimizuka, T. Kawasaki and T. Kunitake, Self-organization of bilayer membranes from amphiphilic networks of complementary hydrogen bonds, *J. Am. Chem. Soc.*, 1993, **115**, 4387–4388. Copyright (1993) American Chemical Society.

diffraction for macroscopically oriented cast films.[62,65] A similar supramolecular membrane was also formed from the pair **3**–**2**, in which single-chained melamine subunits showed the interdigitation of alkyl chains between oppositely aligned amphiphilic hydrogen bond networks (Scheme 3.1). These supramolecular membranes are the first examples of water-soluble supermolecules directed by complementary hydrogen bonds.

In general, the hydrogen bonded motifs in co-crystals are strongly dependent on the structure of the substituents in the constituent molecule. They simultaneously affect the mode of molecular packing in the crystal and the hydrogen bond motif; it is difficult to rationally explain the substituent effect on the packing of tapes.[54,68] However, the present amphiphilic complementary pairs all have two-dimensional motifs of aggregation with linearly extended hydrogen bond networks, which is the most sophisticated amphiphilic structure.

The introduction of the phenyl ring into the cyanuric acid subunit and the ether group in the melamine subunit is indispensable in obtaining stable aqueous dispersions. The phenyl ring introduced between the complementary hydrogen bond pairs and the ammonium group renders the alignment of the hydrogen bond networks located in the hydrophobic interior, thus stabilizing them against the deteriorating action of water molecules. In addition, both the phenyl unit and ether linkage in the alkyl chain unit improves



Scheme 3.1 Chemical structures of alkylated melamine (hydrophobic subunit) and quaternary ammonium-attached cyanuric acid (hydrophilic subunit).

molecular alignment, so that the regular stacking of hydrogen bond networks is possible. The effective stacking of hydrogen bond pairs and consequent stabilization in water is a common feature of DNA double helices. The aqueous supramolecular membrane **1**–**2** has a gel-to-liquid crystalline phase transition temperature around at 53 °C and shows thermally induced dissociation of the complementary pairs on further increasing the temperature to 60–80 °C (Figure 3.7).[65]

Cooling of this dispersion showed reversible phase transition behavior, whereas heating above *ca.* 80 °C increased the turbidity of the dispersion, indicating segregation of the hydrophobic melamine subunits due to their limited solubility in water. The thermal reversible dissociation of hydrogen bond mediated subunits and irreversible segregation at higher temperatures observed for this system are architectural features characteristic of biological supermolecules such as nucleic acids and proteins.

3.4.2 Reconstitution of Supramolecular Membranes in Water

Supramolecular membranes reveal dynamic reconstitution phenomena that are regarded as unique and essential characteristics of biological self-assemblies. The complementary subunits of lipophilic melamine derivatized with L- or D-glutamate **4** and a cyanuric acid subunit with an azobenzene chromophore (**5**, Scheme 3.1) have been employed to spectrophotometrically monitor the hybridization process.[66] Azobenzene chromophores aligned in bilayer assemblies display unique spectral characteristics depending on their molecular orientation[28] and a spectral difference between the aqueous single-component subunit and complementary pairs provides molecular level

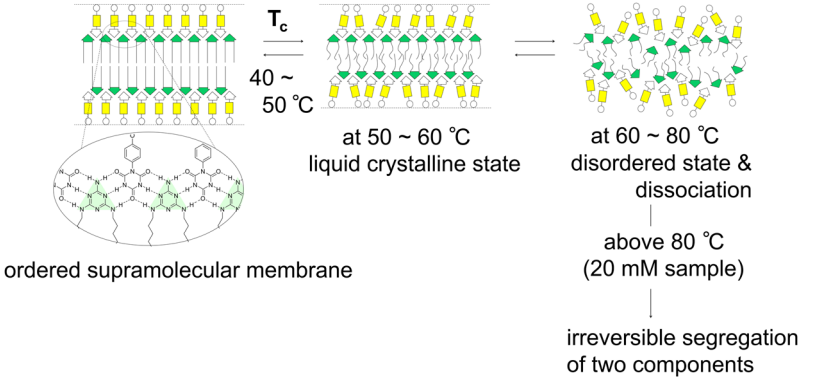


Figure 3.7 Schematic illustration of the gel-to-liquid crystalline phase transition of aqueous supramolecular membrane **1**–**2**. Adapted with permission from N. Kimizuka, T. Kawasaki, K. Hirata and T. Kunitake, Supramolecular membranes, spontaneous assembly of aqueous bilayer membrane *via* formation of hydrogen bonded pairs of melamine and cyanuric acid derivatives, *J. Am. Chem. Soc.*, 1998, **120**, 4094–4104. Copyright (1998) American Chemical Society.

information on their interactions. The lipophilic melamine-containing chiral subunit **4** gave irregular aggregates when injected into water from an ethanol stock solution (Figure 3.8a), whereas the azobenzene-containing cyanuric acid derivative **5** formed globular aggregates when dispersed in water (Figure 3.8b). The absorption λ_{max} of the azobenzene chromophores in this single-component aqueous solution was located at 357 nm, which is comparable with that of the monomeric species in ethanol. There is no interaction

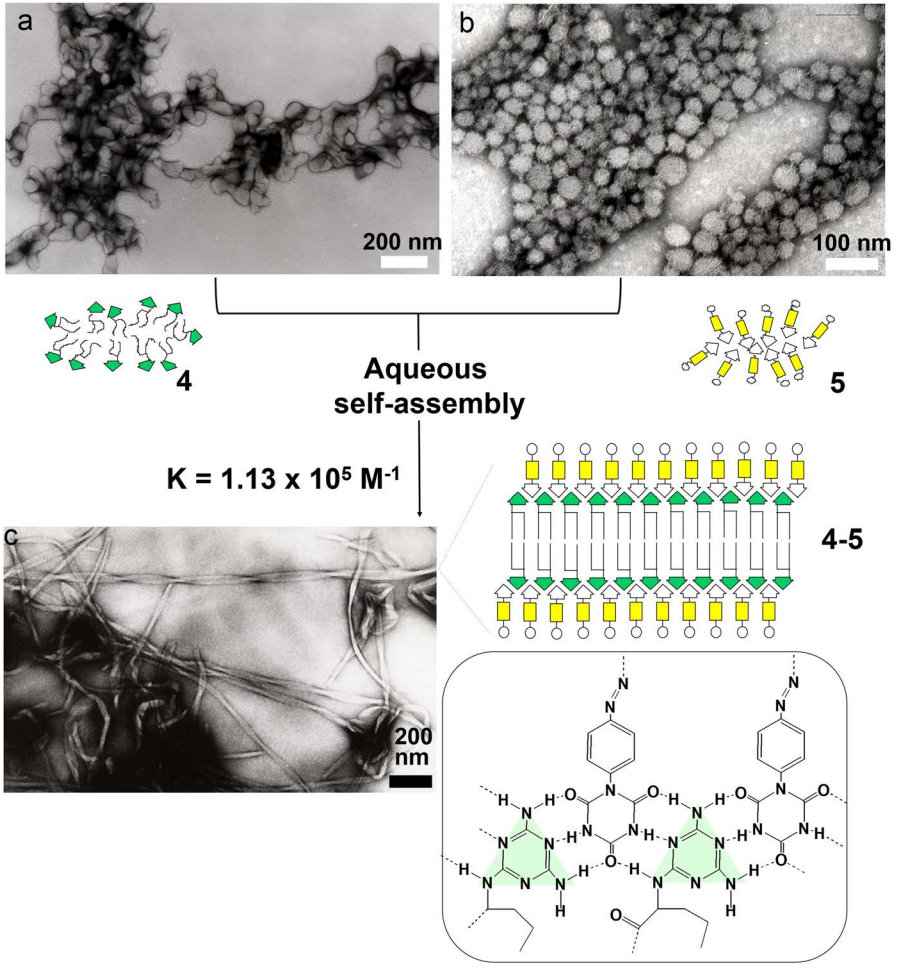


Figure 3.8 Aqueous self-assembly (reconstitution) of hydrogen bond mediated supramolecular membrane **4**–**5**. Transmission electron micrographs of (a) subunit **4**, (b) subunit **5** and (c) equimolar mixture of **4**–**5**. Adapted with permission from T. Kawasaki, M. Tokuhiro, N. Kimizuka and T. Kunitake, Hierarchical self-assembly of chiral complementary hydrogen bond networks in water: reconstitution of supramolecular membranes, *J. Am. Chem. Soc.*, 2001, **123**, 6792–6800. Copyright (2001) American Chemical Society.

among the azobenzene chromophores in the single-component aggregates. Surprisingly, when these single-component aggregates were mixed in water, they were immediately transformed into developed helical superstructures (Figure 3.8c, thickness, 14–28 nm; widths, 30–50 nm; pitches, 180–430 nm) with an association constant of 1.13×10^5 M^{-1}.[66] These helical superstructures are often observed for highly ordered chiral bilayer membranes[69] and are distinct from the aggregate morphology observed for the individual subunits. The observed helical assembly showed a blue-shifted absorption of the azobenzene chromophore at 332 nm, with an exciton coupling in circular dichroism. These observations clearly indicate the presence of excitonic interactions among regularly aligned azobenzene chromophores in the supramolecular membranes **4**–**5**.

The presence of water directs the hydrogen bond mediated ordered self-assembly. The hydrophobic melamine subunits are located in the interior and the ammonium-containing counterparts constitute the hydrophilic surface of the assemblies (Figure 3.8); only the linear network structure was selected among the possible isomorphs, such as circular (rosette) and crinkled tape structures (Figure 3.5). This feature is common to the supramolecular hybridization of biological polymers and also to protein folding. When the azobenzene subunit **5** underwent *trans* to *cis* photoisomerization and the resultant **5**(*cis*) was mixed with **4** in water, self-assembly did not proceed.[66] This indicates that **5**(*cis*) does not form hydrogen bonds with **4** and it is apparent that the molecular shape of the subunits must be designed to secure the ordered molecular orientation. The supramolecular membranes are formed in water when the amphiphilic organization of the components satisfies both the solubility and stabilization of the complementary hydrogen bonds, which requires the simultaneous pursuit of regularly stacked hydrogen bonding and maximized amphiphilicity with the correct relative orientation of hydrophobic and hydrophilic subunits.

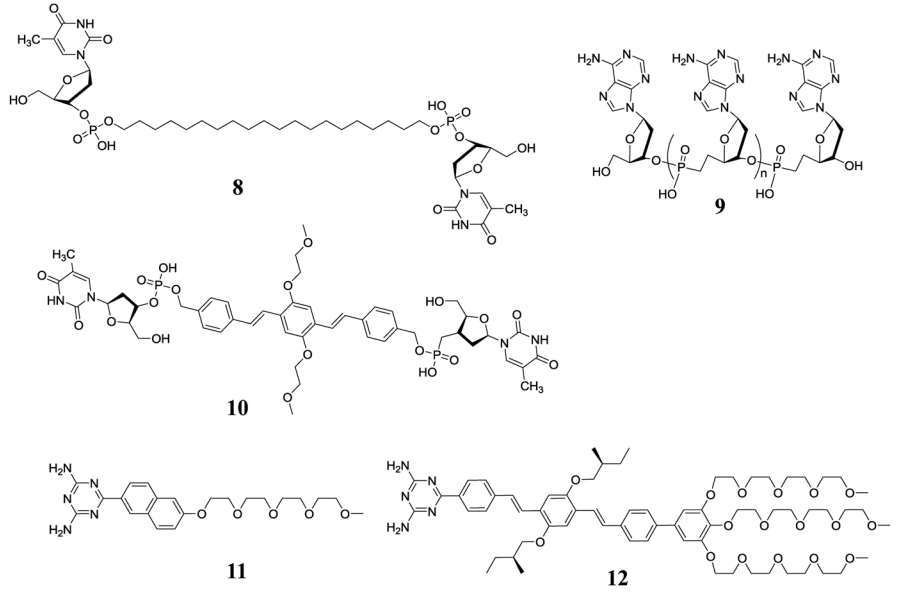
The importance of the hydrophobic environment to achieve complementary hydrogen bonding in aqueous media has been also demonstrated by an amphiphilic peptide **7**, which possess a cyanuric acid group connected to the hydrophobic tail.[70] Because of the hydrophilic nature of cyanuric acid, the single-component peptide amphiphile forms loose micellar aggregates. The addition of the clinical antitumor drug methotrexate (**6**), which has a complementary diaminopyridine unit, resulted in structural conversion to nanorod structures.[70] However, in this case the binding of **6** to the peptide amphiphile **7** was not quantitative and the release of **6** from the mixture occurred especially at basic pH, where the ionization deteriorated the hydrophobic microenvironment.

3.4.3 Oligonucleotide-Templated Self-Assembly Systems

The aqueous self-assembly of complementary hydrogen bonding subunits **1**–**5** in aqueous media to form regular supramolecular membranes established the most sophisticated, yet fundamental, molecular design

principle for multiple hydrogen bond mediated supramolecular amphiphiles. By covalently linking one of the complementary subunits in oligomers, *i.e.* using single-stranded DNA (ssDNA) as a template, the entropic disadvantage associated with the self-assembly of monomeric subunits can be alleviated. Iwaura *et al.* reported hydrogen bonding between oligonucleotides and a nucleotide-derivatized molecular assembly.[71] A nucleotide-appended bola-amphiphile (**8**) formed a nanofibrous assembly and gelatinized water (Scheme 3.2). On mixing **8** and a series of oligoadenylic acids **9** (n = 2–40), helical nanofibers with a width of 7–8 nm were observed on TEM. The nanofiber length and thermal stability increased when longer oligoadenylic acids were used, suggesting oligoadenylic acid templated self-assembly.[72]

This ssDNA-templated self-assembly has been extended to a bola-amphiphile with a π-conjugated oligo(*p*-phenylene vinylene) unit (**10**),[73] donor–acceptor π-conjugated chromophores[74] and viologens.[75] Schenning and coworkers synthesized oligo(ethylene glycol)-derivatized diaminotriazines containing chromophores such as naphthalene (**11**) and π-conjugated oligo(*p*-phenylene)vinylene (**12**).[76,77] These diamino triazine derivatives self-assembled with an oligothymine template to give DNA hybrids stabilized by hydrogen bonding and π–π interactions (Figure 3.9).[76,77] Although the ssDNA-templated self-assemblies are classified as aqueous supramolecular polymers,[12] there is the potential to control the number of chromophores depending on the length of the templates, which may be useful in DNA-based nanotechnology, including molecular electronics.



Scheme 3.2 Chemical structures of nucleotide bola-amphiphiles, oligoadenylic acid and diamino triazine derivatives.

3.4.4 Rosette Nanotubes

Another approach to alleviating the entropic disadvantage of the aqueous two-component self-assembly of complementary hydrogen bond pairs is to use self-complementary hydrogen bonding heterocycles.[78–80] Fenniri *et al.*[81] showed that an equimolar aqueous mixture of complementary melamine subunit **13** and cyanuric acid subunit **14** carrying hydrophilic L-lysine moieties did not undergo self-assembly in aqueous media (Scheme 3.3), which is ascribed to the lack of a suitable molecular design to secure a hydrophobic nano-environment for complementary hydrogen bonding.

A hydrophobic bicyclic subunit (**15**) with the Watson–Crick donor–donor–acceptor H-bond array of guanine and acceptor–acceptor–donor array of cytosine (G∧C motif) self-assembled to form a six-membered supermacrocycle (rosette; Figure 3.10), which hierarchically assembled into nanotubular architectures as indicated by TEM (observed outer diameter *ca.* 4.0 nm; calculated average diameter[82] *ca.* 3.2 nm), nuclear magnetic resonance and circular dichroism spectra.[81] The absorbance spectrum underwent a cooperative hyperchromic effect as the temperature increased (melting temperature T_m^{285nm} = 50 °C), which is a common feature of DNA double helices, and **15** exhibited a cooperative, hierarchical self-assembly process through H-bonding, stacking interactions and hydrophobic effects.

The heteroaromatic bicyclic base **16** contains a crown ether unit, which also self-assembled in water to form rosette nanotubes (RNTs) (Figure 3.10a and b).[83] The average length of the nanotubes as monitored by dynamic light scattering showed an increase on increasing the temperature from 20 to 40 °C, which is consistent with entropy-driven self-assembly, indicating a hydrophobic effect as the major driving force for the formation of RNTs.[83]

In methanol, **16** undergoes hierarchical self-assembly into racemic RNTs with a diameter of *ca.* 4 nm. When L-alanine was added as a guest molecule to crown-RNTs, the ammonium groups electrostatically interacted with the

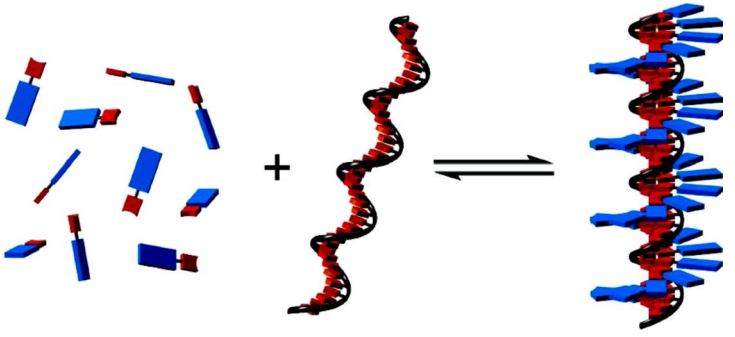
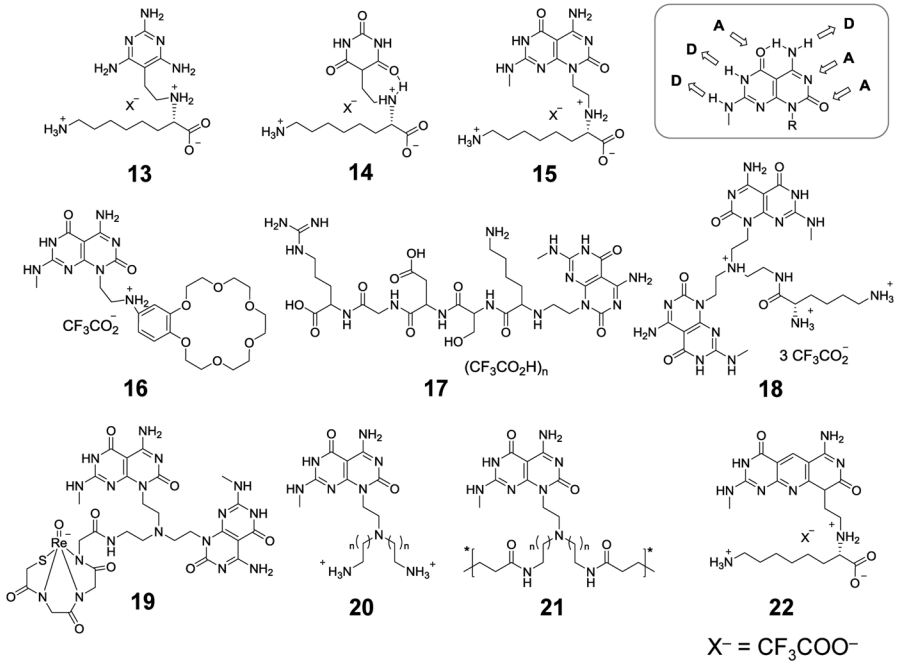


Figure 3.9 Schematic illustration of ssDNA-templated self-assembly. Reprinted with permission from P. G. A. Janssen, J. Vandenbergh, J. L. J. van Dongen, E. W. Meijer and A. P. H. J. Schenning, ssDNA templated self-assembly of chromophores, *J. Am. Chem. Soc.*, 2007, **129**, 6078–6079. Copyright (2007) American Chemical Society.



Scheme 3.3 Chemical structures of rosette nanotube-forming subunits.

crown ether units, which promoted a rapid transition from racemic to chiral RNTs, as indicated by induced circular dichroism.[84] Flexibility in the RNT design has allowed their application in biomedicine. The G∧C motif modified with a cell-adhesive Arg-Gly-Asp-Ser-Lys (RGDSK) peptide (**17**, G∧C–RGDSK) formed aqueous RNTs, which have been coated on hydrogels. The RGDSK–RNT-coated hydrogels showed a 200% increase in osteoblast (bone-forming cell) adhesion relative to hydrogel controls.[85] This indicates that the RGDSK–RNTs provided an environment favorable to cells and served as an excellent interfacial biomaterial.

The twin G∧C motif **18** gave thermally stable RNTs in aqueous media, which were self-assembled from an energetically favorable, *syn*-stacked parallel dimer conformation.[82] This twin G∧C motif was also used to modify the surface of RNTs with gold nanoparticles (Figure 3.10c)[86] and oxorhenium complexes (**19**) (Figure 3.10d and e).[87] Covalent crosslinking of the surface of RNTs has been demonstrated by the self-assembly of an alkyl triamine-derivatized G∧C motif (**20**), followed by surface-initiated polycondensation with adipoyl chloride under basic conditions, which gave the surface-captured polyamide **21**.[88] The diameter of the RNTs can be also tuned by introducing an extended π system to the G∧C motif. A water-soluble tricyclic motif (**22**) had the same hydrogen bonding arrays as the G∧C motif, but was separated by an internally fused pyridine ring.[89] An outer diameter of *ca.* 4.4 nm was observed by TEM, which is consistent with the theoretical value of 4.3 nm.

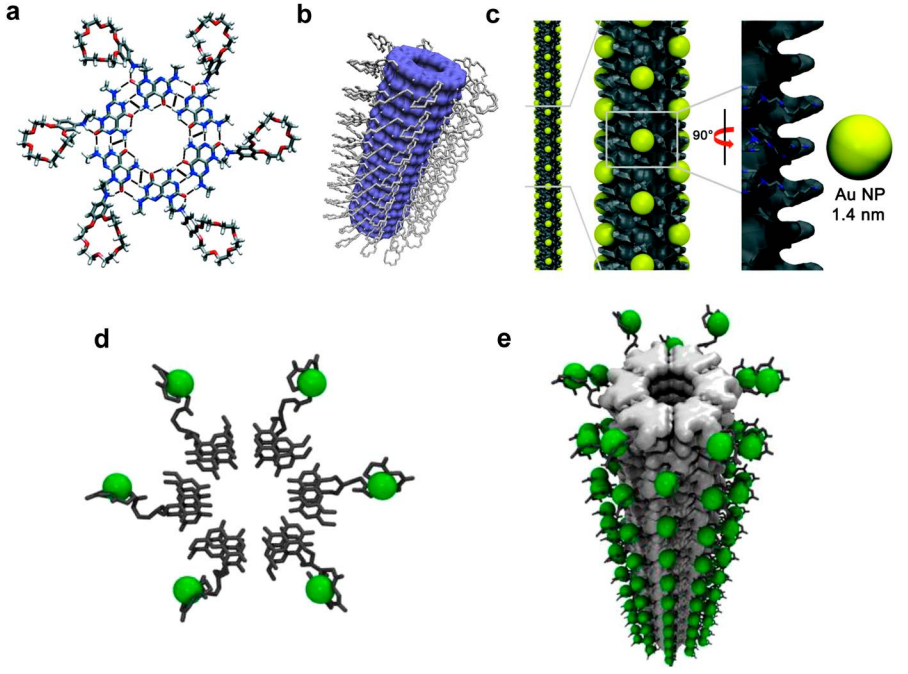


Figure 3.10 Schematic illustrations for (a) cyclic hexamer of **16**,[83] (b) RNTs formed from **16**,[84] (c) gold nanoparticles formed on the surface of RNTs,[86] (d) cyclic hexamer of **19** and (e) RNTs of **19**.[87] Part (a) reprinted with permission from H. Fenniri, B.-L. Deng, A. E. Ribbe, K. Hallenga, J. Jacob and P. Thiyagarajan, Entropically driven self-assembly of multichannel rosette nanotubes, *Proc. Natl. Acad. Sci.*, 2002, **99**, 6487–6492. Copyright (2002) National Academy of Sciences, USA. Part (b) reprinted with permission from H. Fenniri, B. L. Deng and A. E. Ribbe, Helical rosette nanotubes with tunable chiroptical properties, *J. Am. Chem. Soc.*, 2002, **124**, 11064–11072. Copyright (2002) American Chemical Society. Part (c) reprinted with permission from R. Chhabra, J. G. Moralez, J. Raez, T. Yamazaki, J. Y. Cho, A. J. Myles, A. Kovalenko and H. Fenniri, One-pot nucleation, growth, morphogenesis, and passivation of 1.4 nm Au nanoparticles on self-assembled rosette nanotubes, *J. Am. Chem. Soc.*, 2010, **132**, 32–33. Copyright (2010) American Chemical Society. Parts (d) and (e) reprinted from A. Alsbaiee, M. St. Jules, R. L. Beingessner, J. Y. Cho, T. Yamazaki and H. Fenniri, Synthesis of rhenium chelated MAG3 functionalized rosette nanotubes, *Tetrahedron Lett.*, **53**, 1645–1651. Copyright (2012) with permission from Elsevier.

Interestingly, the UV–visible spectra of **22** showed a remarkable red shift with a giant molar ellipticity of 4×10^6 deg M^{-1} m^{-1}, which was ascribed to the J-type alignment of chromophores in the RNTs.[89] The controlled surface, internal structure and diameter of the RNTs enhanced their potential use. For example, the water-insoluble anticancer drug tamoxifen was introduced into their tubular structures by hydrophobic interactions; the RNTs self-assembled from the twin G∧C motif showed enhanced loading of tamoxifen.[90]

This was ascribed to the stronger hydrogen bond networks, stronger π-stacking interactions and, as a result, enhanced stability of the nanotube structure of the twin-base RNTs.

3.4.5 Self-Assembly of Two-Component RNTs *via* Dynamic Chemistry

The introduction of controllable dynamic features to self-assembly has been proposed in terms of constitutional dynamic chemistry, which allows the selection of functional supermolecules from a pool of compounds with all possible constitutions under the given conditions of internal or external perturbations.[3,91,92] The process can be considered as supramolecular combinatorial chemistry from instructed mixtures of molecular components. In this regard, the simultaneous pursuit of conformational diversity and specific molecular interactions provides an alternative perspective for achieving adaptive self-assembly around the molecular to nanosized guests.[93–95] The introduction of chemical reactions in the selection process[3,96] is also expected to promote the molecular evolution of supramolecular entities presenting specific architectures and functions.

Hud and coworkers have shown that RNTs can be also formed from the complementary pairs of melamine and barbituric acid on glycosylation by ribose-5-phosphate (R5P).[97] When barbituric acid is mixed in water with an equimolar amount of R5P at 20 °C, conjugates exceeding 80% in the unpurified reaction mixture were obtained after 24 h. This reaction proceeds through a Knoevenagel condensation and, interestingly, 5-ribofuranosyl-C-barbiturate-5′-monophosphate was formed, as confirmed by nuclear magnetic resonance spectrometry, and the *β*-anomer (*β*-C-BMP) was preferentially formed in a 67 : 33 ratio over the *α*-anomer (Figure 3.11). The glycosylation of melamine with R5P occurred at an exocyclic amine at 20 °C through a reversible Schiff base intermediate to give *N*-ribofuranosyl-melamine-5′-monophosphate (MMP). In this case, the *α*- and *β*-isomers of MMP were in equilibrium to give an almost equimolar mixture in water.

Mixing the crude reaction mixtures in water (pH 4–5) gave linear supramolecular aggregates with an average diameter of 2 nm, which is consistent with the RNTs of hydrogen bonded hexads self-assembled from BMP and MMP. C-BMP and MMP nucleotides also formed water-soluble RNTs when mixed with free melamine and free barbituric acid, respectively. The C-BMP–melamine and MMP–barbituric acid assemblies also formed water-soluble 2 nm assemblies, indicating that the steric interaction and charge provided by conjugation with R5P on one nucleobase favored the formation of RNTs instead of forming water-insoluble melamine–barbituric acid precipitates. *β*-MMP was selectively incorporated into the RNTs over *α*-MMP and the anomerization of *α*-MMP to *β*-MMP occurred in solution. These observations are reminiscent of the enrichment of the *β*-anomeric form of ribonucleotides in living organisms, suggesting such an equilibrium shift occurred for nucleotides on the prebiotic Earth.

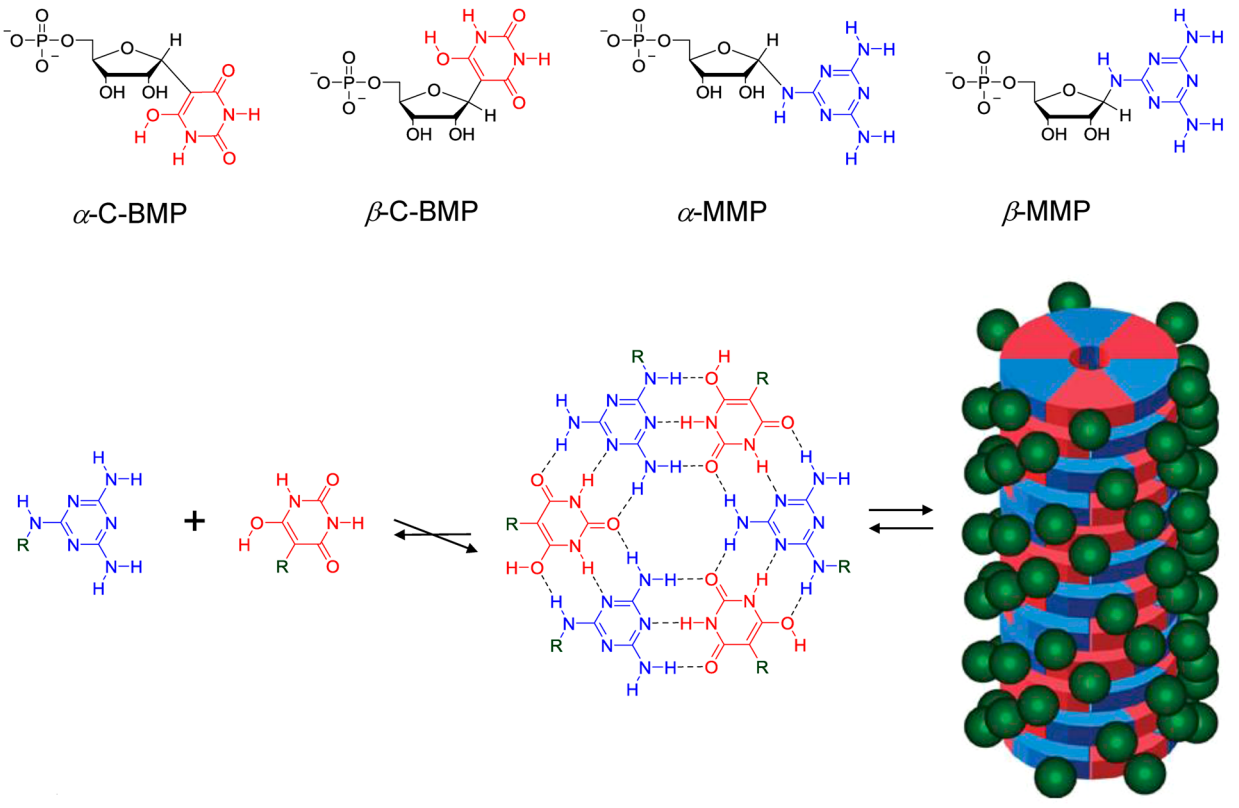


Figure 3.11 Schematic illustration of the aqueous self-assembly of ribose-5-phosphate conjugated melamines and barbituric acid into RNTs. Reprinted with permission from Cafferty, B. J. *et al.* Spontaneous formation and base pairing of plausible prebiotic nucleotides in water, *Nat. Commun.* 7, 11328 doi: 10.1038/ncomms11328 (2016). Published under a Creative Commons Attribution 4.0 International License, http://creativecommons.org/licenses/by/4.0/.

3.5 Conclusions

This chapter has introduced the chemistry of aqueous supramolecular amphiphiles that use complementary hydrogen bonds as indispensable intermolecular interactions. Supramolecular amphiphiles mediated by multiple hydrogen bonding are designed from complementary pairs or molecules with self-complementary aromatic units. The acquisition of an amphiphilic superstructure based on these specific hydrogen bonded interactions is a common feature of these aqueous self-assembly systems. These principles are distinct from the conventional amphiphilic self-assemblies in which multiple hydrogen bonds are used to reinforce intermolecular interactions between amphiphiles.[11,98,99] In a broad sense, amphiphiles that acquire a higher level of amphiphilicity—for example, by the electrostatic binding of second molecular components—can be classified as supramolecular amphiphiles.[7,100,101] For the purpose of applying amphiphilic superstructures, conventional amphiphiles may be advantageous, especially in terms of the cost of production. However, precisely controlled intermolecular relative orientation and the consequent supramolecular architectures may result in specific functions not attainable from classical amphiphilic self-assemblies.

Studies on hydrogen bonded self-assembly in non-aqueous media have been an active field of supramolecular chemistry. Supramolecular polymers are broadly defined as polymeric arrays of repeating molecular units assembled by reversible and directional noncovalent interactions; the formation of soluble primary structures mediated by multiple hydrogen bonding has been demonstrated in the early stages.[102] As discussed in this chapter, amphiphilic self-assembly is a concept that includes organic solvents and ionic liquids. The introduction of amphiphilicity, *i.e.* solvophilic–solvophobic interactions, to control secondary and ternary structures has opened a new dimension to supramolecular chemistry[55,62,65,66] that continues to this day.[103–106]

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References

1. T. Kunitake, *Angew. Chem., Int. Ed.*, 1992, **31**, 709–726.
2. J.-M. Lehn, *Chem. Soc. Rev.*, 2007, **36**, 151–160.
3. J.-M. Lehn, *Angew. Chem., Int. Ed. Engl.*, 2013, **52**, 2836–2850.
4. M. Fujita, M. Tominaga, A. Hori and B. Therrien, *Acc. Chem. Res.*, 2005, **38**, 369–378.
5. C. G. Palivan, R. Goers, A. Najer, X. Zhang, A. Car and W. Meier, *Chem. Soc. Rev.*, 2016, **45**, 377–411.

6. N. Kimizuka, *Curr. Opin. Chem. Biol.*, 2003, **7**, 702–709.
7. N. Kimizuka, *Adv. Polym. Sci.*, 2008, **219**, 1–26.
8. N. Kimizuka, *Supramol. Polym.*, 2nd edn, 2005, ch. 13, vol. 7, pp. 481–507.
9. C. Wang, Z. Wang and X. Zhang, *Acc. Chem. Res.*, 2012, **45**, 608–618.
10. N. Yamada, K. Ariga, M. Naito, K. Matsubara and E. Koyama, *J. Am. Chem. Soc.*, 1998, **120**, 12192–12199.
11. S. I. Stupp and L. C. Palmer, *Chem. Mater.*, 2014, **26**, 507–518.
12. E. Krieg, M. M. C. Bastings, P. Besenius and B. Rybtchinski, *Chem. Rev.*, 2016, **116**, 2414–2477.
13. F. M. Menger, *Proc. Natl. Acad. Sci. U. S. A.*, 2002, **99**, 4818–4822.
14. H. Kuhn and D. Möbius, *Angew. Chem., Int. Ed. Engl.*, 1971, **10**, 620–637.
15. T. Kunitake and Y. Okahata, *J. Am. Chem. Soc.*, 1977, **99**, 3860–3861.
16. H. Ringsdorf, B. Schlarb and J. Venzmer, *Angew. Chem., Int. Ed. Engl.*, 1988, **27**, 113–158.
17. J.-H. Fuhrhop and T. Wang, *Chem. Rev.*, 2004, **104**, 2901–2937.
18. H.-J. Kim, T. Kim and M. Lee, *Acc. Chem. Res.*, 2011, **44**, 72–82.
19. Y. Ishikawa, H. Kuwahara and T. Kunitake, *J. Am. Chem. Soc.*, 1989, **111**, 8530–8531.
20. Y. Ishikawa, H. Kuwahara and T. Kunitake, *J. Am. Chem. Soc.*, 1994, **116**, 5579–5591.
21. N. Kimizuka and T. Nakashima, *Langmuir*, 2001, **17**, 6759–6761.
22. T. Nakashima and N. Kimizuka, *Chem. Lett.*, 2002, **4**, 1018–1019.
23. T. Nakashima and N. Kimizuka, *Polym. J.*, 2012, **44**, 665–671.
24. T. L. Greaves and C. J. Drummond, *Chem. Soc. Rev.*, 2008, **37**, 1709–1726.
25. T. Kunitake, N. Kimizuka, N. Higashi and N. Nakashima, *J. Am. Chem. Soc.*, 1984, **106**, 1978–1983.
26. N. Kimizuka, H. Ohira, M. Tanaka and T. Kunitake, *Chem. Lett.*, 1990, 29–32.
27. T. Kunitake, Y. Okahata, M. Shimomura, S. Yasunami and K. Takarabe, *J. Am. Chem. Soc.*, 1981, **103**, 5401–5413.
28. M. Shimomura, R. Ando and T. Kunitake, *Berichte der Bunsengesellschaft für Phys. Chemie*, 1983, vol. 87, pp. 1134–1143.
29. F. M. Menger and Y. Yamasaki, *J. Am. Chem. Soc.*, 1993, **115**, 3840–3841.
30. Y. Okahata and T. Kunitake, *J. Am. Chem. Soc.*, 1979, **101**, 5231–5234.
31. J.-H. Fuhrhop and T. Wang, *Chem. Rev.*, 2004, **104**, 2901–2938.
32. F. M. Menger and C. A. Littau, *J. Am. Chem. Soc.*, 1993, **115**, 10083–10090.
33. F. M. Menger and J. S. Keiper, *Angew. Chem., Int. Ed.*, 2000, **39**, 1906–1920.
34. E. Kaler, A. Murthy, B. Rodriguez and J. Zasadzinski, *Science*, 1989, **245**, 1371–1374.
35. L. Chiappisi, H. Yalcinkaya, V. K. Gopalakrishnan, M. Gradzielski and T. Zemb, *Colloid Polym. Sci.*, 2015, **293**, 3131–3143.
36. Y. J. Jeon, P. K. Bharadwaj, S. Choi, J. W. Lee and K. Kim, *Angew. Chem., Int. Ed.*, 2002, **41**, 4474–4476.
37. G. Yu, K. Jie and F. Huang, *Chem. Rev.*, 2015, **115**, 7240–7303.
38. X. Chi, H. Zhang, G. I. Vargas-Zúñiga, G. M. Peters and J. L. Sessler, *J. Am. Chem. Soc.*, 2016, **138**, 5829–5832.

39. K. Jie, Y. Zhou, Y. Yao, B. Shi and F. Huang, *J. Am. Chem. Soc.*, 2015, **137**, 10472–10475.
40. J. Suh, K. J. Lee, G. Bae, O.-B. Kwon and S. Oh, *Langmuir*, 1995, **11**, 2626–2632.
41. P. Garcia, J. Marques, E. Pereira, P. Gameiro, B. de Castro and R. Salema, *Chem. Commun.*, 2001, 1298–1299.
42. J. Liu, M. A. Morikawa and N. Kimizuka, *J. Am. Chem. Soc.*, 2011, **133**, 17370–17374.
43. T. Kunitake, Y. Ishikawa, M. Shimomura and H. Okawa, *J. Am. Chem. Soc.*, 1986, **108**, 327–328.
44. N. Kimizuka, *Adv. Mater.*, 2000, **12**, 1461–1463.
45. N. Kimizuka, M. Tokuhiro, H. Miyauchi, T. Wakiyama and T. Kunitake, *Chem. Lett.*, 1997, 1049–1050.
46. T. L. Greaves and C. J. Drummond, *Chem. Soc. Rev.*, 2013, **42**, 1096–1120.
47. P. Terech and R. G. Weiss, *Chem. Rev.*, 1997, **97**, 3133–3160.
48. M. George and R. G. Weiss, *Acc. Chem. Res.*, 2006, **39**, 489–497.
49. B. Alberts, A. Johnson, J. Lewis, M. Raff, K. Roberts and P. Walter, *Molecular Biology of the Cell*, Garland Science, 5th edn, 2008.
50. J. S. Nowick, J. S. Chen and G. Noronha, *J. Am. Chem. Soc.*, 1993, **115**, 7636–7644.
51. J.-M. Lehn, M. Mascal, A. Decian and J. Fischer, *J. Chem. Soc., Chem. Commun.*, 1990, **479**, 479.
52. T. Gulik-Krzywicki, C. Fouquey and J. Lehn, *Proc. Natl. Acad. Sci.*, 1993, **90**, 163–167.
53. J. P. Mathias, E. E. Simanek, J. A. Zerkowski, C. T. Seto and G. M. Whitesides, *J. Am. Chem. Soc.*, 1994, **116**, 4316–4325.
54. J. C. MacDonald and G. M. Whitesides, *Chem. Rev.*, 1994, **94**, 2383–2420.
55. N. Kimizuka, T. Kawasaki, K. Hirata and T. Kunitake, *J. Am. Chem. Soc.*, 1995, **117**, 6360–6361.
56. V. M. Rotello, E. A. Viani, G. Deslongchamps, B. A. Murray and J. Rebek, *J. Am. Chem. Soc.*, 1993, **115**, 797–798.
57. J. H. K. Ky Hirschberg, L. Brunsveld, A. Ramzi, Jef A. J. M. Vekemans, R. P. Sijbesma and E. W. Meijer, *Nature*, 2000, **407**, 167–170.
58. K. Kurihara, K. Ohto, Y. Honda and T. Kunitake, *J. Am. Chem. Soc.*, 1991, **113**, 5077–5079.
59. D. Y. Sasaki, K. Kurihara and T. Kunitake, *J. Am. Chem. Soc.*, 1992, **114**, 10994–10995.
60. M. Onda, K. Yoshihara, H. Koyano, K. Ariga and T. Kunitake, *J. Am. Chem. Soc.*, 1996, **118**, 8524–8530.
61. T. Sawada and M. Fujita, *J. Am. Chem. Soc.*, 2010, **132**, 7194–7201.
62. N. Kimizuka, T. Kawasaki and T. Kunitake, *J. Am. Chem. Soc.*, 1993, **115**, 4387–4388.
63. N. Kimizuka, T. Kawasaki and T. Kunitake, *Chem. Lett.*, 1994, **23**, 33–36.
64. N. Kimizuka, T. Kawasaki and T. Kunitake, *Chem. Lett.*, 1994, **23**, 1399–1402.
65. N. Kimizuka, T. Kawasaki, K. Hirata and T. Kunitake, *J. Am. Chem. Soc.*, 1998, **120**, 4094–4104.

66. T. Kawasaki, M. Tokuhiro, N. Kimizuka and T. Kunitake, *J. Am. Chem. Soc.*, 2001, **123**, 6792–6800.
67. C. T. Seto and G. M. Whitesides, *J. Am. Chem. Soc.*, 1993, **115**, 905–916.
68. J. A. Zerkowski, C. T. Seto and G. M. Whitesides, *J. Am. Chem. Soc.*, 1992, **114**, 5473–5475.
69. N. Nakashima, S. Asakuma and T. Kunitake, *J. Am. Chem. Soc.*, 1985, **107**, 509–510.
70. H. Cheng, Y.-J. Cheng, S. Bhasin, J.-Y. Zhu, X.-D. Xu, R.-X. Zhuo and X.-Z. Zhang, *Chem. Commun.*, 2015, **51**, 6936–6939.
71. R. Iwaura, K. Yoshida, M. Masuda, K. Yase and T. Shimizu, *Chem. Mater.*, 2002, **14**, 3047–3053.
72. R. Iwaura, K. Yoshida, M. Masuda, M. Ohnishi-Kameyama, M. Yoshida and T. Shimizu, *Angew. Chem., Int. Ed.*, 2003, **42**, 1009–1012.
73. R. Iwaura, F. J. M. Hoeben, M. Masuda, A. P. H. J. Schenning, E. W. Meijer and T. Shimizu, *J. Am. Chem. Soc.*, 2006, **128**, 13298–13304.
74. W. Yang, Y. Chen, M. S. Wong and P. K. Lo, *Biomacromolecules*, 2012, **13**, 3370–3376.
75. M. Ciobanu and S. Asaftei, *Opt. Mater. (Amst.).*, 2015, **42**, 262–269.
76. P. G. A. Janssen, J. Vandenbergh, J. L. J. van Dongen, E. W. Meijer and A. P. H. J. Schenning, *J. Am. Chem. Soc.*, 2007, **129**, 6078–6079.
77. M. Surin, P. G. A. Janssen, R. Lazzaroni, P. Leclère, E. W. Meijer and A. P. H. J. Schenning, *Adv. Mater.*, 2009, **21**, 1126–1130.
78. S. C. Zimmerman and B. F. Duerr, *J. Org. Chem.*, 1992, **57**, 2215–2217.
79. A. Marsh, M. Silvestri and J.-M. Lehn, *Chem. Commun.*, 1996, **29**, 1527.
80. Y. Ma, S. V. Kolotuchin and S. C. Zimmerman, *J. Am. Chem. Soc.*, 2002, **124**, 13757–13769.
81. H. Fenniri, P. Mathivanan, K. L. Vidale, D. M. Sherman, K. Hallenga, K. V. Wood and J. G. Stowell, *J. Am. Chem. Soc.*, 2001, **123**, 3854–3855.
82. J. G. Moralez, J. Raez, T. Yamazaki, R. K. Motkuri, A. Kovalenko and H. Fenniri, *J. Am. Chem. Soc.*, 2005, **127**, 8307–8309.
83. H. Fenniri, B.-L. Deng, A. E. Ribbe, K. Hallenga, J. Jacob and P. Thiyagarajan, *Proc. Natl. Acad. Sci.*, 2002, **99**, 6487–6492.
84. H. Fenniri, B. L. Deng and A. E. Ribbe, *J. Am. Chem. Soc.*, 2002, **124**, 11064–11072.
85. L. Zhang, F. Rakotondradany, A. J. Myles, H. Fenniri and T. J. Webster, *Biomaterials*, 2009, **30**, 1309–1320.
86. R. Chhabra, J. G. Moralez, J. Raez, T. Yamazaki, J. Y. Cho, A. J. Myles, A. Kovalenko and H. Fenniri, *J. Am. Chem. Soc.*, 2010, **132**, 32–33.
87. A. Alsbaiee, M. St. Jules, R. L. Beingessner, J. Y. Cho, T. Yamazaki and H. Fenniri, *Tetrahedron Lett.*, 2012, **53**, 1645–1651.
88. B. L. Deng, R. L. Beingessner, R. S. Johnson, N. K. Girdhar, C. Danumah, T. Yamazaki and H. Fenniri, *Macromolecules*, 2012, **45**, 7157–7162.
89. G. Borzsonyi, R. L. Beingessner, T. Yamazaki, J. Y. Cho, A. J. Myles, M. Malac, R. Egerton, M. Kawasaki, K. Ishizuka, A. Kovalenko and H. Fenniri, *J. Am. Chem. Soc.*, 2010, **132**, 15136–15139.
90. S. Sonng, Y. Chen, Z. Yan, H. Fenniri and T. J. Webster, *Int. J. Nanomedicine*, 2011, **6**, 101.

91. J.-M. Lehn, *Science*, 2002, **295**, 2400–2403.
92. J.-M. Lehn, *Proc. Natl. Acad. Sci.*, 2002, **99**, 4763–4768.
93. R. Nishiyabu, N. Hashimoto, T. Cho, K. Watanabe, T. Yasunaga, A. Endo, K. Kaneko, T. Niidome, M. Murata, C. Adachi, Y. Katayama, M. Hashizume and N. Kimizuka, *J. Am. Chem. Soc.*, 2009, **131**, 2151–2158.
94. R. Nishiyabu, C. Aimé, R. Gondo, T. Noguchi and N. Kimizuka, *Angew. Chem., Int. Ed.*, 2009, **48**, 9465–9468.
95. R. Nishiyabu, C. Aimé, R. Gondo, K. Kaneko and N. Kimizuka, *Chem. Commun. (Camb.)*, 2010, **46**, 4333–4335.
96. I. Huc and J. M. Lehn, *Proc. Natl. Acad. Sci. U. S. A.*, 1997, **94**, 2106–2110.
97. B. J. Cafferty, D. M. Fialho, J. Khanam, R. Krishnamurthy and N. V. Hud, *Nat. Commun.*, 2016, **7**, 11328.
98. Y. Hu, R. Lin, K. Patel, A. G. Cheetham, C. Kan and H. Cui, *Coord. Chem. Rev.*, 2016, **320–321**, 2–17.
99. K. Matsuura, K. Fujino, T. Teramoto, K. Murasato and N. Kimizuka, *Bull. Chem. Soc. Jpn.*, 2010, **83**, 880–886.
100. T. Nakashima and N. Kimizuka, *Adv. Mater.*, 2002, **14**, 1113–1116.
101. C. Aime, R. Tamoto, T. Satoh, A. Grelard, E. J. Dufourc, T. Buffeteau, H. Ihara and R. Oda, *Langmuir*, 2009, **25**, 8489–8496.
102. T. Gulik-Krzywicki, C. Fouquey and J. Lehn, *Proc. Natl. Acad. Sci.*, 1993, **90**, 163–167.
103. L. Brunsveld, B. J. B. Folmer, E. W. Meijer and R. P. Sijbesma, *Chem. Rev.*, 2001, **101**, 4071–4097.
104. F. Würthner, *Chem. Commun.*, 2004, 1564–1579.
105. S. Yagai, *Bull. Chem. Soc. Jpn.*, 2015, **88**, 28–58.
106. T. Aida, E. W. Meijer and S. I. Stupp, *Science*, 2012, **335**, 813–817.

CHAPTER 4

Electrostatic Supra-Amphiphiles

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4.1 Introduction

Covalent approaches have traditionally been followed for the production of materials, where the formation of C–C and C–heteroatom bonds (*e.g.* C–S, C–O and C–N) have been extensively explored and exploited for the synthesis of low molecular weight and polymeric compounds. With the expansion of synthetic polymer chemistry routes, it has been possible to traverse more than one length scale and thus new possibilities to access single molecules and structures up to tens of nanometres in size have emerged. Such materials have found wide applications and have been used for both structural and functional purposes. However, solubility and processability are of crucial importance to ensure the general applicability of such materials. Specifically, surface-active agents, or surfactants, play a major part in the processing, dissolution and formulation of active ingredients and materials in pharmaceutical and personal and home care applications.

Over the last three decades, supramolecular or 'chemistry beyond the molecule'[1] approaches have emerged as an alternative route for the formation and fabrication of materials. Researchers have expanded the available tools

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of covalent chemistry, making extensive use of non-covalent interactions, including hydrogen-bonding,[2] charge transfer,[3] van der Waals[4] and electrostatic interactions.[5] These approaches, more specifically termed supramolecular chemistry and self-assembly, have proved to be very successful in producing a wide range of materials.[6] The advantages of these approaches have been shown in many examples; these routes provide real opportunities for designing, tuning and fabricating intricate molecular architectures and topologies that would either be extremely challenging[7] or simply impossible to achieve by traditional covalent synthetic methodologies.

The increased control over assembly that results from understanding these non-covalent interactions allows the preparation of new materials across multiple length scales. Exploitation of these approaches has thus opened new avenues for the preparation of materials with structural features or motifs from the low nanometre to micrometre, and possibly even millimetre, scale.[8] Such impressive structural manipulation has been enabled by the self-assembly of combinations of small and polymeric molecules or, as shown in more recent examples, polymer self-assembly only.[9]

In addition to these simple structural aspects, the inclusion of functionality in such materials remains an achievable, but challenging, goal.[10] Functional units can be added to non-covalent constructs in a facile fashion by designing functional units that possess complementary non-covalent interactions, thus ensuring their inclusion within the self-assembled structures.[11] Current research goes beyond methods for simply including functionality in self-assembled structures and into controlling and fine tuning functional aspects such as switchability.[12] If the correct (covalently formed) tectons or building blocks are chosen, the non-covalent approach is an attractive route for the production of functional materials with a higher degree of hierarchy,[9] order and even function.

In addition to being able to enjoy facile non-covalent synthetic steps for the production of intricate structures and hierarchies, the use of these 'soft' interactions provides real opportunities to induce smart properties such as switchability[13] and dynamic behaviour[14] in new materials. Switchability and a dynamic nature are of crucial importance for the development of future materials to fill new application niches.

Evaluation of the relative strengths, as well as other properties such as directionality, of the various non-covalent interactions (Table 4.1) shows that a wide range of properties and stabilities are accessible through a careful choice of the type of interaction employed. In addition, the ability to exhibit dynamic behaviour when exposed to external stimuli is an extremely attractive feature of these soft, non-covalent interactions. It would therefore be possible, through careful choice and design, to include a range of strengths of interaction, different types of interaction and thus also different ways to address and include orthogonal switchability or addressability (*i.e.* using two or more different stimuli, such as light and pH or pH and enzyme degradability) to ensure full control over changes in both structure and function. The advantages of the inclusion of such dynamic behaviour

Table 4.1 Comparison of the properties of a selection of intermolecular interactions.

Interaction	Bond strength (kJ mol^{-1})	Length (pm)	Directional?
Covalent bond	350	154[a]	Yes
Imine (covalent H_2C=NH) bond	644	130	Yes
Ionic bond	5–200	[b]	No
Hydrogen bond	5–65	150–260[c]	Yes
Van der Waals	2–4	[b]	No
π–π	4–8	330–380[c]	Yes

[a]Value for a C–C bond in diamond.
[b]Variable; strength of interaction varies with separation.
[c]Centroid–centroid distance.

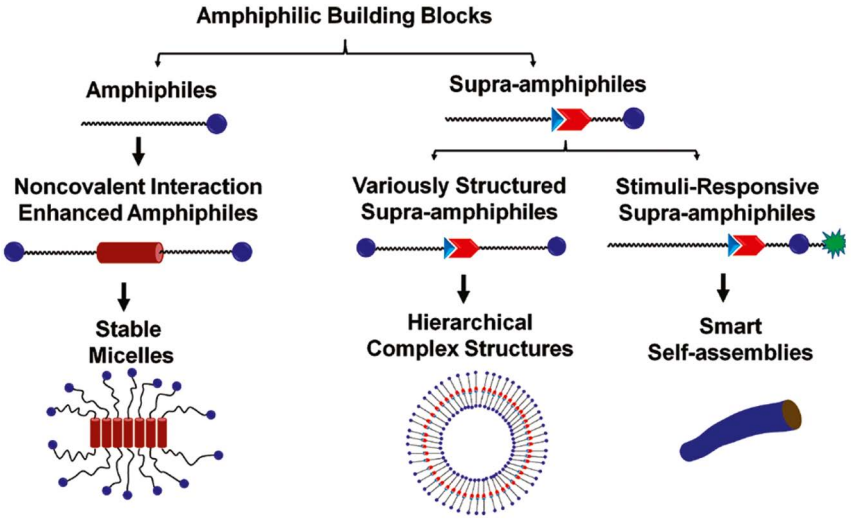
might be obvious, but the disadvantages, such as the long-term stability and robustness of constructs and their functionality, should be kept in mind. These aspects (*i.e.* both the advantages and disadvantages of exploiting such soft interactions for the construction of novel functional materials) will be highlighted in our discussions on the use and applications of supra-amphiphiles (SAs).

Taking a step back from these attractive features across the realms of covalent and non-covalent synthesis, there is now a real opportunity to expand and capitalize on both of these now well-established routes to materials. A new era is approaching where multi-step synthesis can include both covalent and supramolecular synthetic steps as part of a total synthesis scheme, thus combining all the attractive features (stable structures, dynamic behaviour, functionality and switchability) into one approach. This approach would enable the exploration of a wide range of topologies, morphologies, functionalities and 'staggered' stabilities and different levels of dynamic behaviour, which would otherwise be very hard to achieve with an exclusive approach (either covalent only or supramolecular only).

With this background, we now focus our discussion on an exciting class of materials, the so-called SAs. SAs are excellent candidates with which to explore this novel synthetic pathway for the formation of functional materials across multiple length scales. In addition, we will highlight the opportunities to introduce, in a facile fashion, orthogonal functionality (*e.g.* redox activity and pH or light sensitivity), which will enable a much wider range of applications where dynamic behaviour, switchability and addressability are of high importance.

4.2 Definition of Supra-Amphiphiles

Amphiphiles are a class of molecules that have the ability to interact with both hydrophobic and hydrophilic solvents and environments (*i.e.* 'loving' both) and can be both low molecular weight or polymeric in nature. Such amphiphiles, also known as surfactants (*i.e.* surface-active agents) because



Scheme 4.1 Schematic explanation of structure formation and rich topological features accessible using a general SA approach. Reproduced with permission from C. Wang, Z. Wang and X. Zhang., Amphiphilic building blocks for self-assembly: from amphiphiles to supra-amphiphiles, *Acc. Chem. Res.*, 2012, **45**(4), 608. Copyright (2012) American Chemical Society.

of their ability to populate interfaces and thus modify their properties, are generally produced from covalent synthetic chemistry pathways.

Following the logic presented in the introduction, we could therefore expect that it should also be possible to produce amphiphiles using a supramolecular approach, *i.e.* SAs. This approach has indeed been introduced in recent years[15] and, formally, SAs have been defined as 'amphiphiles constructed of non-covalent or dynamic covalent bonds'.[16] This definition is explained in more detail in Scheme 4.1.

There is a range of different non-covalent interactions available for exploitation in the construction of self-assembled materials. It can therefore be reasonably expected that a similar range of strategies (and combinations of strategies) would also have been used for the construction of SAs. SAs have already been formed by the following interactions: electrostatic, charge transfer, host–guest, hydrogen bonding, coordination and dynamic covalent interactions.

4.3 Electrostatic Supra-Amphiphiles

This chapter focuses on the use of electrostatic interactions for the formation of SAs; *i.e.* electrostatic supra-amphiphiles (eSAs). We explore both low and high molecular weight approaches and highlight the inclusion of (orthogonal) functionality, which makes these materials attractive for further

expansion and exploration in future applications. The eSAs are a subset of SAs in which the construction of the fundamental amphiphilic building block (SA) utilizes primarily electrostatic interactions of oppositely (permanently) charged species.

Electrostatic interactions are fundamental interactions found throughout nature. Here, we restrict the discussion of electrostatic interactions to those arising from formally charged species, rather than including the gamut of interactions that result from partial or induced charges (*e.g.* dipole–dipole, van der Waals). Electrostatic interactions are fully described by the Poisson equation. However, Coulomb's law can be successfully applied when the charge distribution can be described in terms of a set of point charges.[17] Coulomb's law, given in eqn (4.1), describes the force F acting between two charged particles q_1 and q_2 separated by a distance r. Oppositely charged particles experience an attractive force, whereas particles with the same sign of charge experience a repulsive force. The constant of proportionality k_e is Coulomb's constant ($k_e = 8.99 \times 10^9$ N m^2 C^{-2}) and ε is the relative permittivity of the medium through which the force acts:

$$F = k_e \frac{q_1 q_2}{\varepsilon r^2} \tag{4.1}$$

The strength of electrostatic interactions therefore depends strongly on the separation of charges, as well as on the medium through which the electrostatic interaction force acts. Water screens electrostatic interactions effectively because of its high relative permittivity of $\varepsilon = 80.1$ (at 20 °C). However, organic media screen electrostatic interactions much less strongly, thus a stronger force is experienced between charges in these media. This dependence on the medium can be used to direct the self-assembly of charged species. For example, charges are screened less in the hydrophobic interiors of proteins than in water. Thus the hydrophobic medium allows charged substrates to bind more strongly to oppositely charged groups buried within a hydrophobic enzyme active site than would be possible in water, making enzymes effective catalysts. In this way, the self-assembly of synthetic systems may also be promoted or hindered in solvents of different polarity.

The energy of interactions between charged species, treated as point charges, can be calculated using eqn (4.2), where E is the energy (J) and the other variables are as in eqn (4.1). Thus the energy of the attractive electrostatic interaction between two atoms, each having single and opposing charges and separated by 3 Å in water, is 5.78 kJ mol^{-1}:

$$E = k_e \frac{q_1 q_2}{\varepsilon r} \tag{4.2}$$

A comparison of the interaction energies of various non-covalent interactions is shown in Table 4.1. Electrostatic interactions can be among the strongest non-covalent intermolecular interactions, but their strength is highly dependent on the system in question and varies with the separation, number of charges and medium.

One feature of electrostatic interactions that sets them apart from other non-covalent interactions is their ability to provide both attractive and repulsive forces between charged species. A balance of attractive and repulsive forces is crucial for the formation of highly ordered self-assembled structures. If the attractive forces between self-assembling components are too strong, then the components will aggregate irreversibly and form disordered structures. A degree of reversibility is required to allow the self-correction of misplaced, misaligned or incorrectly bound components, thus increasing the order in the final structure. Repulsive interactions are therefore crucial to balance the attractive forces, providing reversibility and thus more ordered self-assembled structures. Electrostatic repulsion between like charges is a factor in several self-assembling systems, such as between surfactant headgroups during micellization. In this case, the electrostatic repulsion between headgroups is one factor that contributes to the repulsive interactions that oppose the hydrophobic effect driven aggregation of surfactants in water. These repulsive interactions together prevent total phase separation of the surfactant solution; various micellar phases are formed instead.

Electrostatic interactions are inherently variable. This variability can be harnessed to tune the interactions between molecules. The selection of appropriate solvents can boost the strength of electrostatic attraction by reducing screening. The addition of salts to a solution also changes its ability to screen charges, which can attenuate the strength of interactions. Charges may also be induced in molecules that are Brønsted acids or bases, which can become either charged or neutral in response to changes in pH, allowing electrostatic interactions to be switched on or off by an external stimulus. Molecules can thus be designed either to include permanent charges in their molecular structure (*e.g.* $-NMe_3^+$), or to have the ability to become charged, by the inclusion of acidic (*e.g.* –COOH) or basic (*e.g.* $-NH_2$) groups. These electrostatic design handles allow aggregation into ordered structures to be controlled, and even switched on and off, *i.e.* it provides opportunities to switch between ordered and disordered structures, or functional assemblies and their constituent (non-functional) tectons.

A number of material construction methodologies based on electrostatic interactions have been developed with the advent of supramolecular chemistry and self-assembly. The two most well-known are the so-called layer-by-layer (LbL) and ionic self-assembly (ISA) routes. The LbL route utilizes the sequential multi-step deposition of oppositely charged polyelectrolyte layers (thus the LbL designation) to build up electrostatically stabilized planar (membrane-like) or hollow (constructed around soluble template particles) structures.[18,19] The opportunity exists to make use of a wide range of polyelectrolytic constituents. It has also been shown that it is possible to make use of other non-covalent interactions placed along a polymer backbone structure (such as hydrogen bonding) to construct materials in a similar sequential fashion.

The ISA route[5,20] has been defined as a process in which small charged surfactant species bind to oppositely charged poly- or oligo(electrolytes) to form poly(electrolyte)–surfactant (PE–S) or oligo(electrolyte)–surfactant (OE–S) complexes.[20] More specifically, this process has been defined (and experimentally verified through the determination of binding isotherms) as being a cooperative process.[21,22] In such processes, which are sometimes described as exhibiting a zipper-like binding behaviour, binding of the surfactant only takes place once the critical aggregation concentration on addition of free surfactant has been reached. Binding then proceeds rapidly until a degree of binding close to unity is reached, yielding a sigmoidal binding curve. As all the charges are neutralized in the ISA process, this leads to precipitation and the formation of soft, nanostructured liquid crystalline materials.[23] The similarities between the LbL and ISA processes and the production of eSAs are reflected by the fact that stable electrostatic interactions are utilized to prepare robust materials from the combination of oppositely charged species. Functional tectons can be included in an extremely facile fashion to produce stable functional materials in both cases; however, the production of soluble amphiphilic species is not achieved in the ISA route.

The ability to use strong electrostatic interactions, in conjunction with other addressable or switchable moieties and interactions, to produce stable supramolecular constructs that exhibit amphiphilic behaviour (and thus the ability to assembly into larger, hierarchical constructs) will be explored. The ways in which such electrostatic interactions are exploited for the production of both low molecular weight and polymeric eSAs are described in detail in the two following sections. Aspects of structure, function, dynamic behaviour and switchability of structure and (orthogonal) functionality will be discussed for both these groups of eSAs.

4.4 Classes and Examples of Electrostatic SAs

SAs that use electrostatic interactions may be seen as a natural progression from the large existing body of work on PE–S (or OE–S) complexes.[24] Despite the cooperativity shown in the formation of seemingly simple complexes between poly(electrolyte)s and oppositely charged surfactants, these systems remain distinct from eSAs. The main requirement for classification as an eSA that is lacking for PE–S/OE–S complexes is that, once formed, the PE–S complex is the final (non-water-soluble and precipitated) product, as all the charges have been neutralized. No further structural complexity or hierarchy is attained in solution; PE–S/OE–S complexes typically precipitate, only then forming highly ordered mesophases, especially when re-dissolved in an organic solvent and allowed to be re-cast and solvent-annealed. By contrast, eSAs achieve hierarchical structures in solution through their ability to undergo further self-assembly because the eSA complex provides a soluble building block that can aggregate further as directed by other non-covalent interactions.

4.4.1 Polymeric eSAs

PE–S complexes were presumably the inspiration for the first reported systems qualifying as eSAs. These early eSA systems were typically based on a mixture of oppositely charged block co-polymers or on a mixture of block co-polymer and oppositely charged surfactants, termed polyion complexes (PICs). Simply mixing the precursors to PICs in aqueous solution resulted in a surprising array of highly monodisperse self-assembled structures, such as PIC micelles[25] and vesicles.[26] PIC structures also exhibited self-sorting behaviour, with micelles selectively forming only for block co-polymers with matching charge block lengths, even in the presence of other block co-polymers with charged blocks of different lengths.[27]

Although conceptually similar to PE–S complexes, the PIC-based eSA systems are unique because of their use of a block co-polymer as at least one of the constituents. This distinction is the basis for their classification as eSAs and is illustrated by a PIC complex formed from a poly(ethylene oxide)-*b*-poly(sodium methacrylate) block co-polymer and oppositely charged alkyl trimethylammonium bromide surfactants.[26] The addition of a poly(ethylene oxide) (PEO) block improved the aqueous solubility of the surfactant-bound poly(sodium methacrylate) (PMANa) block. The electrostatically assembled water-soluble (block co-polymer)–surfactant complex then resembles a surfactant with a hydrophilic PEO 'head' and a hydrophobic PMANa–surfactant 'tail' and can act as a building block for further assembly and hierarchical structure formation. In this case, vesicles with low polydispersity and the ability to encapsulate hydrophilic molecules were formed when electroneutrality (between the PMANa and added surfactant) was achieved. This condition of electroneutrality differs from vesicle-forming systems of cationic and anionic surfactants, which require an excess of one of the charged components. The vesicle-forming (block co-polymer)–surfactant system was further distinguished as an eSA by an important control experiment, wherein the PMANa homopolymer–surfactant complex was found to precipitate in the manner typical of PE–S complexes.

Since this initial work describing polymeric eSAs, many polymeric eSA systems have been developed. Polymeric eSAs are a versatile platform for the production of interesting hierarchical structures, some of which display inherent functionality or stimuli responsiveness. Simple synthetic modifications to the polymers or other charged components allow the inclusion of functional motifs to enable systems to respond to stimuli such as oxidation and reduction, light, pH and the presence of enzymes. Their tendency to form vesicles and micelles has also led to eSAs being widely investigated for delivery and encapsulation applications.

Vesicular structures are often formed by polymeric eSA systems. The accompanying hydrophilic block prevents the precipitation of the hydrophobic charge–neutral complexes formed either by oppositely charged block co-polymers or by charged block co-polymers and oppositely charged surfactants. However, the hydrophobic effect drives the aggregation of the

hydrophobic blocks, often resulting in the formation of lamellar structures. The hydrophilic polymer blocks shield the faces of these lamellae from unfavourable interactions with the bulk aqueous medium, but a high-energy interface arises at the lamellae edges where the hydrophobic blocks remain exposed. Minimization of this interface drives the formation of vesicles; the lamellae curve to form spheres with no exposed hydrophobic edges.[26,28]

Vesicles formed from biocompatible block co-polymers, such as PEO-*b*-poly(*α*,*β*-aspartic acid) (PAA),[29] PEO-*b*-poly(lysine)[25] and surfactants [or even non-classical 'surfactant' structures such as charged adenosine triphosphate (ATP)[30]] are of particular interest for applications in nanomedicine. Semi-permeable polymer vesicles were developed from such eSA constructs and have been shown to remain stable under physiologically relevant salt and protein concentrations. The vesicular structure was also retained against the osmotic pressure induced from the encapsulation of a dextran polymer (M_n = 40 000 Da).[29] These characteristics show the viability of eSA polymer capsules for biomedical applications.

The promise of biomedical applications has further driven the development of biocompatible stimuli-responsive eSAs, which have the capability to respond to the presence of enzymes relevant to various disease types. One such therapeutically relevant enzyme is phosphatase. A biocompatible eSA system capable of responding to the presence of phosphatase was designed, harnessing the ability of this enzyme to hydrolyse ATP to adenine and phosphate.[30] The eSA was based on ATP, which contains four negative charges, making it effective at cross-linking the cationic block co-polymer methoxy-poly(ethylene glycol)$_{114}$-*b*-poly(L-lysine hydrochloride)$_{200}$ (PEG-*b*-PLKC). Once cross-linked, the PEG-*b*-PLKC–ATP complex formed spherical aggregates, with full complexation occurring at charge ratios of 1 : 1. The eSA aggregates were capable of taking up a model guest molecule from aqueous solution, which was released on hydrolysis of the utilized ATP by phosphatase (Figure 4.1).

Several similar enzyme-responsive systems have been developed, with variations in the block co-polymer and the cross-linking unit. The original work on a phosphatase-responsive polymeric eSA was followed up with a study in which it was possible to remove the requirement for block co-polymer synthesis. The PEG-*b*-PLKC polymer was replaced by the naturally occurring biopolymer chitosan. Complexation with ATP again resulted in spherical aggregates of chitosan–ATP, which were destroyed by phosphatase-induced ATP hydrolysis.

The charged molecule myristoylcholine chloride, a substrate for the enzyme acetylcholinesterase (AChE), was able to direct the formation of spherical eSA aggregates by cross-linking a PEG-*b*-PAA block co-polymer to produce myristoylcholine-PEG-*b*-PAA.[31] In a similar manner to the previous systems, exposure to AChE hydrolysed the myristoylcholine cross-linker, causing the breakdown of the eSA by removal of the electrostatic cross-linking species and thereby restoring the hydrophilicity of the PAA block. A dye, Nile Red, was encapsulated within the eSA aggregates, allowing the breakdown

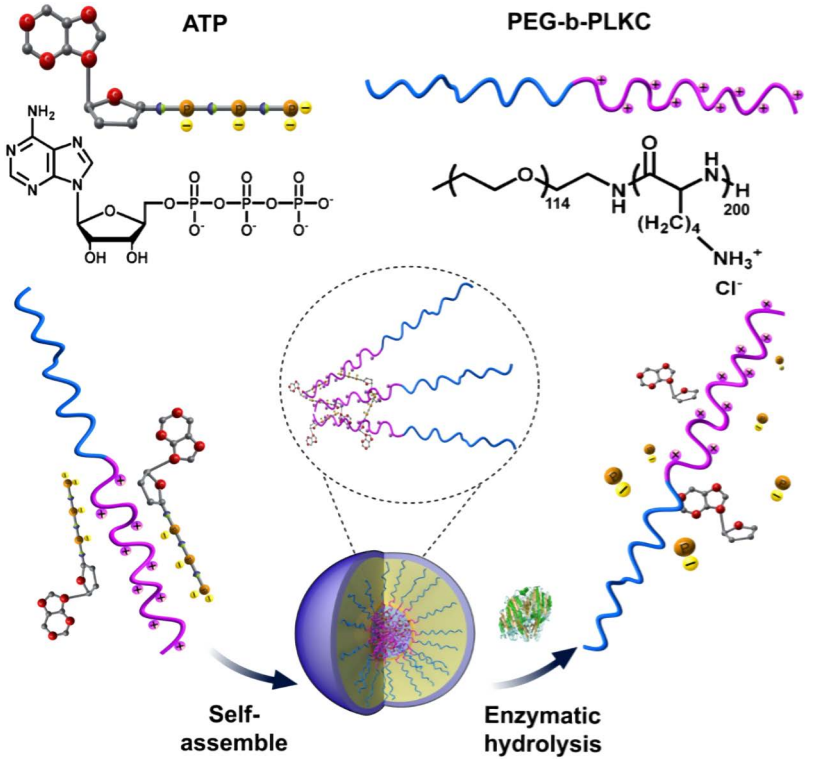


Figure 4.1 Schematic diagram of eSA self-assembly based on ATP cross-linking a PEG-*b*-PLKC block co-polymer and the phosphatase-induced release of a guest molecule. Reproduced with permission from C. Wang, Q. Chen, Z. Wang and X. Zhang, An enzyme-responsive polymeric superamphiphile, *Angew. Chem. Int. Ed.*, 2010, **49**, 8612. Copyright © 2010 Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim.

of aggregates to be followed spectroscopically, as well as demonstrating the effectiveness of this controlled release strategy. The release rate of Nile Red on exposure to AChE was much faster than by diffusion alone.

Although the enzyme-induced hydrolysis of one component of the eSA assembly provides an irreversibly switchable functionality that is biologically relevant, it can be advantageous to be able to reversibly switch the state of assembly of eSAs (*i.e.* between assembly and disassembly). External stimuli capable of reversibly addressing eSAs include pH, redox reactions and light. Although eSA systems that can respond to these stimuli require extra synthetic adaptation to include particular functional groups, the overall synthetic effort to modify the eSA precursors remains less than would be required to produce the final assembled eSA structures. Thus eSA self-assembly is an efficient route to complex and hierarchically ordered functional structures.

Redox-responsive eSAs were achieved by modification of the multi-charged, cross-linking surfactant. The inclusion of a redox-active Se centre in the surfactant imparted redox responsiveness to the eSA assemblies,

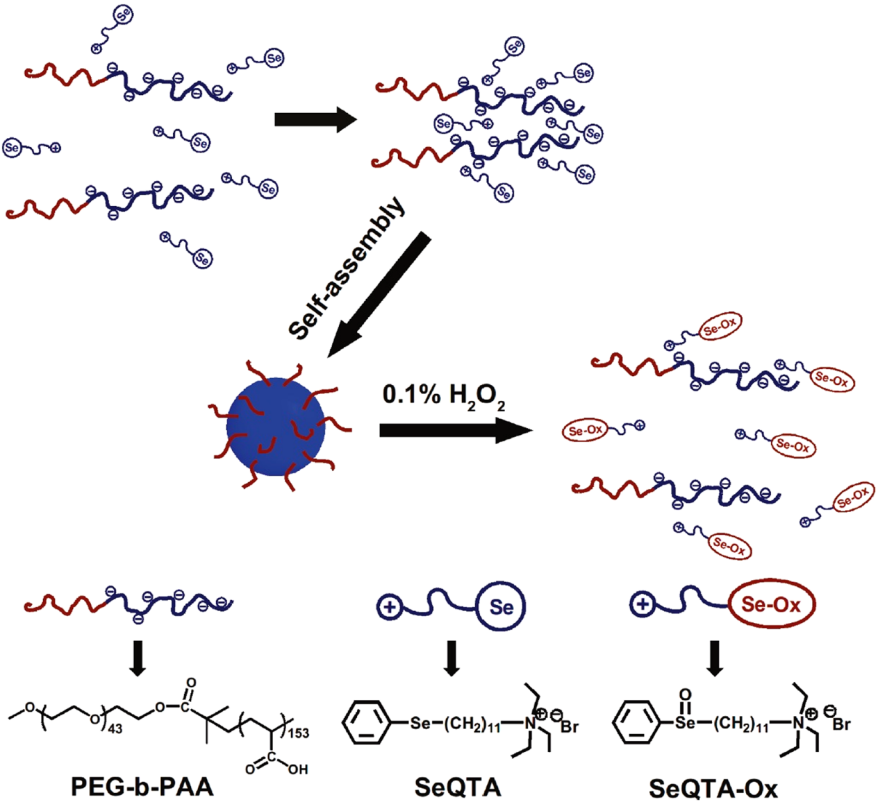


Figure 4.2 Oxidation-responsive micelles based on polymeric superamphiphiles formed by SeQTA and PEG_{43}-*b*-PAA_{153}. Reproduced with permission P. Han, N. Ma, H. Ren, H. Xu, Z. Li, Z. Wang and X. Zhang, Oxidation-responsive micelles based on a selenium-containing polymeric superamphiphile, *Langmuir*, 2010, **26**, 14414. Copyright (2010) American Chemical Society.

which were used to direct the formation of eSA micelles by combination with a PEG-*b*-PAA block co-polymer.[32] This process is shown schematically in Figure 4.2. The subtle difference in hydrophilicity between the reduced form of Se-containing surfactant (SeQTA) and the oxidized selenoxide-containing form (SeQTA-ox) was enough to disrupt the micellar structure. This meant that a mild oxidative treatment with a low concentration solution of oxidant (H_2O_2, 0.1%) could induce the release of a host molecule, in this case the simple fluorescent probe fluorescein sodium.

Light-switchable functional groups are readily incorporated into both small surfactant molecules and polymers. Light-induced switching is one of the most versatile methods of controlling molecular systems because it is easy to tune the absorbance of the system by making minor variations to the molecular structure through synthetic (covalent) chemistry approaches. The transfer of energy (absorbed from light) into a physical change of structure

has been used to drive molecular actuators[33] and finds similar applications in the control over eSA self-assembly. One functional group that is commonly used for a reversible photoswitch, as well as for ISA complexes,[34] is the azobenzene moiety; this moiety switches from its *trans*/*E* isomer to its *cis*/*Z* isomer on exposure to UV light and reverses on exposure to visible light.

A photoresponsive azobenzene surfactant was the basis for an eSA formed by a cationic azobenzene surfactant and a PEG-*b*-PAA block co-polymer.[35] A combination of the surfactant and block co-polymer at charge ratios of up to $Z = 1.25$ led to assembly into polymeric vesicles that were stable in solution, in contrast with control experiments where the precipitation of the homopolymer–azobenzene surfactant PE–S complex occurred at charge ratios greater than $Z = 0.5$. Once formed, irradiation by UV light (365 nm) was used to switch the azobenzene isomer, triggering large structural changes within the eSA aggregate. Transmission electron microscopy (TEM) images (Figure 4.3) showed the destruction of the micellar morphology of the aggregates. Subsequent irradiation of the solution with visible light (450 nm) reversed the disruption and

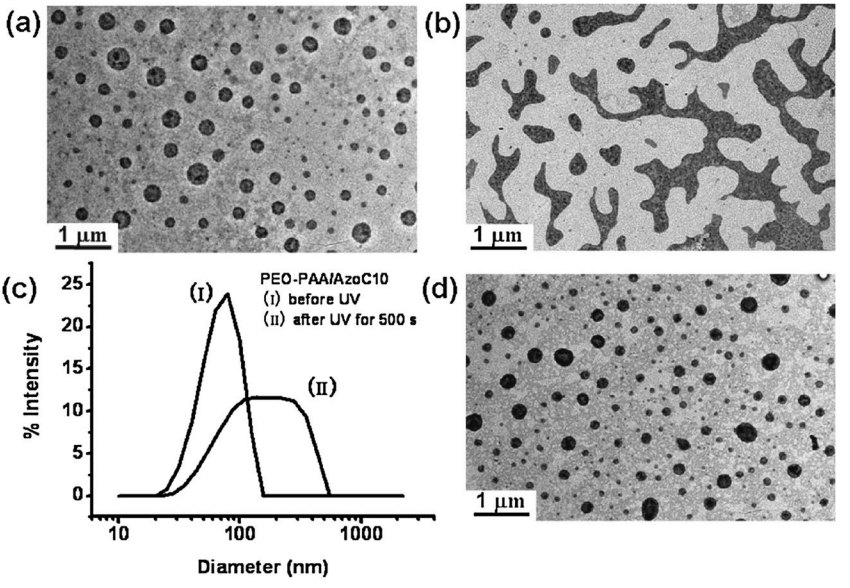


Figure 4.3 Reversible switching of an azobenzene-containing surfactant-based eSA system. (a) TEM image of eSA micelles before UV irradiation. (b) TEM image of the same system after UV irradiation. (c) Dynamic light scattering results comparing the size of aggregates before and after UV irradiation. (d) TEM image showing the re-formed eSA micelles after reversal of the azobenzene isomer by visible light irradiation. Reproduced with permission from Y. Wang, P. Han, H. Xu, Z. Wang, X. Zhang and A. V. Kabanov, Photocontrolled self-assembly and disassembly of block ionomer complex vesicles: a facile approach toward supramolecular polymer nanocontainers, *Langmuir*, 2010, **26**, 709. Copyright (2010) American Chemical Society.

allowed reversible switching between the assembled and disassembled states, as shown by TEM and UV–visible spectrophotometry. As in previous studies, fluorescent probes (fluorescein and sodium 1-pyrenesulfonate) were encapsulated and released on assembly and disassembly, respectively, of the eSA micelles.

Further light-responsive eSA assemblies were prepared using the less conventional photo-ionizable UV chromophore malachite green (MG).[36] MG is a neutral dye with a triphenylcyanomethane group that is susceptible to UV photolysis, which cleaves the C–CN bond to leave a triphenylmethane cation. In its neutral form, MG was functionalized with an anionic surfactant-like headgroup, allowing it to electrostatically complex with the cationic block co-polymer PEG-*b*-PKLC to form an eSA. Aggregation of the PEG-*b*-PKLC–MG eSA, led to the formation of raft- or sheet-like structures, but none of these structures remained after UV irradiation for 300 s. This change to the eSA structures was attributed to the formation of a zwitterionic MG surfactant species by cleavage of the C–CN bond and formation of the triphenylmethane cation. The formation of this zwitterion increased the solubility of the MG surfactant in water, overcoming the driving force for aggregation of the eSA and leading to the destruction of the aggregates. As in previous studies, the release of a fluorescent probe (Nile Red) was used to confirm the disassembly of aggregates.

eSA systems that are capable of responding to changes in environmental pH have been developed. pH is a key factor by which the charge of surfactants and polymers containing acidic or basic groups can be influenced. An eSA that encapsulated the enzyme lysozyme at physiological pH (7.4) was constructed by the complexation of an anionic PEG-*b*-poly[(*N*-citraconyl-2-aminoethyl)aspartamide] block co-polymer with positively charged lysozyme.[37] The citraconic amide groups provided negative charges that could electrostatically complex lysozyme, but also served to mask the underlying primary amines. Citraconic amides are stable at neutral and basic pH, but labile at pH $\leq$ 5.5. The removal of the citraconic amides by switching to a more acidic environment therefore revealed the primary amines and induced a charge inversion in the block co-polymer from anionic to cationic. This pH-sensitive degradation mechanism allowed the release of the complexed lysozyme by reversing the electrostatic attraction between the lysozyme and polymer, leading to a repulsive interaction (Figure 4.4). This change from neutral to acidic pH is representative of the conditions inside intracellular endosomal compartments, suggesting that this system could be used for drug or gene delivery applications. However, once the charge conversion had released lysozyme, the block co-polymer was found to interfere with the activity of the lysozyme, reducing its activity from expected levels. These initial results suggest that further work is needed in this promising, but complex, area.

4.4.2 Small Molecule eSAs

Small molecule eSAs are typically based on a mixture of oppositely charged surfactants. In general, these ion complexes tend to lose their water solubility because both ion components have hydrophobic moieties, which are

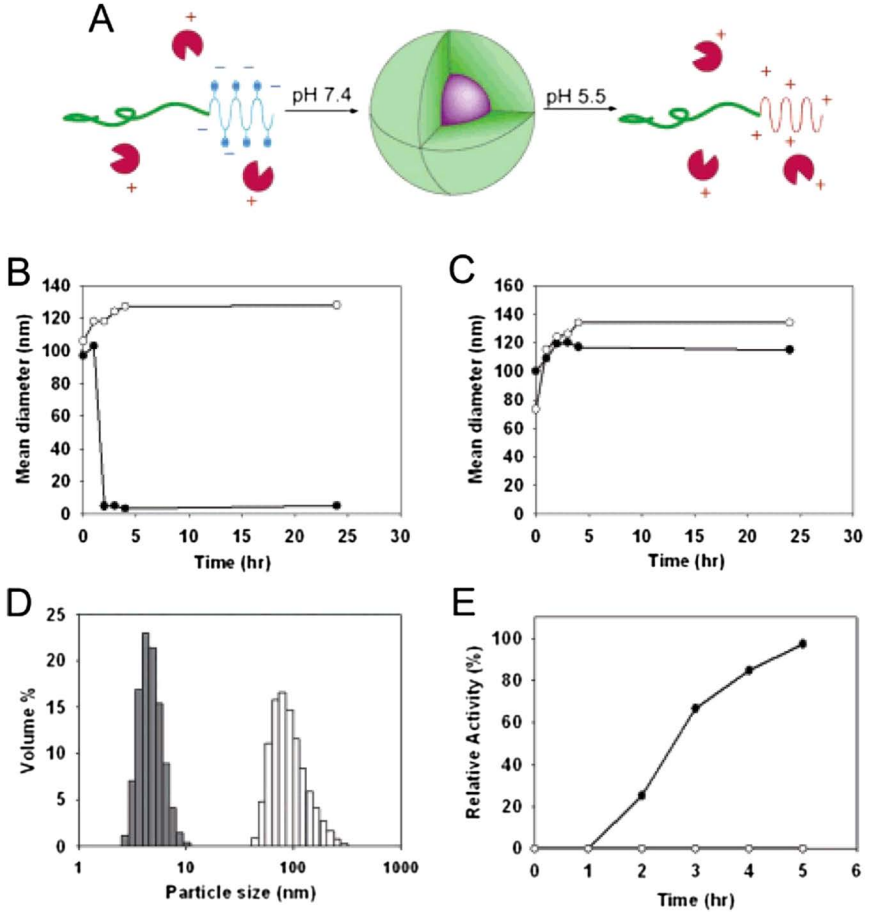
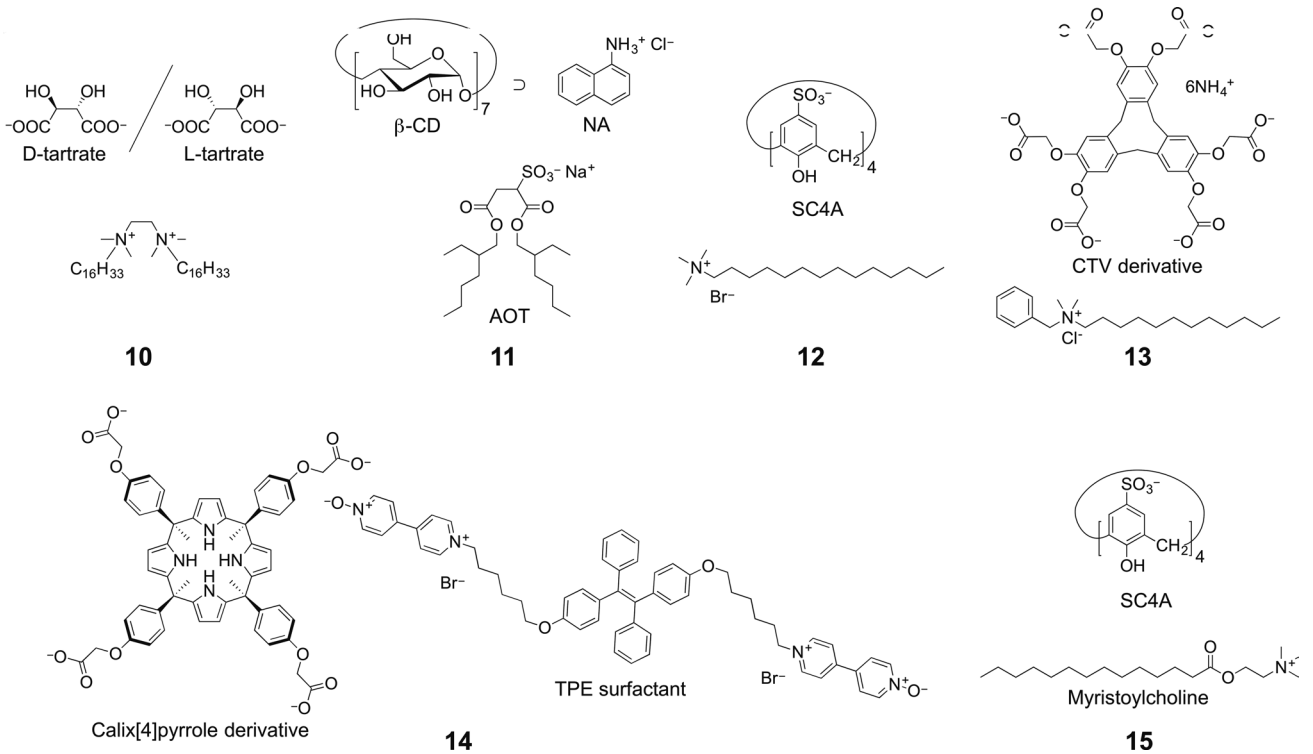
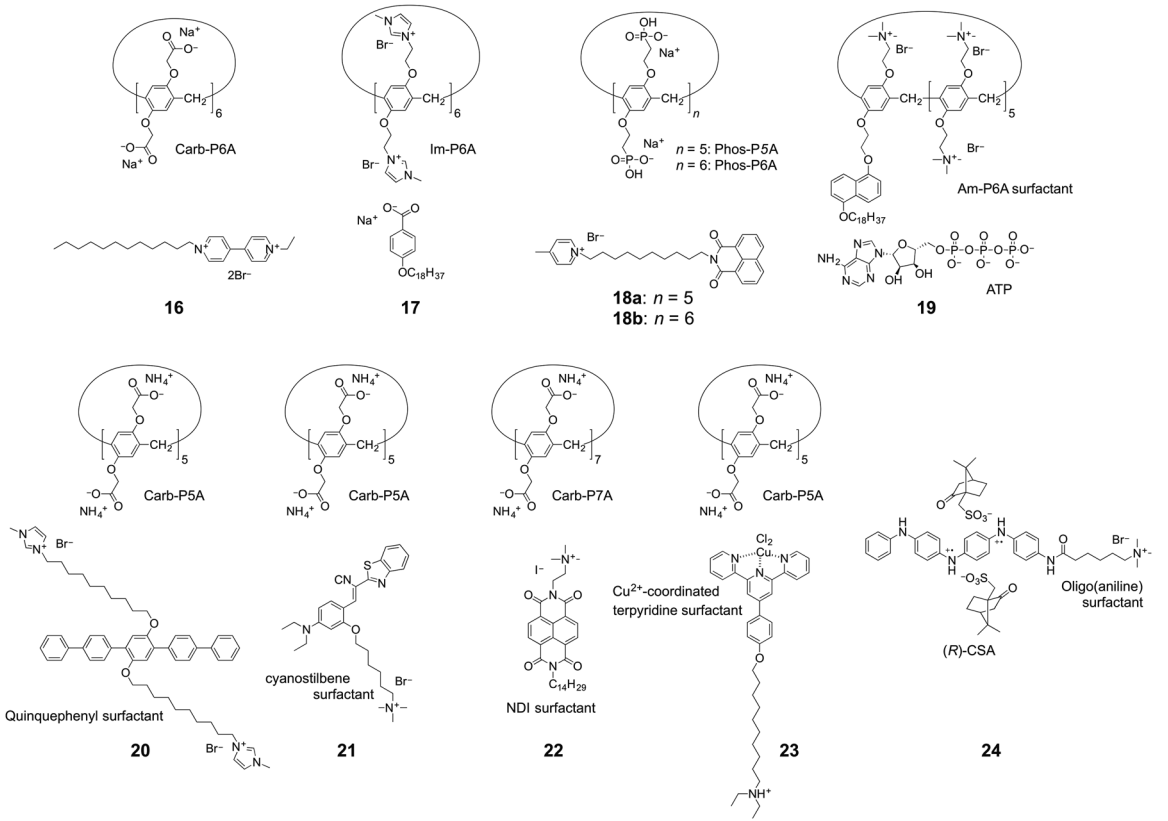


Figure 4.4 Formation and dissociation of the PIC micelles. (A) Schematic diagram of the formation and dissociation of the PIC micelles. Evolution of the mean diameter of the PIC micelles of (B) PEG-pAsp(EDA-Cit) and (C) PEG-pAsp(EDA-Suc). (D) Dynamic light scattering histogram of the PIC micelles at 0 h (white) and at 2 h (grey) at pH 5.5. (E) Relative lysozyme activity of the PIC micelles. The black dots represent the data at pH 5.5 and the white dots are at pH 7.4. Reproduced with permission from Y. Lee, S. Fukushima, Y. Bae, S. Hiki, T. Ishii and K. Kataoka, A protein nanocarrier from charge-conversion polymer in response to endosomal pH, *J. Am. Chem. Soc.*, 2007, **129**, 5362. Copyright (2007) American Chemical Society.

forced to phase separate (precipitate) once the solubilizing charges have been neutralized. Thus once the ion pair forms, its dissociation is difficult and is reminiscent of the so-called catanionic systems, which form stable vesicle systems from non-stoichiometric mixtures of anionic and cationic surfactants.[38] The range of small molecule eSAs that are discussed in the following sections are summarized in Schemes 4.2 and 4.3.



Scheme 4.2 Molecular structures of small molecule eSAs based on calixarene-type structures.



Scheme 4.3 Molecular structures of small molecule eSAs based on pillararenes.

In the initial stages of development, precursors to the current small molecule eSAs were developed from the ionic complexation of oppositely charged surfactants, one of which contained hydrophilic or polar groups. An example of the early efforts to produce such constructs comes from Antonietti and Hentze, who produced the so-called counter ion-coupled gemini surfactant (cocogem) phases.[39] They further developed this concept through the addition of monomers to lyotropic phases of their cocogems for the production of highly cross-linked porous materials. Oda *et al.* then showed that such an eSA was formed from a combination of the cationic gemini surfactant ethylene-1,2-bis(dimethylhexadecylammonium) and anionic chiral L-/D-tartrates, which have two hydrophilic hydroxyl groups.[40] The self-assembled eSA (**10**) is a charge-neutralized non-ionic surfactant and forms multilamellar twisted ribbon structures in water. The supramolecular organization (twist pitch, handedness) of these structures was elegantly controlled by varying the enantiomeric excess (e.e.) of the anionic tartrate; when the tartrate was racemic, the eSA formed flat ribbons, whereas the twist pitch of the self-assembled ribbons decreased to 200 nm with increasing e.e. (Figure 4.5a–d).

In a later, but similar, non-ionic approach, a cationic 1-naphthylammonium (NA) was wrapped with β-cyclodextrin (β-CD) and anionic bis(2-ethyl-1-hexyl)sulfosuccinate (AOT).[41] As β-CD has 21 hydroxyl groups, the eSA formed (**11**) presented a hydrophilic polyhydroxyl head to the aqueous surroundings. The formation of vesicles (30–200 nm; Figure 4.5e) in aqueous solution was induced for this eSA by sonicating all the components at room temperature. However, the long-term stability of the vesicles was shown to be an issue, with the vesicles partially transforming into flake-like aggregates (with the apparent separation of β-CD from NAs) (Figure 4.5f and g). The control ionic complex of NA-AOT also formed flake-like aggregates, which showed a highly ordered crystal structure due to π–π, electrostatic and hydrophobic interactions.

4.4.3 Calixarene-type eSAs

Anionic calixarenes such as *p*-sulfonatocalix[*n*]arenes are known to be good receptors for organic ammonium cations in aqueous media.[42–47] Ionic complexes consisting of anionic calixarenes and cationic guests are prototypical examples of small molecule eSAs. Even after forming an eSA with oppositely charged surfactants, the calixarenes remain charged (*i.e.* only partially charge-neutralized). The remaining ionic groups act as a hydrophilic polar moiety of the eSA, whereas the alkyl chain of the cationic surfactant acts as a hydrophobic tail.

In a very simple example of these principles, an eSA (**12**) consisting of *p*-sulfonatocalix[4]arene (SC4A) and tetradecyltrimethylammonium with a molar ratio of 1 : 2.5 formed unilamellar vesicles (*ca.* 57 nm) after sonication of the aqueous dispersion.[48] The surfactant cationic head was located in the aromatic cavity of the calixarene (as shown by the chemical shift change of the $N^+(CH_3)_3$ headgroup in ^{1}H NMR spectra). The vesicles formed from these

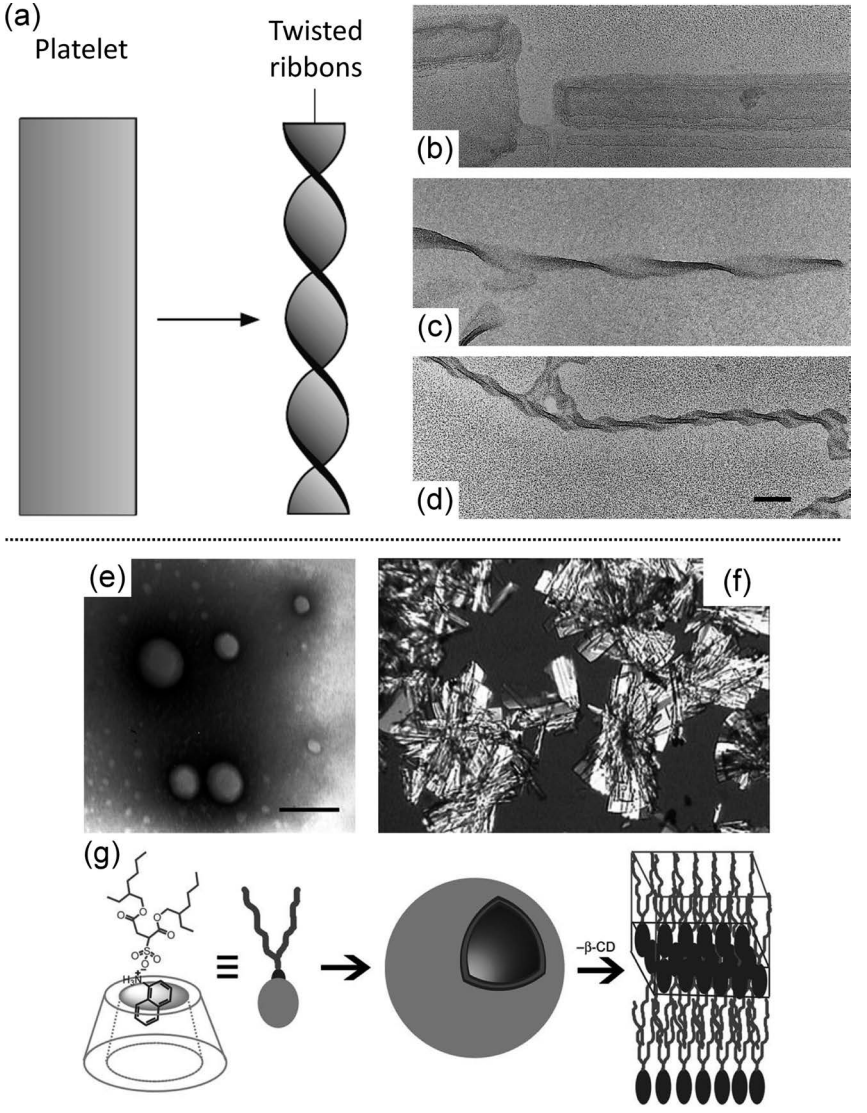


Figure 4.5 Non-ionic small-molecule eSAs. (a) Schematic representation of platelets and twisted ribbons formed by eSA **10**. (b–d) TEM images of the ribbons formed by **10** at 0.1% in water for various values of e.e. of L-tartrate: (b) 0% e.e. (racemate); (c) 50% e.e.; and (d) 100% e.e. (pure L-tartrate). Scale bar 100 nm. (e) TEM image of the vesicle of eSA **11** with AOT/NA molar ratio = 1.0. Scale bar 100 nm. (f) Micrograph of the flake-like NA–AOT ionic complex under cross-polarized light. (g) Schematic representation of vesicle formation of eSA **11** and transformation to flake-like aggregates. a–d reprinted by permission from Macmillian Publishers Ltd, R. Oda, I. Huc, M. Schmutz, S. J. Candau and F. C. MacKintosh, Tuning bilayer twist using chiral counterions, *Nature*, 1999, **399**, 566. Copyright 1999. e–g reproduced with permission from B. Jing, X. Chen, X. Wang, C. Yang, Y. Xie and H. Qiu, Self-assembly vesicles made from a cyclodextrin supramolecular complex, *Chem. Eur. J.*, 2007, **13**, 9137. Copyright © 2007 Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim.

supramolecular constructs were robust, with no change in shape and size of the vesicles even after lyophilization and rehydration.

Moving towards responsive systems, Yao and co-workers investigated the use of an anionic cyclotriveratrylene (CTV) carboxylate derivative and a cationic benzyldimethyldodecylammonium surfactant (Figure 4.6).[49] The CTV derivative had six carboxylate groups, which were protonated under acidic conditions. Once combined, the CTV–surfactant eSA (**13**) self-assembled into vesicles in water (Figure 4.6c), whereas the cationic surfactant on its own formed micelles (Figure 4.6b). The vesicles were stable at pH > 7, but disassembled under acidic conditions (pH < 7), with the eSA disassociating into the two constituent amphiphiles; this transformation was reversible and was observed by TEM (Figure 4.6d and e). These researchers successfully demonstrated the preparation of drug-loaded vesicles by encapsulating the hydrophilic anticancer drug doxorubicin (DOX) into the vesicles and the release of this drug by decreasing the pH (Figure 4.6a).

Continuing on the theme of functional eSAs and controlled drug release, an eSA (**14**) was constructed from an anionic calix[4]pyrrole derivative and a bola-type cationic surfactant.[50] The cationic surfactant contained an aggregation-induced emission (AIE)-active tetraphenylethene core and two cationic pyridinium pendant headgroups; the calix[4]pyrrole had four (anionic) carboxylate groups. This eSA formed multilamellar vesicles in water and, in the same manner as (**13**), the vesicles disassembled under acidic conditions and changed into micelles. The researchers successfully demonstrated the pH-controlled assembly and disassembly of vesicles containing the (non-fluorescent) anticancer drug gemcitabine. When the eSA formed vesicles, the AIE-active tetraphenylethene cores aggregated and thus formed fluorescent vesicles in water. On disassembly and vesicle collapse, the fluorescence intensity decreased, acting as an internal fluorescent probe to signal the release of the payload.

In another example of a vesicle-forming eSA (**15**, from an anionic SC4A and a cationic myristoylcholine), hydrophilic drugs were loaded into the interior cavities of these hollow structures.[51] Myristoylcholine, a substrate for cholinesterase enzymes, was chosen as the enzyme-susceptible cationic component of this eSA. Specifically, butyrylcholinesterase (BChE) was used in this eSA system, leading to the cleavage of the ester bond on the cationic myristoylcholine surfactant. The enzymatic activity triggered a cascade of events: the loss of the hydrophilic–hydrophobic balance of the eSA, followed by disassembly of the vesicle with the consequent release of the entrapped drugs. This process is described schematically in Figure 4.6f. The suprastructures (Figure 4.6g and h) from this enzyme-susceptible eSA exhibit highly specific and efficient responsiveness, which points towards routes for precisely controlled switchable, functional drug-delivery vehicles.

4.4.4 Pillararene-Based eSAs

Pillararenes are a class of macrocyclic hosts with repeating arene (mainly phenylene) units linked at *para*-positions to adjacent units through methylene bridges, forming a pillar-like polygonal-tube architecture. This structure

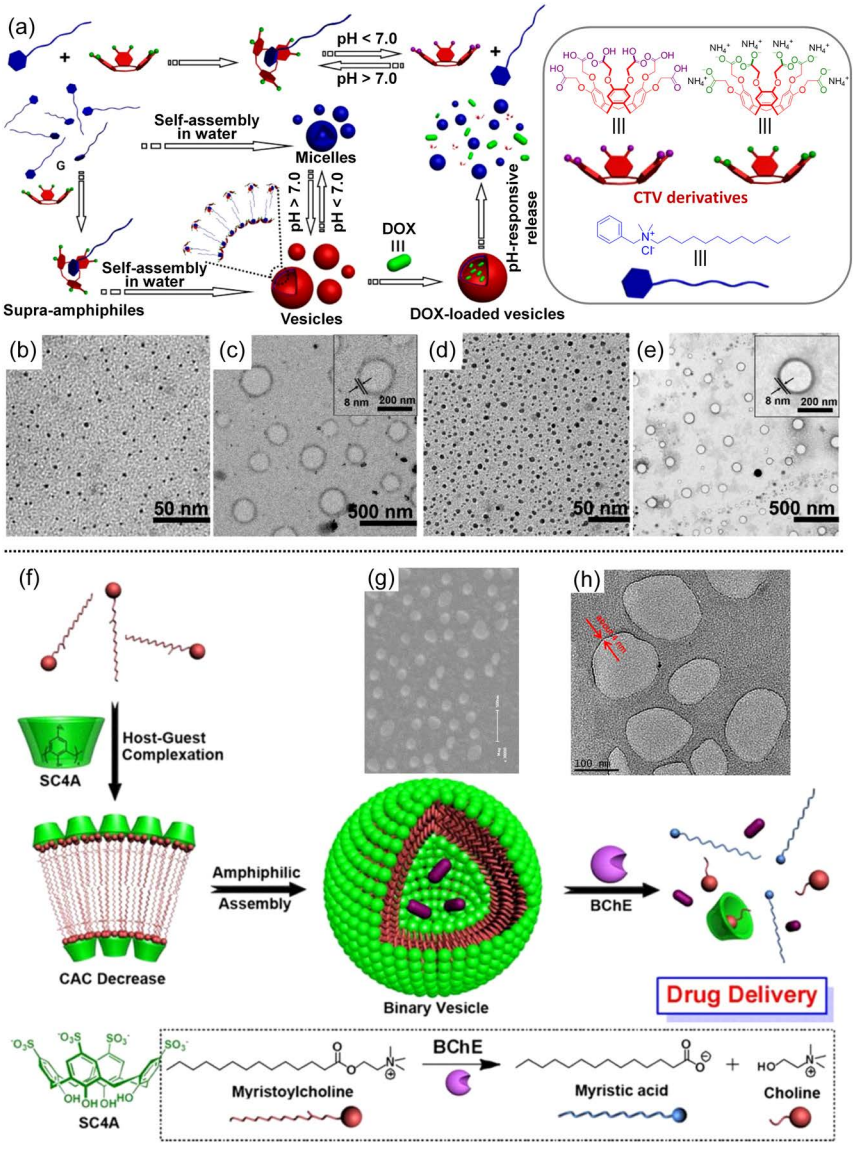


Figure 4.6 Drug delivery by calixarene-type eSAs. (a) Schematic representation of the pH-responsive self-assembly of eSA **13** and its application in controlled drug release. (b) TEM image of the micelles formed by cationic benzyldimethyldodecylammonium surfactant in water. (c–e) TEM images of: (c) vesicles formed by eSA **13** in water; (d) aggregates formed after adding excess HCl solution to (c); and (e) aggregates formed after adding excess NaOH solution to (d). (f) Schematic illustration of self-assembly of eSA **15** into vesicles and its targeted disassembly by BChE leading to the release of entrapped hydrophilic drugs (rods). (g) SEM and (h) high-resolution TEM images of eSA **15** vesicles. a–e reproduced with permission from D. Xia, Y. Li, K. Jie, B. Shi and Y. Yao, A water-soluble cyclotriveratrylene-based supra-amphiphile: synthesis, pH-responsive self-assembly in water, and its application in controlled drug release, *Org. Lett.*, 2016, **18**, 2910. Copyright (2016) American Chemical Society. f–h reproduced with permission from D. S. Guo, K. Wang, Y. X. Wang and Y. Liu, Cholinesterase-responsive supramolecular vesicle, *J. Am. Chem. Soc.*, 2012, **134**, 10244. Copyright (2012) American Chemical Society.

is in contrast to the basket- or bowl-shaped structure of meta-bridged calixarenes. The cavity inside the pillararenes enables them to selectively bind various guest molecules. It is easy to customize their molecular selectivity by functionalizing the arenes from which the pillararenes are formed. Hence ion-functionalized pillararenes are good candidates for use in eSAs and can act as the hydrophilic head of the eSA because of the presence of multiple charges. The molecular structures of the species discussed in the following section are shown in Scheme 4.3.

The first pillararene–type eSA discussed here (**16**) has a stable 1:1 structure in water consisting of an anionic pillar[6]arene derivative Carb-P6A (with anionic carboxylate groups) and a cationic bipyridinium surfactant, which is threaded into the cavity of the pillararene.[52] The complexation is driven and stabilized by electrostatic, hydrophobic and π–π interactions to yield bilayer-walled vesicles with an average diameter of about 170 nm. The association constant in water was estimated to be about 1.0×10^8 M^{-1} using a simple analogue, dimethyl bipyridinium dibromide, instead of the surfactant. The bipyridinium surfactant alone forms spherical micelles with an average diameter of 7 nm.

The reversible transformation between micelles and vesicles was demonstrated by simply adjusting the pH of the solution, thus exploiting the switchable electrostatic interactions and pH responsiveness of the pillar[6]arene. Vesicles were formed under basic conditions of pH > 7, whereas micelles were formed under acidic conditions of pH < 7 owing to the protonation of the carboxylate anion groups on the pillar[6]arene (inducing a loss of electrostatic interactions with the cationic bipyridinium component). This behaviour implies that the electrostatic interaction between the two amphiphilic components of the eSA was the key factor for formation of the SA. A hydrophilic small molecule could be encapsulated inside the vesicles under neutral or weakly basic conditions and then released by decreasing pH and inducing the pH-triggered vesicle–micelle transformation.

In the case where charges are reversed, an eSA (**17**) was produced consisting of a pillar[6]arene derivative bearing imidazolium cations (Im-P6A) and an anionic *p*-octadecyloxybenzoate surfactant.[53] The behaviour of this eSA is very similar to that described for **16**—namely, that the eSA self-assembles into vesicles while the anionic surfactant forms micelles. The vesicle collapsed under acidic conditions and hydrophilic small molecules could be encapsulated and released by decreasing the pH. The only difference between **16** and **17** was the association constant, which was estimated to be 3.2×10^6 M^{-1} using a simple analogue, *p*-hydroxybenzoate, showing that **16** (prepared from an anionic pillararene) was significantly more stable than **17**.

In order to be able to deliver hydrophobic drugs and other payloads, alternative structures (*i.e.* other than vesicles) need to be formed. A cationic pyridinium surfactant was complexed with both a phosphate-based pillar[5]arene (Phos-P5A) and a phosphate-based pillar[6]arene (Phos-P6A) to give eSAs (**18a** and **18b**, respectively; Figure 4.7). The eSA formed by the pillar[5]arene, **18a**, self-assembles into micelles (Figure 4.7b and c), which

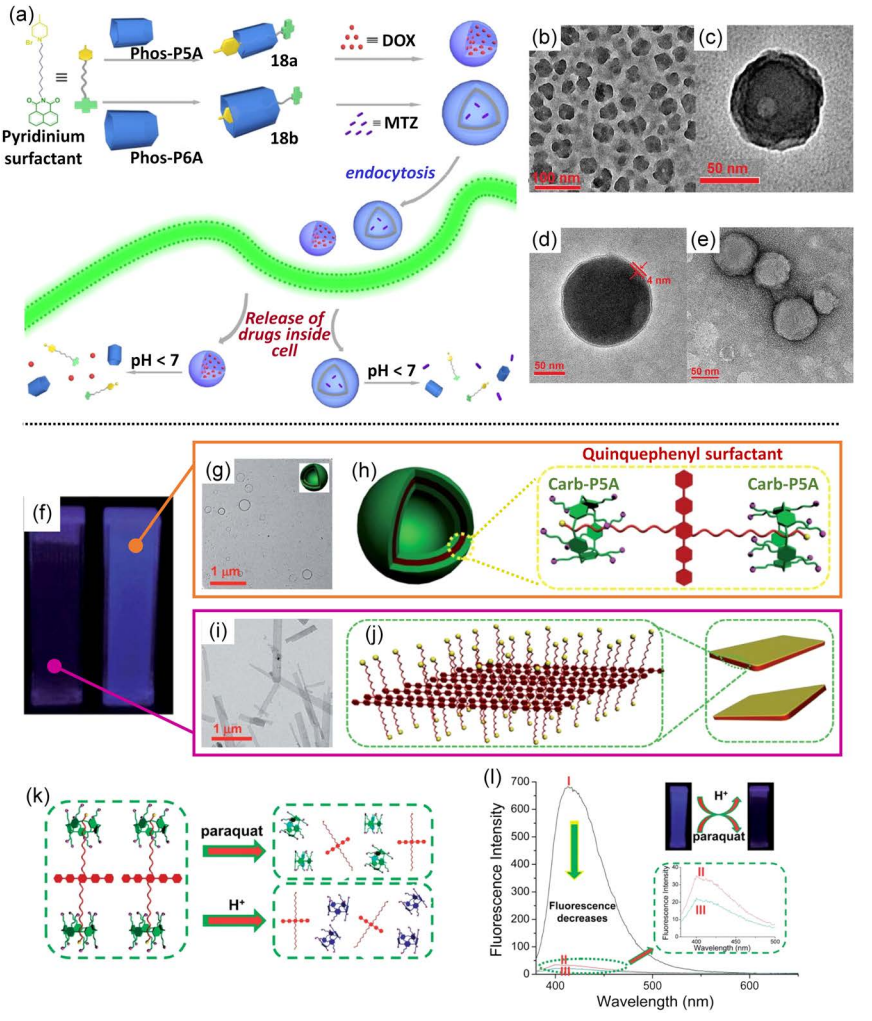


Figure 4.7 Pillararene-based eSAs. (a) Schematic illustration of pH-responsive self-assembled micelles (**18a**) and vesicles (**18b**) and their application in drug delivery. (b, c) TEM images of micelles of eSA **18a.** TEM images of (d) a vesicle of eSA **18b** and (e) vesicles of **18b** stained with uranyl acetate. (f) Fluorescent images of a quinquephenyl surfactant (left) and eSA **20** (right) in water. (g) TEM image of **20** in water. (h) Schematic representation of a vesicle self-assembled from **20**. (i) TEM image of aggregates of the quinquephenyl surfactant in water. (j) Schematic representation of the nanosheet structure of the quinquephenyl surfactant. (k) Schematic representation of the disassociation of **20** treated by paraquat or H^+. (l) Fluorescence spectra: I, eSA **20**; II, after treatment with H^+, pH 4.0; III, after treatment with paraquat. Inset: fluorescent images of the aqueous solutions of **20** on irradiation with a 365 nm light source before (left) and after (right) treatment with H^+ or paraquat. a–e reproduced with permission from X.-Y. Hu, X. Liu, W. Zhang, S. Qin, C. Yao, Y. Li, D. Cao, L. Peng and L. Wang, Controllable construction of biocompatible supramolecular micelles and vesicles by water-soluble phosphate pillar[5,6]arenes for selective anti-cancer drug delivery, *Chem. Mater.*, 2016, **28**, 3778. Copyright (2016) American Chemical Society. f–l reproduced from ref. 56 with permission from The Royal Society of Chemistry.

can encapsulate hydrophobic anticancer drugs such as DOX into their interior.[54] The eSA of pillar[6]arene, **18b**, self-assembles into vesicles (Figure 4.7d and e), which encapsulate the hydrophilic anticancer drug mitoxantrone (MTZ). Both the supramolecular micelle and vesicle are responsive to pH or the addition of Zn^{2+} ions, known to strongly complex with phosphate ions. Thus two triggers can be used to release the drugs loaded in both the micelle (hydrophobic) and the vesicle (hydrophilic): either a low pH environment or with the introduction of Zn^{2+} ions. This example is shown schematically in Figure 4.7a.

Moving away from the classical charged amphiphiles, eSA constructs (**19**) were formed from a cationic ammonium-functionalized pillar[6]arene surfactant and anionic ATP, a well-known and biologically relevant anionic small molecule.[55] In aqueous solution the eSA self-assembles into bilayer vesicles with an average diameter of *ca.* 150 nm. The addition of the enzyme alkaline phosphatase, which acts as a trigger for the disassembly of ATP by hydrolysis, caused a vesicle-to-micelle transition (the pillararene surfactant on its own self-assembles into micelles), with the consequent release of the hydrophilic small molecule.

The eSA **20**, an anionic pillar[5]arene carboxylate (Carb-P5A) and a bola-type cationic imidazolium-functionalized quinquephenyl surfactant, self-assembles into blue fluorescent vesicles in aqueous solution (Figure 4.7f right, Figure 4.7g and h), the fluorescence of which derives from the quinquephenyl core.[56] By contrast, the quinquephenyl surfactant alone self-assembled into monolayer nanosheets with the thickness of a single molecule (1 μm length, 100 nm width and 3.1 nm thickness), driven by the hydrophobic and π–π interactions of the quinquephenyl core (Figure 4.7i and j). As a result, the core exhibited no fluorescence (Figure 4.7f, left) because of the electronic coupling between the closely packed adjacent cores. However, the formation of the eSA with the pillar[5]arene removed the quenching effect of coupling by the steric action of the two bulky pillar[5]arene headgroups, which suppressed π-stacking between adjacent quinquephenyl aromatic cores as well as the electronic coupling of the cores. The eSA, and therefore the formed vesicles, disassociated either by the addition of cationic *N*,*N*′-dimethyl-4,4′-bipyridinium dichloride (paraquat) or by decreasing the pH (Figure 4.7k). Cationic paraquat can bind the pillar[5]arene more strongly than the bola-type surfactant used for the formation of the eSA, causing disassociation of the eSA. The carboxylate anions on the pillar[5]arene are protonated at low pH, resulting in the disassociation of the eSA. Hence the eSA can be used to detect the presence of paraquat or protons by the change in fluorescence intensity (as a function of its assembly or disassembly; Figure 4.7l).

In a further exploration of the use of fluorescence as an indicator, the eSA **21** [consisting of the same anionic pillar[5]arene (Carb-P5A) as **20** and a cationic cyanostilbene surfactant] was prepared.[57] In the aggregated state, the cyanostilbene surfactant exhibited an intense red to near-infrared (NIR) fluorescence on the formation of a dimer (*i.e.* the surfactant is an AIE-active

material). The surfactant on its own produced nanoribbon-like self-assembled structures with relatively weak emission, whereas the eSA self-assembled into nanoparticles that exhibited intense NIR fluorescence due to host–guest complexation-enhanced aggregation. The nanoparticles formed by the eSA strongly absorbed visible light and emitted brightly with red to NIR fluorescence. The nanoparticles thus provide bright emission without irradiation with cell-damaging UV light (for excitation) and hence this eSA is available as an imaging agent for living cells. The fluorescent nanoparticles are pH-responsive and disassemble after treatment with acid.

Examples of nanofibre-to-vesicle transformation are displayed as a further exploration of the pillararene motif. The eSA **22** [consisting of an anionic pillar[7]arene carboxylate (Carb-P7A) and a cationic 1,4,5,8-naphthalene-tetracarboxylic diimide (NDI) surfactant] was shown to exhibit reversible transformation between vesicles and nanofibres through a change in pH.[58] The NDI surfactant alone tends aggregate through π–π interaction between the NDI cores, forming nanofibres. By contrast, when the eSA is formed, the pillar[7]arene suppresses the π–π interaction by wrapping around the NDI core, resulting in vesicle formation. In the same manner as the eSAs discussed earlier, the charges of the carboxylate groups can be controlled by pH and hence the eSA reversibly associates or disassociates depending on the presence or absence of the electrostatic interactions. In addition, the vesicles can be transformed into nanoparticles by the addition of α-CD. For the eSA **23**, a Cu^{2+}-coordinated terpyridine surfactant was shown to self-assemble into nanofibres on its own. By adding Carb-P5A, the combination formed an eSA with a corresponding transformation from nanofibres to vesicles.[59]

4.4.5 Tuneable Conjugated eSAs

As another example of a new class of rather atypical eSAs, an oligo(aniline)-conjugated aromatic moiety was incorporated into the hydrophobic tail of a cationic trimethylammonium bromide surfactant. The presence of further non-covalent interaction-inducing moieties, including hydrogen-bond donors and acceptors and π-stacking aromatic groups, provided further opportunities for supramolecular tuning of the self-assembled structures. Functionality (redox activity and conductivity) was also incorporated into the amphiphile *via* the ability of the aniline-based tail structures to undergo its well-known acid–base (electrostatic) doping chemistry.[60]

On its own, the half-oxidized (emeraldine base state) oligo(aniline) surfactant assembled into well-defined fibre-like structures with widths of 3 nm. Through the addition of inorganic acids, it was possible to not only switch between conductive and non-conductive states as expected, but also to produce a pH-responsive eSA—by protonation of the iminic nitrogen atoms in the oligo(aniline) structure, electrostatic interactions between the cationic protonated imines and the counter ions of the added acid produced an eSA (**24**).[61]

The addition of a base to remove the acidic proton and its counter ion resulted in re-formation of the original fibres. Such a dynamic, tuneable approach opens up a range of new opportunities based on using the conjugate acid–base counter ions formed in acid–base reactions to control further the self-assembled structures, including inducing chirality/helicity into self-assembled nanofibres, the formation of vesicles and further supramolecular constructs.

4.5 Conclusions

The emerging and growing topic of SAs is an exciting area of research and future activity. It is within the framework of these supramolecular constructs, which present researchers with all the opportunities afforded by self-assembly and 'chemistry beyond the molecule' approaches to tune structure, function, switchability and hierarchies, that we have aimed to provide an overview of an exciting sub-class of SAs—that is, those SAs formed through electrostatic interactions (eSAs).

We believe that the outlook for eSAs is promising for future exploitation and application because electrostatic interactions provide a powerful, stable, but dynamic handle on achieving customizable and tuneable structures, properties and functions.

Polymeric eSA systems have already received considerable attention, with real in-roads made in the direction of applications in biologically relevant environments or being addressed or switched by bioactive triggers (*e.g.* enzymes). We foresee that these dynamic and switchable polymeric systems, especially those with orthogonal switching mechanisms [such as pH and ion (Zn^{2+}) or pH and enzyme responsivity] will continue to be attractive for further development. The fact that some block co-polymer systems have already been used within nanobiomedical and general drug-delivery applications provides easy access routes to such applications for newly developed eSA systems.

In the case of low molecular weight eSAs, there are considerable opportunities for novel materials and the exploration of dynamic behaviour (*i.e.* switching both structure and function) beyond calixarene and pillararenes. We foresee that this area will be a challenging, but potentially rewarding, area for continued exploration. The ability to tune the packing parameter of such small eSAs, as exemplified by the electroactive oligo(aniline)-based system, seems especially promising to tune structure and function for future applications. Bolaform amphiphiles are an area (for both small molecular and polymeric systems) that is underdeveloped, both from the perspective of using bolaform amphiphiles in eSAs or from the production of eSA bolaform constructs.

We therefore envisage an exciting array of new SAs with new orthogonal functional and switchable structures, intricate topologies, tuneable hierarchical structures and novel applications.

References

1. J.-M. Lehn, *Angew. Chem., Int. Ed.*, 1988, **27**, 89.
2. O. Ikkala and G. ten Brinke, *Science*, 2002, **295**, 2407.
3. M. Asakawa, W. Dehaen, G. L'abbé, S. Menzer, J. Nouwen, F. M. Raymo, J. F. Stoddart and D. J. Williams, *J. Org. Chem.*, 1996, **61**, 9591.
4. K. J. M. Bishop, C. E. Wilmer, S. Soh and B. A. Grzybowski, *Small*, 2009, **5**, 1600.
5. C. F. J. Faul and M. Antonietti, *Adv. Mater.*, 2003, **15**, 673.
6. O. Ikkala and G. ten Brinke, *Chem. Commun.*, 2004, 2131.
7. H. Qiu, Z. M. Hudson, M. A. Winnik and I. Manners, *Science*, 2015, **347**, 1329.
8. G. M. Whitesides and M. Boncheva, *Proc. Natl. Acad. Sci. U. S. A.*, 2002, **99**, 4769.
9. H. Qiu, C. E. Boott, R. L. Harniman, S. E. D. Webb, M. A. Winnik and I. Manners, *Science*, 2016, **89**, 697.
10. W. Zhang, W. Jin, T. Fukushima, A. Saeki, S. Seki and T. Aida, *Science*, 2011, **334**, 340.
11. E. Busseron, Y. Ruff, E. Moulin and N. Giuseppone, *Nanoscale*, 2013, **5**, 7098.
12. C. Maity, W. E. Hendriksen, J. H. van Esch and R. Eelkema, *Angew. Chem., Int. Ed.*, 2015, **54**, 998.
13. Z. Wei, T. Laitinen, B. Smarsly, O. Ikkala and C. F. J. Faul, *Angew. Chem., Int. Ed.*, 2005, **44**, 751.
14. M. Fialkowski, K. J. M. Bishop, R. Klajn, S. K. Smoukov, C. J. Campbell and B. A. Grzybowski, *J. Phys. Chem. B*, 2006, **110**, 2482.
15. C. Wang, Z. Wang and X. Zhang, *Small*, 2011, **7**, 1379.
16. X. Zhang and C. Wang, *Chem. Soc. Rev.*, 2011, **40**, 94.
17. K. A. Sharp and B. Honig, *Annu. Rev. Biophys. Biophys. Chem.*, 1990, **19**, 301.
18. F. Caruso, R. A. Caruso and H. Mohwald, *Science*, 1998, **282**, 1111.
19. F.-X. Xiao, M. Pagliaro, Y.-J. Xu and B. Liu, *Chem. Soc. Rev.*, 2016, **45**, 3088.
20. C. F. J. Faul, *Acc. Chem. Res.*, 2014, **47**, 3428.
21. K. Hayakawa, J. P. Santerre and J. C. T. Kwak, *Macromolecules*, 2002, **16**, 1642.
22. C. F. J. Faul and M. Antonietti, *Chem.–Eur. J.*, 2002, **8**, 2764.
23. R. Ahmed, S. K. Patra, I. W. Hamley, I. Manners and C. F. J. Faul, *J. Am. Chem. Soc.*, 2013, **137**, 2455.
24. M. Antonietti, J. Conrad and A. F. Thuenemann, *Macromolecules*, 1994, **27**, 6007.
25. A. Harada and K. Kataoka, *Macromolecules*, 1995, **28**, 5294.
26. A. V. Kabanov, T. K. Bronich, V. A. Kabanov, K. Yu and A. Eisenberg, *J. Am. Chem. Soc.*, 1998, **120**, 9941.
27. A. Harada and K. Kataoka, *Science*, 1999, **283**, 65.
28. T. K. Bronich, A. V. Kabanov and V. A. Kabanov, *Macromolecules*, 1997, **30**, 3519.

29. A. Koide, A. Kishimura, K. Osada, W. D. Jang, Y. Yamasaki and K. Kataoka, *J. Am. Chem. Soc.*, 2006, **128**, 5988.
30. C. Wang, Q. Chen, Z. Wang and X. Zhang, *Angew. Chem., Int. Ed.*, 2010, **49**, 8612.
31. Y. Xing, C. Wang, P. Han, Z. Wang and X. Zhang, *Langmuir*, 2012, **28**, 6032.
32. P. Han, N. Ma, H. Ren, H. Xu, Z. Li, Z. Wang and X. Zhang, *Langmuir*, 2010, **26**, 14414.
33. Y. Yu and T. Ikeda, *Angew. Chem., Int. Ed.*, 2006, **45**, 5416.
34. R. Ahmed, A. Priimagi, C. F. J. Faul and I. Manners, *Adv. Mater.*, 2012, **24**, 926.
35. Y. Wang, P. Han, H. Xu, Z. Wang, X. Zhang and A. V. Kabanov, *Langmuir*, 2010, **26**, 709.
36. P. Han, S. Li, C. Wang, H. Xu, Z. Wang, X. Zhang, J. Thomas and M. Smet, *Langmuir*, 2011, **27**, 14108.
37. Y. Lee, S. Fukushima, Y. Bae, S. Hiki, T. Ishii and K. Kataoka, *J. Am. Chem. Soc.*, 2007, **129**, 5362.
38. E. W. Kaler, A. K. Murthy, B. E. Rodriguez and J. A. Zasadzinski, *Science*, 1989, **245**, 1371.
39. M. Antonietti and H.-P. Hentze, *Adv. Mater.*, 1996, **8**, 840.
40. R. Oda, I. Huc, M. Schmutz, S. J. Candau and F. C. MacKintosh, *Nature*, 1999, **399**, 566.
41. B. Jing, X. Chen, X. Wang, C. Yang, Y. Xie and H. Qiu, *Chem.–Eur. J.*, 2007, **13**, 9137.
42. J. L. Atwood, L. J. Barbour, P. C. Junk and G. W. Orr, *Supramol. Chem.*, 1995, **5**, 105.
43. H. J. Buschmann, L. Mutihac and E. Schollmeyer, *J. Inclusion Phenom. Macrocyclic Chem.*, 2003, **46**, 133.
44. N. Douteau-Guével, A. W. Coleman, J.-P. Morel and N. Morel-Desrosiers, *J. Chem. Soc., Perkin Trans. 2*, 1999, 629.
45. F. Perret, A. N. Lazar and A. W. Coleman, *Chem. Commun.*, 2006, 2425.
46. N. Douteau-Guével, F. Perret, A. W. Coleman, J.-P. Morel and N. Morel-Desrosiers, *J. Chem. Soc., Perkin Trans. 2*, 2002, 524.
47. D.-S. Guo and Y. Liu, *Chem. Soc. Rev.*, 2012, **41**, 5907.
48. V. Francisco, N. Basilio, L. Garcia-Rio, J. R. Leis, E. F. Maques and C. Vázquez-Vázquez, *Chem. Commun.*, 2010, **46**, 6551.
49. D. Xia, Y. Li, K. Jie, B. Shi and Y. Yao, *Org. Lett.*, 2016, **18**, 2910.
50. X. Chi, H. Zhang, G. I. Vargas-Zúñiga, G. M. Peters and J. L. Sessler, *J. Am. Chem. Soc.*, 2016, **138**, 5829.
51. D. S. Guo, K. Wang, Y. X. Wang and Y. Liu, *J. Am. Chem. Soc.*, 2012, **134**, 10244.
52. G. Yu, X. Zhou, Z. Zhang, C. Han, Z. Mao, C. Gao and F. Huang, *J. Am. Chem. Soc.*, 2012, **134**, 19489.
53. Y. Yao, J. Li, J. Dai, X. Chi and M. Xue, *RSC Adv.*, 2014, **4**, 9039.
54. X.-Y. Hu, X. Liu, W. Zhang, S. Qin, C. Yao, Y. Li, D. Cao, L. Peng and L. Wang, *Chem. Mater.*, 2016, **28**, 3778.
55. J. Zhou, M. Chen and G. Diao, *Chem. Commun.*, 2014, **50**, 11954.

56. Y. Yao, X. Chi, Y. Zhou and F. Huang, *Chem. Sci.*, 2014, **5**, 2778.
57. B. Shi, K. Jie, Y. Zhou, J. Zhou, D. Xia and F. Huang, *J. Am. Chem. Soc.*, 2016, **138**, 80.
58. L. Shao, J. Zhou, B. Hua and G. Yu, *Chem. Commun.*, 2015, **51**, 7215.
59. K. Jie, Y. Zhou, B. Shi and Y. Yao, *Chem. Commun.*, 2015, **51**, 8461.
60. T. G. Dane, P. T. Cresswell, O. Bikondoa, G. E. Newby, T. Arnold, C. F. J. Faul and W. H. Briscoe, *Soft Matter*, 2012, **8**, 2824.
61. O. A. Bell, G. Wu, J. S. Haataja, F. Brömmel, N. Fey, A. M. Seddon, R. L. Harniman, R. M. Richardson, O. Ikkala, X. Zhang and C. F. J. Faul, *J. Am. Chem. Soc.*, 2015, **137**, 14288.

CHAPTER 5

Supra-Amphiphiles Based on Charge Transfer Interactions

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5.1 Introduction

Amphiphiles created by non-covalent interactions or dynamic covalent bonds between multiple moieties are classified as supra-amphiphiles and have attracted much interest in recent years.[1–4] Unlike classical amphiphiles, where the packing parameters primarily determine the structure,[5] supra-amphiphiles offer further structural diversity depending on the nature of the interaction(s) involved in the construction of the amphiphile. Therefore it is important to identify complementary and directional non-covalent interactions suitable for the design of specific supra-amphiphiles. In this context, charge transfer (CT) interactions[6] driven by alternating stacks of aromatic donor (D) and acceptor (A) chromophores have been recognized as important tools. CT interactions resemble the more widely studied hydrogen (H) bonding interactions because of their inherent complementary nature in the alternate placement of the D and A units. Various aromatic D–A pairs (Figure 5.1) have been identified as forming CT complexes.[7,8] D–A co-crystals are known[9,10] and there has been renewed interest in D–A complexes in the field of organic electronics for ambipolar charge transport, ferroelectricity and

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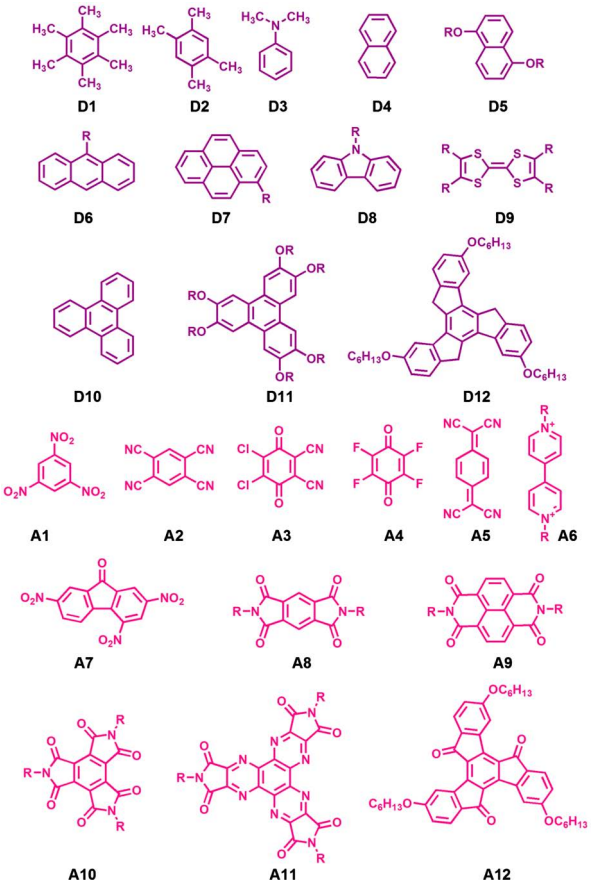

Figure 5.1 Structure of some common donor (D) and acceptor (A) chromophores. Reproduced with permission from A. Das and S. Ghosh, Supramolecular assemblies by charge-transfer interactions between donor and acceptor chromophores, *Angew. Chem., Int. Ed.*, 2014, **53**, 2038. Copyright © 2014 Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim.

other applications.[11–14] Thus CT complexes not only provide an opportunity to design molecular assemblies, but they are also promising organic materials.

Unlike H bonding, CT interactions operate in the orthogonal direction (Figure 5.2)[15] and thus the assembly of the supra-amphiphile constructed by D–A interactions can be unique. A CT band occurs as a result of electronic transitions from the highest occupied molecular orbital of the donor to the lowest unoccupied molecular orbital of the acceptor and thus can be unambiguously probed by new absorption band(s) at relative lower energies than the original peaks of the individual donor and acceptor components. These features have inspired the exploration of CT complexes for diverse supramolecular systems, including foldamers, organogels and liquid crystals.[8] However, a major obstacle is the low to moderate association constant for the majority of D–A complexes. In this regard, in addition to the structure

of the particular D–A pair, solvent polarity plays a critical part and higher association constants have been reported in poorly ionizing solvents. For example, the value of K_a for the D1–A1 (Figure 5.1) complex in cyclohexane was reported to be about 20 times higher than that in $CHCl_3$.[16] In contrast with the majority of earlier reports on supramolecular structures based on CT complexes in less polarizable organic solvents, Iverson and co-workers[17] recognized strong CT complex formation in very high polarity solvents such as MeOH and H_2O. For a given D–A pair, an almost three orders of magnitude increase in K_a was reported (Table 5.1) by changing the medium from $CDCl_3$ to D_2O. By analysing the thermodynamics of CT complexes in a wide range of solvents, they correlated the values of K and $\Delta G°$ with $E_T(30)$ (an empirical solvent polarity parameter), which revealed favourable complex formation in either highly polar or highly non-polar media. This is because electrostatic forces dominate in low polarity solvents, whereas in highly polar media solvophobically driven aromatic interactions lead to the formation of stable CT complexes, which corroborates the solvent polarity effects on supramolecular assemblies in other π systems.[18,19]

The inherently weak association constant of D–A complexes is therefore not an obstacle in aqueous media and D–A interactions are useful in designing

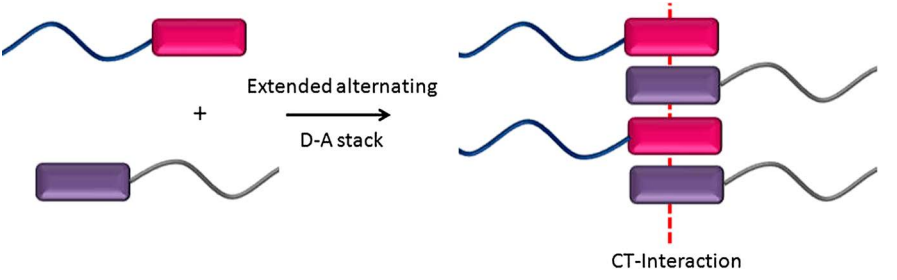

Figure 5.2 D–A assembly in the orthogonal directions.

Table 5.1 Solvent effect on D5-A9 binding parameters at $T = 298$ K. Reproduced with permission from A. Das and S. Ghosh, Supramolecular assemblies by charge-transfer interactions between donor and acceptor chromophores, *Angew. Chem., Int. Ed.*, 2014, **53**, 2038. Copyright © 2014 Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim.

Solvent	$E_T(30)$ (kcal mol^{-1})[a]	K (M^{-1})	$-\Delta G°$ (kcal mol^{-1})
$CDCl_3$	39.1	2 ± <0.5	0.4
Acetone-d_6	42.2	8 ± <0.5	1.2
DMSO-d6	45	3 ± <0.5	0.7
CD_3CN	45.6	11 ± <0.5	1.4
CD_3OD	55.5	30 ± <0.5	2.0
3 : 1 CD_3OD/D_2O	57	63 ± 2	2.5
1 : 1 CD_3OD/D_2O	58.9	254 ± 41	3.3
1 : 3 CD_3OD/D_2O	60.8	952 ± 64	4.1
D_2O	63	2045 ± 63	4.5

[a]Empirical solvent polarity parameter for non-deuterated solvents.

supra-amphiphiles. This chapter collates examples of supra-amphiphiles (in the strict sense) mediated by CT interactions and also expands the scope by including related examples in highly non-polar media, particularly those that closely resemble supra-amphiphiles in terms of molecular design.

5.2 D–A Small Molecule Supra-Amphiphiles in Aqueous Media

One of the early examples of D–A supra-amphiphiles was reported by Zhang and co-workers.[20] They showed the possibility of modulating the self-assembly behaviour (Figure 5.3) of a donor (pyrene)-containing surfactant (8-hydroxypyrene-1,3,6-trisulfonic acid trisodium salt; PYR) in the presence of a hydrophobic acceptor ethane-1,2-diyl bis(3,5-dinitrobenzoate) (DNB) with two dinitrobenzene groups. PYR exhibits tubular assembly driven by

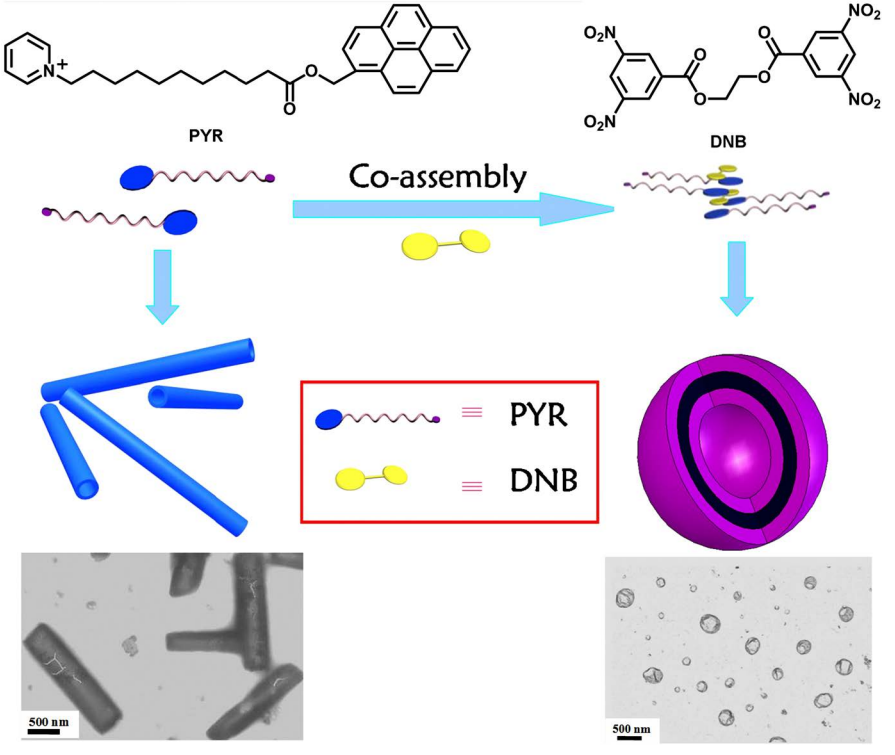

Figure 5.3 Schematic diagram showing the nanotubular and vesicular structures formed by PYR and PYR + DNB (2:1). Reproduced with permission from C. Wang, S. Yin, S. Chen, H. Xu, Z. Wang and X. Zhang, Controlled self-assembly manipulated by charge-transfer interactions: from tubes to vesicles, *Angew. Chem., Int. Ed.*, 2008, **47**, 9049. Copyright © 2008 Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim.

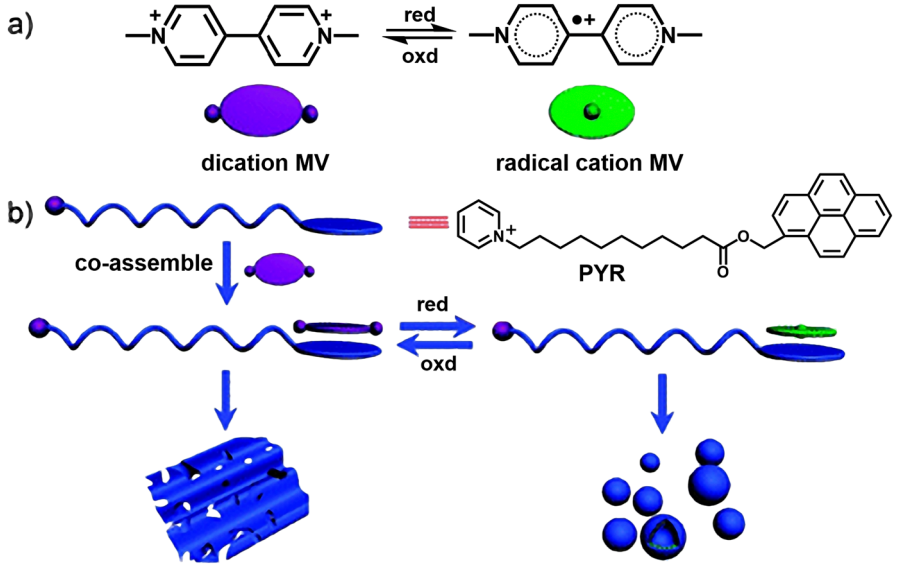

Figure 5.4 (a) Redox-responsive structural change of MV. (b) Schematic diagram showing redox-responsive assembly of PYR–MV supra-amphiphile. Reproduced from ref. 21 with permission from The Royal Society of Chemistry.

aromatic interactions between the pyrene chromophores. In the presence of 0.5 mole equivalent of DNB, co-assembly by CT interactions results in the formation of vesicles. This has been attributed to the shorter radius of curvature of the alternating D–A stack.

In a subsequent paper,[21] Zhang and co-workers examined the redox-responsive assembly of PYR in the presence of methyl viologen (MV) as an acceptor. A 1 : 1 ratio of PYR : MV showed the formation of a CT complex and thereby the formation of irregular continuous aggregates. Interestingly, MV, when reduced, generates a radical cation and is thus no longer an acceptor moiety for efficient D–A interactions. Therefore the assembly changed to a vesicle-like structure on the chemical reduction of MV and this change was reversible (Figure 5.4). This is one of the rare examples of a stimuli-responsive supra-amphiphile.

In another paper, Zhang and co-workers[22] reported the CT-mediated amphiphilic assembly of a derivatized viologen (RV) acceptor and an anionic pyrene donor (PYR) (Figure 5.5). RV forms a vesicular structure on its own in water, whereas the 1:1 complex with PYR pre-assembles into a supra-amphiphile driven by D–A interactions and Coulombic attraction, transforming vesicles into nanofibres. The straightness of the CT nanofibres could be tuned by changing the pH of the solution. With an increase in pH from 9 to 10, the curly fibres reversibly transformed to straight fibres. As the hydrophilic PYR remained at the surface, increasing the pH of the solution enhanced the extent of ionization of the hydroxyl group of PYR, which further enhanced charge repulsion on the surface and promoted the formation of straight fibres.

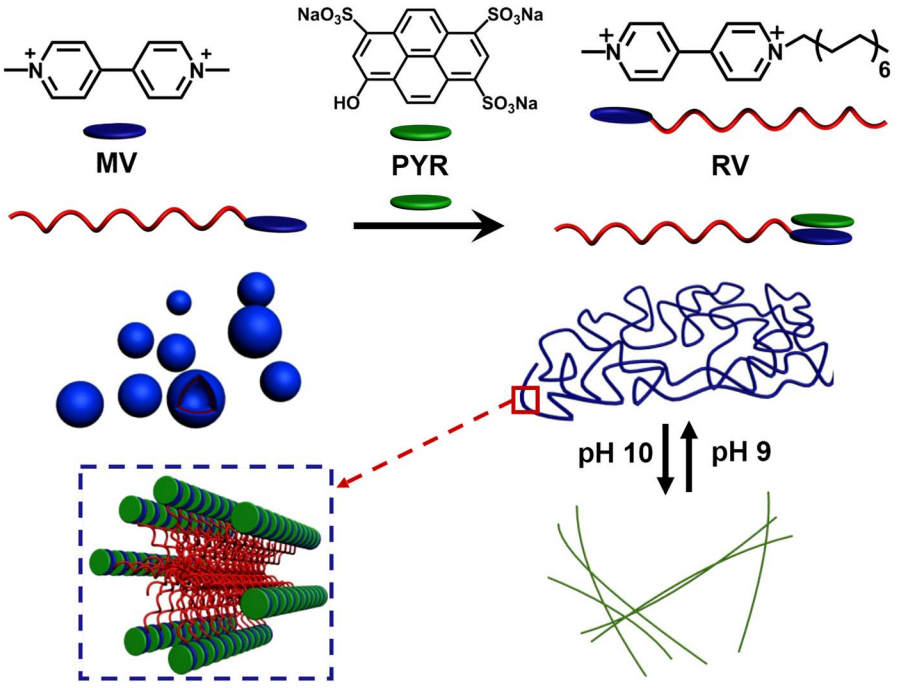

Figure 5.5 Schematic diagram showing CT interaction mediated structural evolution of vesicles to nanofibres and its pH responsiveness. Reproduced with permission from C. Wang, Y. Guo, Y. Wang, H. Xu, R. Wang and X. Zhang, Supramolecular amphiphiles based on a water-soluble charge-transfer complex: fabrication of ultralong nanofibres with tunable straightness, *Angew. Chem., Int. Ed.*, 2009, **48**, 8962. Copyright © 2009 Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim.

In a subsequent report,[23] the tuneable pH-responsiveness of CT complexes, formed by the same acceptor RV and another donor 6,8-dihydroxypyrene-1,3-disulfonic acid disodium (DHP), was demonstrated (Figure 5.6). An 1 : 1 RV–DHP complex assembled to form a supra-amphiphile at pH 9 driven by CT interactions and electrostatic attraction and generating a single-layered nanoribbon. As DHP molecules contain two phenol groups, it was anticipated that changing the pH of the solution would facilitate additional H bonding, which could eventually lead to a change in the packing geometry and the evolution of a different morphology. At pH 8 (the pK_a of the first ionization of the phenol groups is around 8), the single-layered nanoribbons underwent hierarchical assembly to form multi-layer nanoribbons *via* the lateral packing of single-layer nanoribbons by virtue of hydrophobic interactions, reduced electrostatic repulsion and H bonding between the DHP moieties. This indicates the possibility of designing CT supra-amphiphiles with a reversible tuneable morphology by the rational control of various associated interactions.

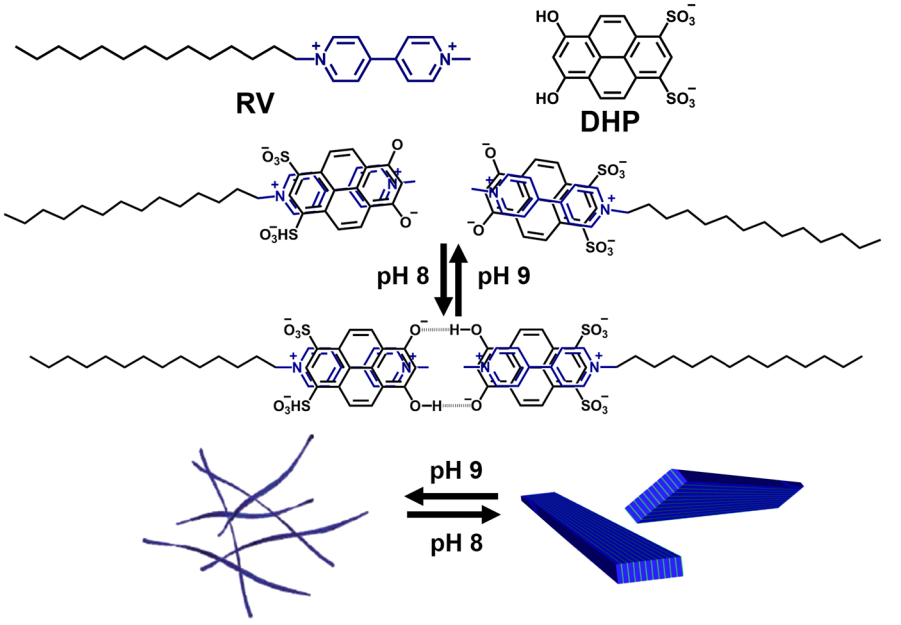

Figure 5.6 pH-responsive self-assembly of RV-DHP supra-amphiphile. Reproduced with permission from C. Wang, Y. Guo, Z. Wang and X. Zhang, Super-amphiphiles based on charge transfer complex: controllable hierarchical self-assembly of nanoribbons, *Langmuir*, 2010, **26**, 14509. Copyright (2010) American Chemical Society.

The same research group[24] has reported CT supra-amphiphiles based on a bola-amphiphile-bearing azulene moiety (PAL) and pyrene as the building blocks. TEM images showed that PAL itself self-assembled into cylindrical micelles in an aqueous medium. After complexation with one equivalent of pyrene, the resulting solution turned green, suggesting the formation of a CT complex between the electron-deficient PAL and electron-rich pyrene. After complexation this transformed to disc-like nanostructures, whereas after the removal of pyrene its initial cylindrical micelle structure was formed, with a concomitant decrease in the green colour confirming the destruction of the CT complex. Such systems where the change in morphology is reversible and highly dependent on guest insertion have been projected to practical applications such as in smart nanomaterials.

Other D–A supra-amphiphiles based on a naphthalenediimide (NDI)-based bola-amphiphilic system (BNDIV) have been reported[25] (Figure 5.7). These consisted of an electron-poor hydrophobic NDI moiety connected with a positively charged hydrophilic MV at each end. In an aqueous medium, BNDIV self-assembled as a typical bola-amphiphile where the hydrophobic NDI cores adopted a slipped head-to-tail orientation with respect to each

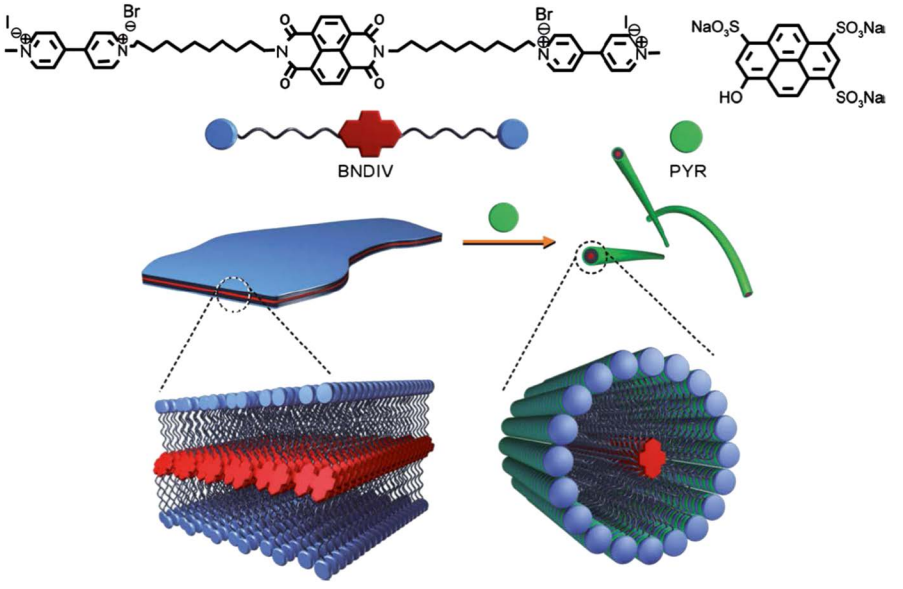

Figure 5.7 Supra-amphiphile formation and programmable evolution of different architectures by CT interactions. Reproduced with permission from K. Liu, Y. Yao, C. Wang, Y. Liu, Z. Li and X. Zhang, From bola-amphiphiles to supra-amphiphiles: the transformation from two-dimensional nanosheets into one-dimensional nanofibers with tunable-packing fashion of n-type chromophores, *Chem.–Eur. J.*, 2012, **18**, 8622. Copyright © 2012 Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim.

other, forming a two-dimensional (2D) nanosheet. Mixing BNDIV and PYR in a 1 : 2 molar ratio generated a green solution with a broad absorption band centred around 550 nm, indicating CT complex formation between the viologen and PYR moieties. BNDIV aggregated at pH 9, exhibiting a zeta potential of +16 mV as a result of the presence of the positively charged viologen units. After complexation with the negatively charged PYR, the zeta potential changed to −31 mV and concomitantly the morphology changed from 2D nanosheets to one-dimensional (1D) nanofibres, as revealed by TEM and cryo-TEM studies. An increase in the solution pH led to the transformation of curly fibres to straight fibres due to the enhanced electrostatic repulsions mentioned in earlier examples.

By extending this concept, Zhang and co-workers[26] have also reported supra-amphiphiles formed by dual CT interactions (Figure 5.8). Two types of bola-amphiphile have been studied containing viologen units attached to either arm of a dialkoxynaphthalene (DAN) donor or an NDI acceptor. In a 1 : 1 mixture, DAN–NDI forms an efficient CT complex that can be confirmed by routine spectroscopy, including UV–visible spectrophotometry, fluorescence spectrometry and nuclear magnetic resonance (NMR) spectrometry. The resulting supra-amphiphile exhibited a 2D nanosheet-like morphology in an aqueous medium. In the presence of a second donor (PYR), which

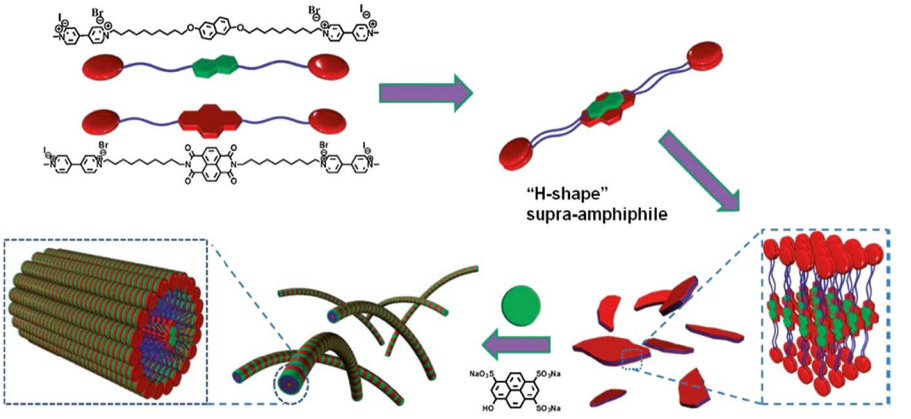

Figure 5.8 Representation of the formation of different nanostructures driven by single and dual CT interactions. Reproduced with permission from K. Liu, Y. Yao, Y. Liu, C. Wang, Z. Li and X. Zhang, Self-assembly of supra-amphiphiles based on dual charge-transfer interactions: from nanosheets to nanofibers, *Langmuir*, 2012, **28**, 10697. Copyright (2012) American Chemical Society.

interacts with the terminal viologen units by CT interactions and columbic attraction, the morphology changed from 2D sheets to 1D nanofibres.

George and co-workers[27] studied D–A supra-amphiphiles using a dodecyl-functionalized MV derivative (DMV) as the acceptor moiety and a coronene tetracarboxylate tetrapotassium salt (CS) as the electron donor counterpart, giving a DMV–CS complex with an ionic headgroup and hydrophobic dodecyl chain that formed a nanostructured assembly (Figure 5.9) in water. DMV self-assembled to form a vesicular structure in water due to its amphiphilic nature, whereas 1 : 1 DMV–CS exhibited a cylindrical micellar structure with a high aspect ratio that further combined to form bundle of fibres glued together by electrostatic attraction, leading to hydrogel formation. These supramolecular fibres were found to be potent conductors of electricity with a high field-effect mobility.

Rao and George[28] extended this strategy to design a D–A supra-amphiphile with a T-shaped oligo(phenylenevinylene) (T-OPV) the donor and a perylene derivative (C-PBI) as the acceptor. T-OPV and C-PBI formed supra-amphiphiles through synergistic CT interactions and electrostatic attraction (Figure 5.10) and produced nanotubular structures leading to hydrogelation. These CT nanotubes showed a fairly good conductivity of 0.02 S cm^{-1}, which is one of the highest reported values for small molecular assemblies, indicating their great promise in supramolecular electronics applications.

Zhang and co-workers[29] have shown an interesting example of the subtle effects of a change in the geometry of one of the components in the resulting assembly of D–A supra-amphiphiles. They studied the self-assembly of the electron-deficient bola-amphiphile BNDI with the electron-rich bola-amphiphile BNAPH or IBNAPH (Figure 5.11). Individually, BNDI self-assembles

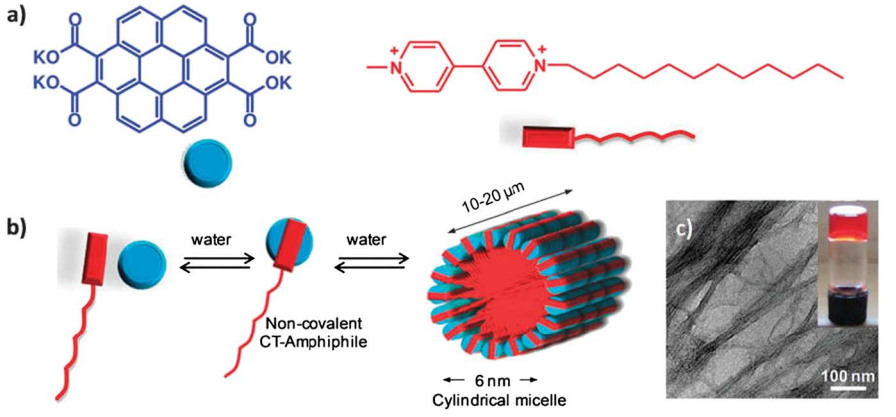

Figure 5.9 (a) Structure of DMV and CS. (b) DMV-CS supra-amphiphile formation. (c) TEM image of the CT gel (inset shows photo of gel). Reproduced with permission from K. V. Rao, K. Jayaramulu, T. K. Maji and S. J. George, Supramolecular hydrogels and high-aspect-ration nanofibers through charge-transfer-induced alternate coassembly, *Angew. Chem., Int. Ed.*, 2010, **49**, 4218. Copyright © 2010 Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim.

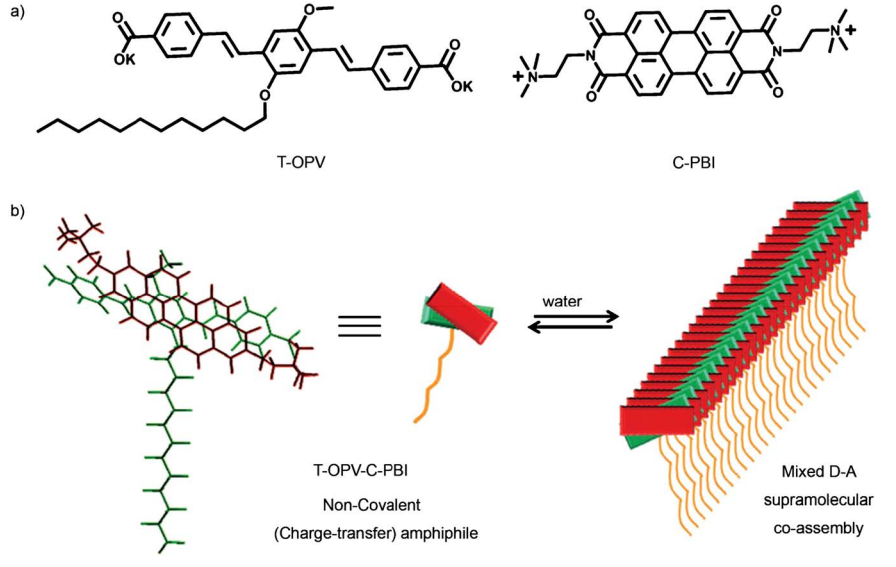

Figure 5.10 (a) Structure of T-OPV and C-PBI. (b) Formation of 1D nanofibres by the T-shaped CT amphiphile. Reproduced with permission from K. V. Rao and S. J. George, Supramolecular alternate co-assembly through a non-covalent amphiphilic design: conducting nanotubes with a mixed D–A structure, *Chem.–Eur. J.*, 2012, **18**, 14286. Copyright © 2012 Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim.

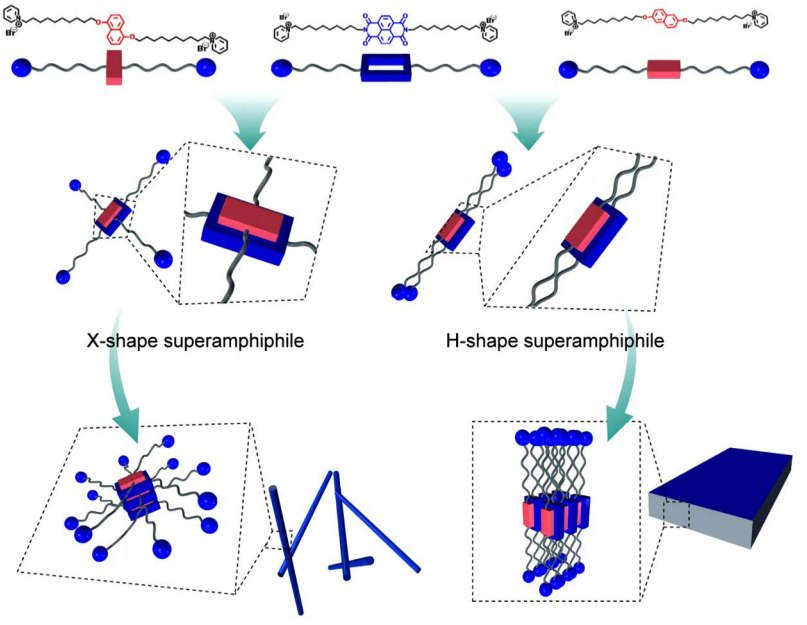

Figure 5.11 Formation of X- and H-shaped supra-amphiphiles and their distinct aggregation motifs. Reproduced with permission from K. Liu, C. Wang, Z. Li and X. Zhang, Superamphiphiles based on directional charge-transfer interactions: from supramolecular engineering to well-defined nanostructures, *Angew. Chem., Int. Ed.*, 2011, **50**, 4952. Copyright © 2011 Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim.

into fibres, whereas both the DAN-based amphiphiles form micellar structures in aqueous media. After co-mixing, 1 : 1 BNDI and BNAPH mixtures in water initially formed X-shaped supra-amphiphiles due to face-centred packing along the long axes of the DAN and NDI aromatic cores, assisted by CT and hydrophobic interactions, and then further self-assembled to generate a 1D rod-like morphology as revealed by TEM. By contrast, when the same acceptor was mixed with IBNAPH, which is a positional isomer of BNAPH, the resulting supra-amphiphile exhibited a 2D nanosheet-like structure owing to the formation of an H-shaped complex. The disparity in the relative orientation of the hydrophilic tail with respect to the hydrophobic core unit and the successive energy difference was proposed as the reason for this variation between the first-order assembly, *i.e.* an X-shaped or H-shaped amphiphile that eventually undergoes second-order assembly to generate a different morphology. This example clearly indicates that, by a minor variation in the structure and the rational choice of building blocks, it is possible to achieve programmable nanostructures, thus enriching the domain of supramolecular materials.

The supra-amphiphiles discussed so far are primarily constructed based on CT interactions together with hydrophobic and electrostatic

interactions. Ghosh and co-workers[30] envisaged that involving H bonding in CT amphiphiles could impart additional stability to such systems and enhance structural diversity. They synthesized a NDI-based non-ionic symmetrical bola-amphiphile (NDI-1, Figure 5.12) with trialkoxy aryl wedges as the hydrophilic headgroups and the hydrazide group as the H bonding functionality. It showed spontaneous vesicular assembly in water by synergistic π-stacking and H bonding. Control experiments showed that site isolation of the H bonding is a prerequisite for intermolecular H bonding among the hydrazide groups instead of among bulk water in aqueous media. They also showed shown that electron-rich pyrene can intercalate into the electron-deficient NDI assembly, leading to a stable CT complex with a high binding constant ($K = 9.69 \times 10^3\ M^{-1}$). Pyrene inclusion led to a morphological transition from vesicles to nanofibres, where the pyrene unit was flanked between two NDI moieties by virtue of CT interactions with a retention of H bonding (Figure 5.12). Apart from tuning the supramolecular architecture by CT interactions, non-covalent surface modification was demonstrated using carboxylate-appended pyrene as the donor molecule. The surface charge of the mixed vesicle could be tuned by varying the amount of negatively charged pyrene intercalator. This approach, with the capitalization of H bonding for the post-functionalization of the vesicular surface, may find important relevance in sensing and biological applications.

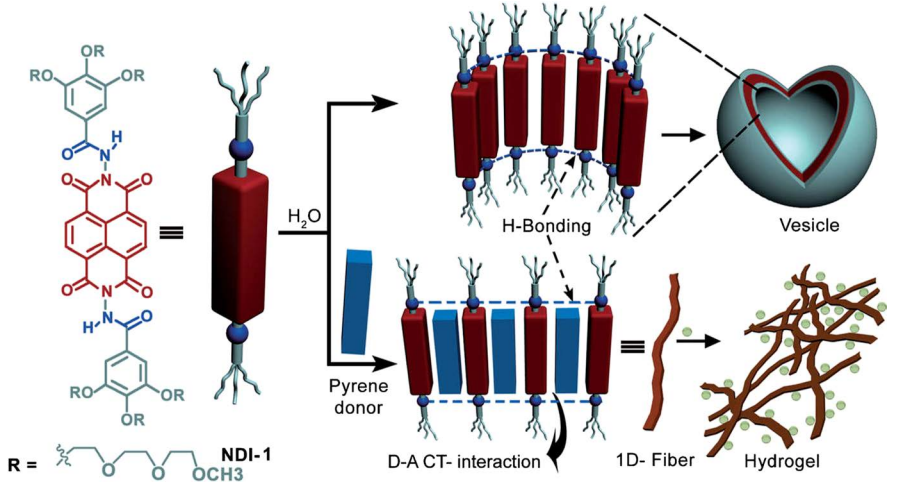

Figure 5.12 Vesicular assembly of NDI-based bola-amphiphile and CT interaction driven vesicle-to-fibre morphology transition in the presence of pyrene. Reproduced with permission from M. R. Molla and S. Ghosh, Hydrogen-bonding-mediated vesicular assembly of functionalized naphthalene–diimide-based bolaamphiphile and guest-induced gelation in water, *Chem. Eur. J.*, 2012, **18**, 9860. Copyright © 2012 Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim.

Kim and co-workers[31] established host-stabilized charge transfer (HSCT) interactions that could be utilized to produce effective supra-amphiphiles. They have demonstrated[32] giant vesicles from stable CT amphiphiles *via* a host–guest inclusion complex. MV linked with a C_{12} or C_{16} alkyl chain ($C_1VC_{12}^{2+}$ or $C_1VC_{16}^{2+}$, respectively) was chosen as the acceptor molecule, whereas 2,6-dihydroxynaphthalene (DHNp) served as the donor counterpart and cucurbit[8]uril (CB[8]), a macrocyclic cavitand consisting of eight glycoluril units, was utilized as the host molecule (Figure 5.13).

A mixture of one equivalent $C_1VC_{12}^{2+}$ (or $C_1VC_{16}^{2+}$), DHNp and CB[8] in water led to a change in the colour of the solution from transparent to violet. The UV–visible spectra of this solution showed an additional peak at 550 nm corresponding to the CT complex. Without the addition of CB[8], *i.e.* only a 1:1 mixture of $C_1VC_{12}^{2+}$ or $C_1VC_{16}^{2+}$, DHNp did not show any colour, reflecting the formation of the CT complex inside the CB[8] cavity. $C_1VC_{12}^{2+}$ and $C_1VC_{16}^{2+}$ formed micelles in water, whereas the host-stabilized D–A ternary complex formed vesicles, as shown by the TEM images. In the presence of cerium(IV) ammonium nitrate, DHNp was oxidized to naphthoquinone and was no longer an electron donor. This led to disruption of the HSCT, which eventually resulted in collapse of the vesicular structure. Such redox-responsive vesicles from host-stabilized D–A supra-amphiphiles can be further explored in developing smart materials.

Zhang and co-workers[33] have recently formulated stable CT supra-amphiphiles using HSCT as a specific non-covalent interaction using naphthyl glucosamine (GlcNap) as a glycolipid acceptor molecule and alkyl viologen (RV8) as the donor component. A 1:1 mixture of GlcNap and RV8 did not form a CT complex in water, but the addition of 1 equivalent of CB[8] instantly turned the transparent solution to yellow, indicating CT complex formation (Figure 5.14). A new band appeared between 360 and 450 nm in the UV–visible spectrum due to the host-promoted CT complex. Such a 1:1:1 ternary complex further aggregated in aqueous media to form a redox-responsive vesicular structure.

This group also has reported the synthesis of water-soluble supramolecular polymers based on multiple HSCT interactions.[34] Making

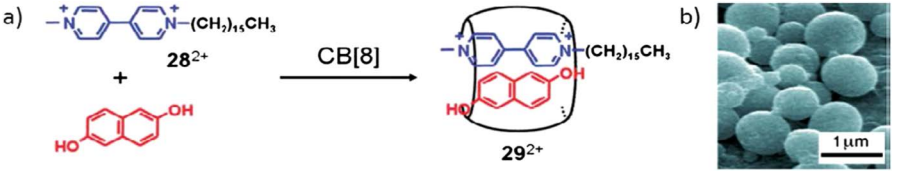

Figure 5.13 (a) Structure of $C_1VC_{12}^{2+}$, DHNp and the ternary complex. (b) TEM image of vesicles formed by the ternary complex. Reproduced with permission from Y. J. Jeon, P. K. Bharadwaj, S. W. Choi, J. W. Lee and K. Kim, Supramolecular amphiphiles: spontaneous formation of vesicles triggered by formation of a charge-transfer complex in a host, *Angew. Chem., Int. Ed.*, 2002, **41**, 4612. Copyright © 2002 Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim.

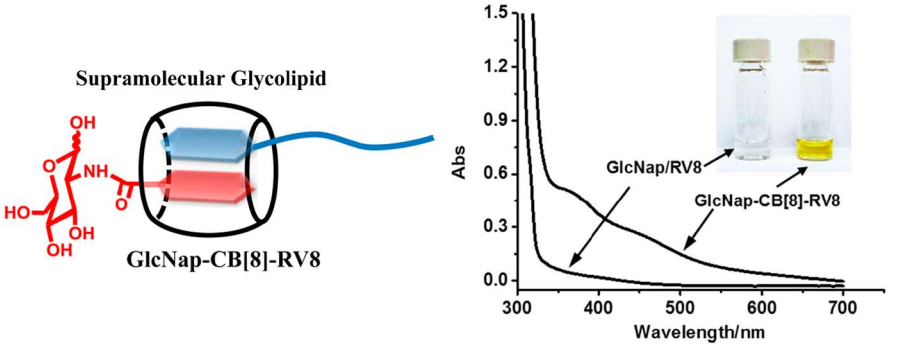

Figure 5.14 (Left) Formation of host-assisted D–A supramolecular glycolipid. (Right) Photograph (inset) and UV–visible spectra of D+A solution without and with CB[8]. Reproduced with permission from L. Yang, H. Yang, F. Li and X. Zhang, Supramolecular glycolipid based on host-enhanced charge transfer interaction, *Langmuir*, 2013, **29**, 12375. Copyright (2013) American Chemical Society.

supramolecular polymers with higher degrees of polymerization based on host–guest chemistry is difficult, primarily because of the low binding constant in a single HSCT interaction and the low orientation selectivity, which leads primarily to the formation of a cyclic structure. To solve these problems, they synthesized a multifunctional monomer 1′,1″-(butane-1,4-diyl) bis(1-(anthracen-2-ylmethyl)-4,4′-bipyridine-1,1′-diium) bromide (DADV), consisting of two electron-rich anthracene and two electron-poor viologen moieties linked by a short spacer (Figure 5.15). A mixture of CB[8] and DADV monomers (2 : 1) formed CT supra-amphiphiles in water, producing a purple-coloured solution *via* double-HSCT interactions. An increase in the monomer concentration led to elongated nanofibres, producing a hydrogel. In this particular case, the possibility of the formation of a 1 : 1 cyclic structure was suppressed due to the strain arising from the short linker and the 2 : 2 cyclic structures were prevented because of charge repulsion between the two positively charged viologen units. As a result, DADV, arranged in a head-to-tail fashion and encapsulated in CB[8], favoured supramolecular polymerization.

5.3 D–A Supra-Amphiphiles in Hydrocarbon Solvents

Amphiphiles classically contain hydrophobic and hydrophilic segments and thereby hydrophobicity driven aggregates such as micelles, vesicles, cylindrical micelles and other structures are formed in water. In the discussions so far in this chapter, engineered amphiphiles of a similar nature have been exemplified with D–A CT interactions, where the D and A chromophores

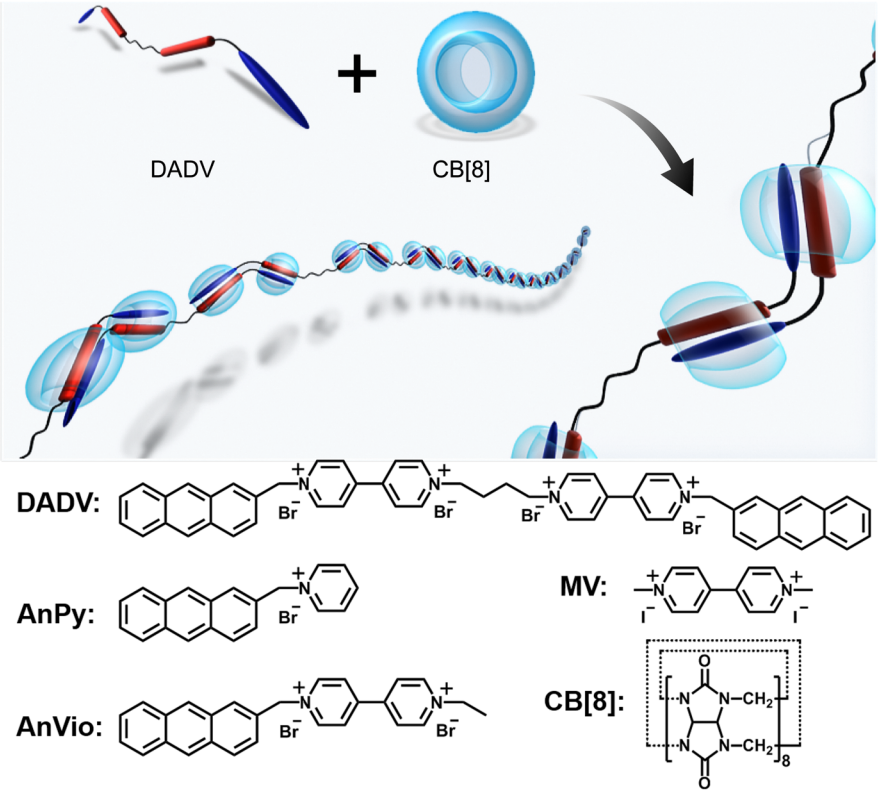

Figure 5.15 Schematic diagram of supramolecular polymerization by dual HSCT interaction between DADV and CB[8]. Reproduced with permission from Y. Liu, Y. Yu, J. Gao, Z. Wang and X. Zhang, Water-soluble supramolecular polymerization driven by multiple host-stabilized charge-transfer interactions, *Angew. Chem., Int. Ed.*, 2010, **49**, 6576. Copyright © 2010 Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim.

mostly act as hydrophobic segments. Such rigid π-systems are immiscible with hydrocarbons or less polarizable solvents and thus if they are derivatized by alkyl chains, amphiphilic-like structure formation can be expected, particularly because the D–A CT interaction is equally favourable in hydrocarbons. Thus although in classical terms these structures are not amphiphilic, in practice their assembly behaviour in non-polar media closely resembles that of supra-amphiphiles.

This section outlines recent progress in the assembly of alkyl chain derived D–A units in hydrocarbons or similar non-polar media. Zhang and co-workers[35] showed the H bonding driven self-assembly of a urea-functionalized tetrathiafulvalene (TTF) derivative in cyclohexane leading to a fibrillar network and gelation. TTF is a well-known donor that forms CT complexes

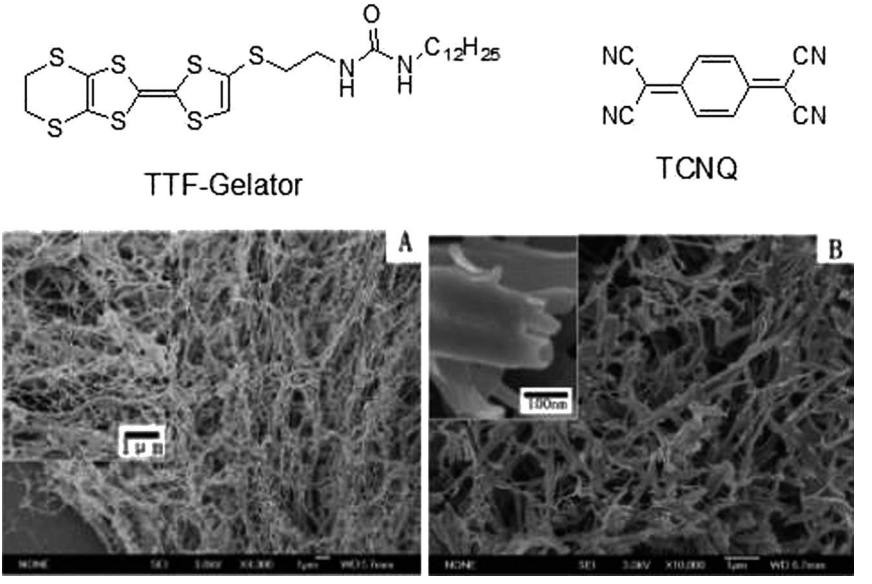

Figure 5.16 (Upper panel) Structure of TTF gelator and TCNQ. (Lower panel) SEM images of TTF (left) and TTF-TCNQ (1 : 1) gel (right) in cyclohexane. Reproduced with permission from C. Wang, D. Zang and D. Zhu, A low-molecular-mass gelator with an electroactive tetrathiafulvalene group: tuning the gel formation by charge-transfer interaction and oxidation, *J. Am. Chem. Soc.*, 2005, **127**, 16372. Copyright © 2005 American Chemical Society.

with acceptor molecules such as 7,7,8,8-tetracyanoquinodimethane (TCNQ). These researchers showed that in the presence of TCNQ the fibrillar structure converted to a tubular structure (Figure 5.16), which was ascribed to the formation of a CT complex between TTF and TCNQ. This was further confirmed by sharp change in colour of the gel from orange to dark green. When the orange-coloured TTF gel was mixed with the same TCNQ acceptor in 1,2-dichloroethene instead of cyclohexane, the gel converted to a dark green solution. This study thus demonstrated the possibility of tuning the self-assembly of donor-containing amphiphile-like molecules in the presence of acceptor molecules due to CT interactions.

We have been working on the supramolecular assembly of bis-amide functionalized DAN/NDI D–A systems (Figure 5.17) in which the distances between the two amide groups (L_D and L_A) are comparable, so that H bonding and CT interactions can operate simultaneously. For NDI-2 + DAN-4, a stable red gel with a typical fibrillar network was seen in trichloroethylene (TCE).[36] By simply increasing the spacer length of NDI by one methylene unit, NDI-3 + DAN-4 showed a more intense CT band, but no gelation, which became clear by its spherical morphology (similar to reverse vesicles) instead of a fibrillar network. The morphology could be further tuned by varying the D : A ratio.[37] For example, with the NDI-3 + DAN-4 pair, for a 1 : 2 ratio of D–A, instead of

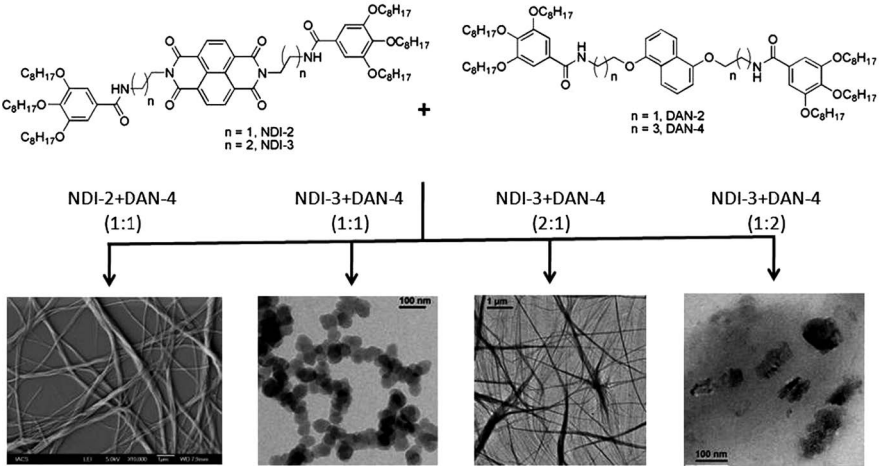

Figure 5.17 Structure and stoichiometry dependent diverse morphologies generated by the co-assembly of the DAN–NDI pair in TCE.

a spherical structure, a fibrillar network and resultant gelation were again seen because in this case the assembly was mostly governed by an AA interaction of the initially formed ADA nuclei. Similarly, with excess donor (D:A = 2:1), the initially formed DAD nuclei did not generate any specific structure because chain extension by DD interaction was less pronounced due to electrostatic repulsion among the donor units. On changing from TCE to methylcyclohexane (MCH), the alternating stacking mode was destroyed and the initially formed red gel converted to a yellow gel over time as a result of reorganization to the segregated homo-assembly of the individual components.[38]

We have also studied the co-assembly of monoamide functionalized D–A (pyrene–NDI) chromophores with the primary objective of establishing a strategy for efficient structure formation driven by D–A recognition.[39] We have shown that H bond supported D–A recognition can influence the formation of structures with long-range order between NDI-2 + Py-3 (Figure 5.18). In a unique way, self-complementary amide groups, when attached to donor and acceptor chromophores, become complementary to each other and, in turn, operate synergistically with the D–A CT interaction, resulting in significantly enhanced efficacy of the binding event. The propensity for alternating stacks strongly depends on *n* as this determines the matching spacer length between the chromophore and the amide group in two different chromophores. Such distinct molecular recognition propagates in the orthogonal direction, resulting in the extended alternating co-assembly of two different appended structural entities. As the D–D interaction was negligible compared with the D–A interaction, the length of the supramolecular polymer could be precisely controlled simply by using a stoichiometric excess of the donor unit, similar to the modulation of the degree of polymerization in step-growth polymerization by a stoichiometric imbalance of the two monomers. The possibility of executing

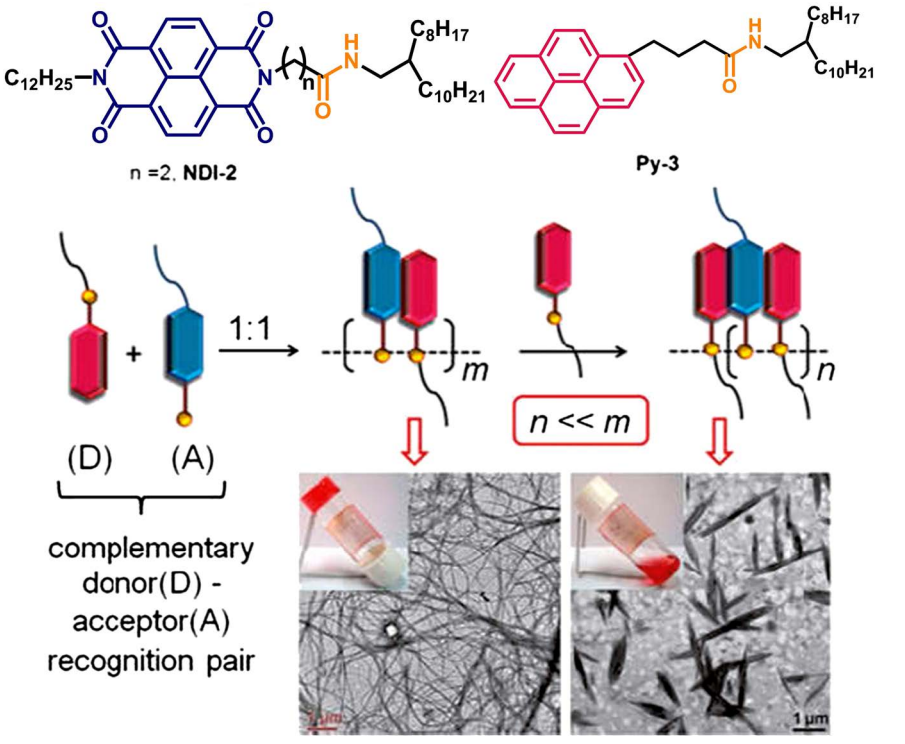

Figure 5.18 Complementary D–A recognition pair and their stoichiometry-dependent morphology. Reproduced with permission from A. Sikder, B. Ghosh, S. Chakraborty, A. Paul and S. Ghosh, Rational design for complementary donor–acceptor recognition pairs using self-complementary hydrogen bonds, *Chem.–Eur. J.*, 2016, **22**, 1908. Copyright © 2016 Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim.

this design in aqueous media (by hydrophobic shielding of the amides by the D–A chromophores), extending the strategy to produce yet unexplored supramolecular alternating graft copolymers (like supramolecular block copolymers by complementary H bonding), is unique opportunity that is not available without the successful hybridization of the two individual non-covalent forces (*e.g.* H bonding and D–A interactions), as demonstrated with this system.

The discussion so far has been restricted to intermolecular D–A interactions; there are very few examples of supra-amphiphiles formed by intra-chain CT interactions. We have reported the formation of a complex non-covalent structure by the stepwise assembly of an amide-functionalized D–A dyad in MCH, an apolar organic solvent, by manoeuvring multiple weak interactions involving H bonding, CT interactions, π–π stacking and solvophobic forces.[40] The primary D–A building unit of NDI–PY (Figure 5.19) adopted a folded conformation by intra-chain CT interactions and subsequently formed a pair by intermolecular H bonding to produce a folded dimer (FD) with a DAAD sequence.

The FD presents one face consisting of stacked rigid chromophores and another face with long alkyl chains and it can thus be viewed as an analogue

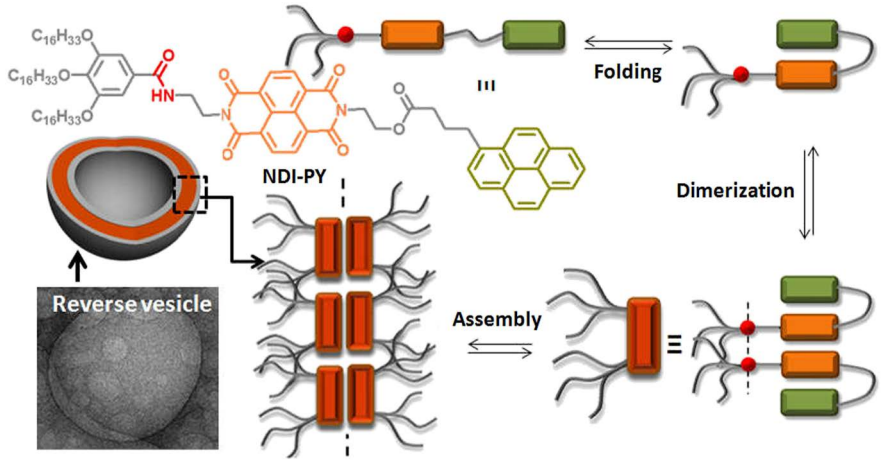

Figure 5.19 Schematic diagram showing folding and assembly of a supra-amphiphile by intra-chain CT interactions and H bonding. Reproduced from ref. 40 with permission from The Royal Society of Chemistry.

of a facial amphiphile.[41,42] In MCH, the selective incompatibility of the aromatic stacked face triggers macroscopic assembly by solvophobically driven edge-to-edge sticking of the FD, with concomitant growth in the orthogonal direction by D–D π-stacking leading to the formation of a bilayer reverse vesicle. Amid numerous possibilities, the formation of a specific structure involving intra-chain folding followed by macroscopic assembly is reminiscent of the three-dimensional structural evolution of proteins by considering the foldamer, FD and the bilayer membrane as synthetic mimics of the secondary, tertiary and quaternary structure of proteins, respectively.

We have further studied[43] a supra-amphiphile consisting of non-covalently linked D–A chromophores (Figure 5.20). This system explored a supramolecular design using a functional NDI synthon (**1**, Figure 5.20) consisting of two different self-complementary H bonding functional groups, namely, hydrazide (H1) and hydroxyl (H2).

By design: (1) they can operate simultaneously in the orthogonal directions (parallel and perpendicular to the direction of π-stacking); (2) one of them (H2, perpendicular to the π-stacking) can be selectively dissociated by thermal energy; and (3) H2 can change its self-complementary nature in the presence of another complementary functional group and can thus carry an appropriately derivatized second chromophore to produce a multi-chromophoric assembly. Self-assembly studies in a non-polar solvent (MCH) revealed the following three results. First, reverse vesicular assembly by orthogonal H bonding and its thermally induced dual-phase transition to a 'denatured' state, followed by a recaptured (reverse micelle) state at the lower (LCST) and upper critical solution temperature (UCST), respectively. This is related to the selective dissociation of the relatively weaker H bond while keeping the other H bond unbroken over the temperature window tested. Second, co-assembly of the same building block with a pyridine-functionalized, electron-rich pyrene (**2**, Figure 5.20)

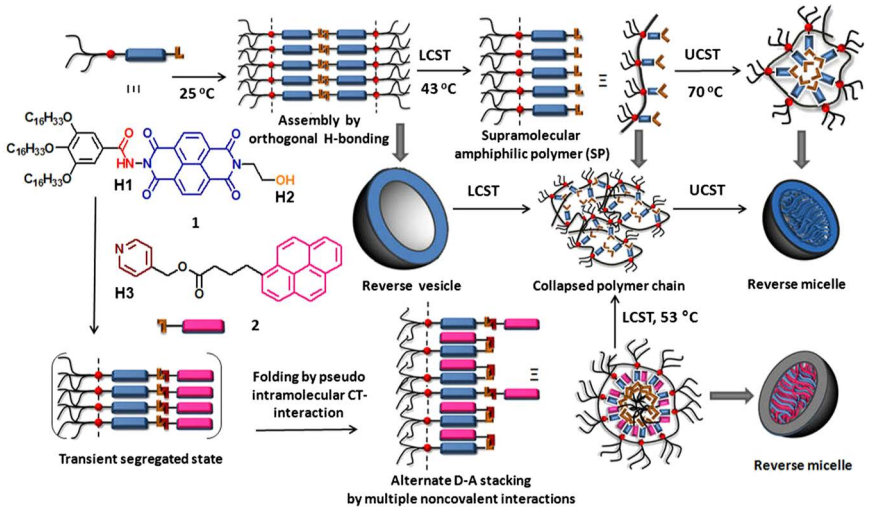

Figure 5.20 Complex self-assembly and thermo-responsive morphology transformation of **1** and **1**+**2** in MCH. Reproduced with permission from A. Das and S. Ghosh, *Angew. Chem. Int. Ed.*, 2014, **53**, 1092–1097. © 2014 Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim.

by a different mode of orthogonal H bonding to produce a transient segregated D–A complex. This complex gradually transformed to an alternate D–A stack by a rather slow folding process as a result of enthalpy-driven pseudo-intramolecular CT interactions. Third, two thermal transitions (LCST and UCST) were also exhibited by the mixed D–A assembly and a morphology transition was noticed from a reverse micelle (a core containing a D–A mixed stack) below the LCST to another reverse micelle (core containing only the NDI acceptor) above the UCST *via* a 'denatured' intermediate between the LCST and UCST windows. These are unprecedented features with immense implications. Although there have been many reports on the LCST and relatively less on the UCST, most deal with aqueous polymer solutions and depend on solute–solvent interactions. This is the first example of such an observation in an organic medium governed by solute–solute interactions and thus provides a generalized guideline based on an untested pathway for new stimuli-responsive supramolecular materials of biological relevance. The second feature demonstrates a highly complex supramolecular assembly involving the cooperative of operation of two independent H bonding motifs and CT interactions.

5.4 D–A Polymeric Supra-Amphiphiles

Supramolecular D–A amphiphiles have attracted much attention as a result of their attractive features for use as smart nanomaterials, their sensing properties and biomedical applications. Using a similar approach, polymeric amphiphiles can also be fabricated based on CT interactions. Because the building blocks in polymeric D–A supra-amphiphiles are attached by

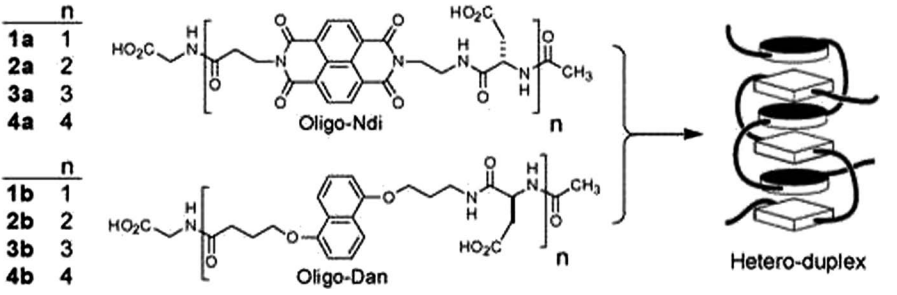

Figure 5.21 Molecular structures of DAN and NDI containing oligomers and formation of hetero-duplexes. Reproduced with permission from G. J. Gabriel and B. L. Iverson, Aromatic oligomers that form hetero duplexes in aqueous solution, *J. Am. Chem. Soc*., 2002, **124**, 15174. Copyright (2002) American Chemical Society.

non-covalent interactions, they have the added advantage of a more dynamic nature over conventional amphiphilic polymers.

In 2002, Gabriel and Iverson[44] reported hetero-duplexes in an aqueous medium formed by the CT-induced folding of oligomers containing electron-rich DAN and electron-deficient NDI units in the backbone (Figure 5.21). A series of oligomers was prepared with varying numbers of DAN or NDI units and it was been shown by NMR spectrometry and isothermal titration calorimetry that, along with the association constant, various other thermodynamic parameters were highly dependent on the number of D and A moieties. For example, the value of association constant (K_a) increased by three orders in magnitude when the number of increases from 1 to 4 (Table 5.2). This example illustrates the potential of such systems in molecular recognition in aqueous media reinforced by complementary π–π interactions.

D–A based molecular recognition was further exploited by De and Ramakrishnan[45] to construct engineered superstructures with D–A ionenes. Ionenes are polymers (ionic) that are built up by the covalent attachment of surfactant molecules in a head-to-tail fashion to grow longer chains. Ionenes are an interesting class of polymers due to their dynamicity, in which the solution state conformation can be altered by minor variations in the polymer structure (the manipulation of either charge periodicity or counter ions). These researchers designed a novel class of ionenes bearing tertiary ammonium groups with a backbone of DAN donor and pyromellitic diimide (PDI) acceptor molecules alternately connected by alkylene spacers (Figure 5.22). In aqueous media, these D–A ionenes undergo transition from an extended structure to a folded accordion-type conformation driven by solvophobically assisted CT interactions between the DAN and PDI moieties. The CT band was monitored in various solvents and it was shown that the extension of folding was highly dependent on the polarity of the solvent. Polar solvents bring the donor and acceptor moieties into closer proximity by solvophobic interactions to give a more intense CT band.

Table 5.2 Binding data[a] of oligo-DAN and oligo-NDI chains obtained from NMR and ITC experiments. Reproduced with permission from G. J. Gabriel and B. L. Iverson, Aromatic oligomers that form hetero duplexes in aqueous solution, *J. Am. Chem. Soc.*, 2002, **124**, 15174. Copyright (2002) American Chemical Society.

	K_a (T = 298 K)	$\Delta G°$	$\Delta H°$ [b]	$\Delta S°$ [b]
1a:1b	3.0 (0.1) × 10^2	−3.4	–	–
2a:2b[c]	7.5 (0.5) × 10^3	−5.3	–	–
2a:2d[d]	7.6 (0.1) × 10^3	−5.3	−10.4 (0.2)	−17.2
	K_a (T = 318 K)	$\Delta G°$	$\Delta H°$ [b]	$\Delta S°$ [b]
1a:1b[c]	1.3 (0.1) × 10^2	−3.1	–	–
2a:2b[c]	2.8 (0.1) × 10^3	−5.0	–	–
2a:2d[d]	2.7 (0.1) × 10^3	−5.0	−12.3(0.3)	−23.0
3a:3b[d]	4.5 (0.1) × 10^4	−6.8	−17.7 (0.1)	−34.0
4a:4b[d]	3.5 (0.2) × 10^5	−8.1	−19.3(0.2)	−35.3

[a]Units: K_a (M^{-1}), $\Delta G°$ (kcal mol^{-1}), $\Delta H°$ (kcal mol^{-1}), $\Delta S°$ (cal mol^{-1} K^{-1}). $\Delta G°$ calculated from average K_a values and $\Delta S°$ calculated from average $\Delta G°$ and $\Delta H°$ values.
[b]For NMR data, $\Delta H°$ and $\Delta S°$ were not calculated.[15]
[c]Analysed by NMR.
[d]Analysed by ITC.

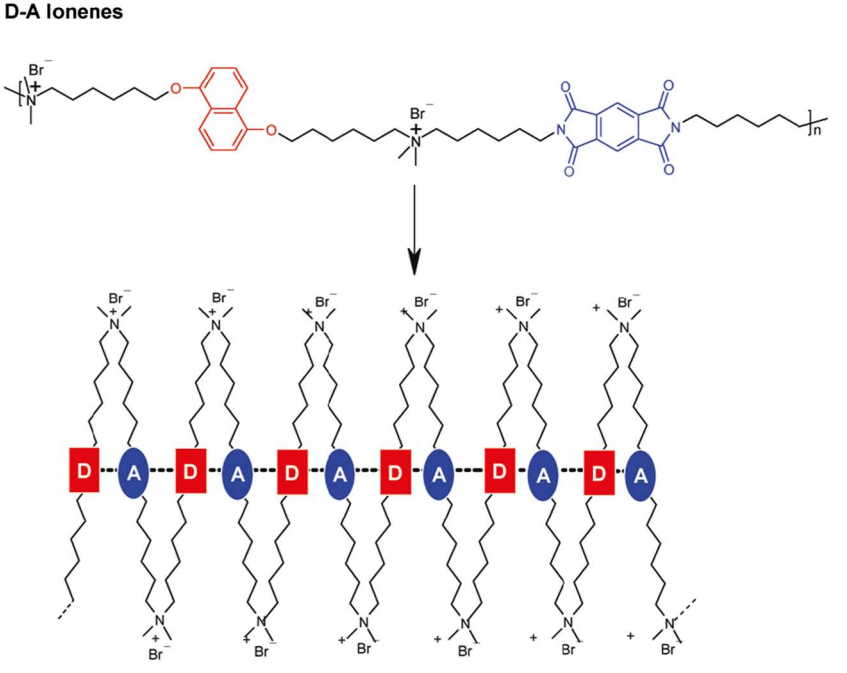

Figure 5.22 Ionenes stabilized by D–A CT interactions. Reproduced with permission from S. De and S. Ramakrishnan, Charge-transfer reinforced folding of novel ionenes, *Macromolecules*, 2009, **22**, 42. Copyright (2009) American Chemical Society.

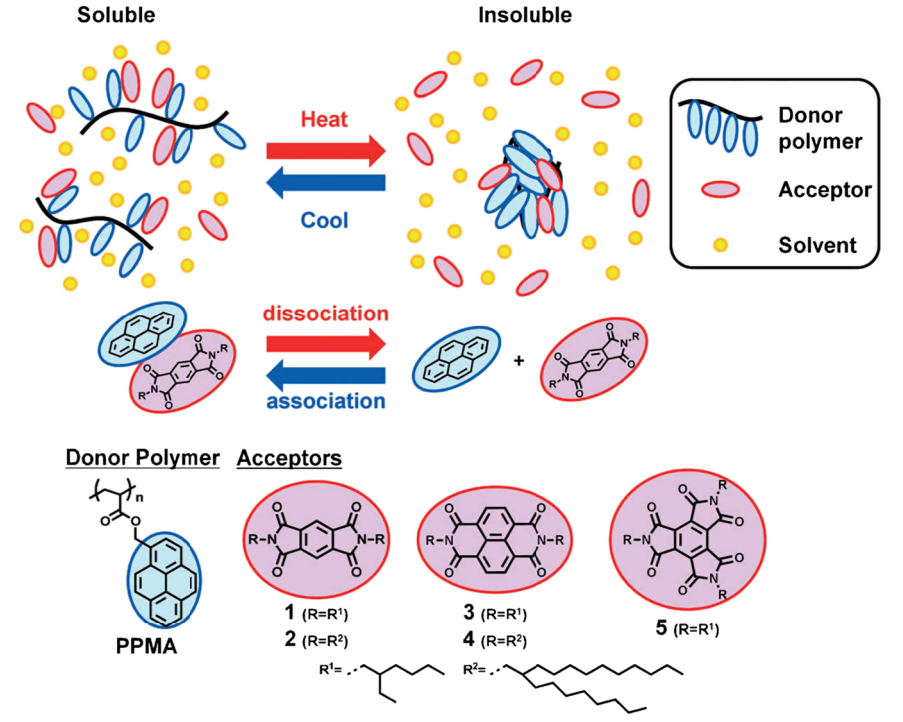

Figure 5.23 Donor-appended polymer and tuning of its solubility by formation of CT interaction mediated supra-amphiphiles in the presence of small molecule acceptors. Reproduced with permission from S. Amemori, K. Kokado and K. Sada, Polymer phase-transition behaviour driven by a charge-transfer interaction, *Angew. Chem., Int. Ed.*, 2013, **52**, 4174. Copyright © 2013 Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim.

Sada and co-workers[46] reported precise control over the LCST of donor-containing polymer solutions by virtue of CT interactions with small molecular acceptors (Figure 5.23). They synthesized a poly((1-pyrene)methyl acrylate) (PPMA) polymer in which the pendent pyrene groups assembled *via* π–π interactions and thereby lowered the overall solubility, making the polymer insoluble in an organic medium (1,2-dichloroethane).

However, the solubility was increased when the PPMA polymer was complexed with small acceptor molecules connected with a branched alkyl chain. At elevated temperatures, due to disintegration of the D–A complex, the polymer became insoluble again, which can be termed as an LCST. They showed that it is possible to fine tune the LCST behaviour of the polymer by varying either the acceptor molecule or the alkyl chain length attached to the acceptor molecule because the solubility of the polymer and the temperature at which CT complex disruption occurs is highly dependent on the stability of the CT complex. This concept is unique because solubility of a polymer and its LCST property deviates from classical theory and relies on non-covalent CT interactions, where the insoluble polymers become soluble by complexation with other small molecules bearing solubilizing groups.

5.5 Summary and Outlook

This chapter has collated representative recent examples of CT supra-amphiphiles based on a diverse range of aromatic donor and acceptor building blocks. It is evident that, as a result of the directional nature of the CT interaction, such supra-amphiphiles can produce wide-ranging nanostructures including micelles, vesicles, fibres and nanotubes. Although major activity in this area is still restricted to investigations of the formation of structure, a few examples show great promise for these supra-amphiphiles to be used in materials science and biological applications. Of particular interest is the possibility of developing stimuli-responsive materials because CT complexes are highly redox-sensitive. The stability of D–A complexes is an important issue that has been addressed by stabilizing them either by auxiliary forces such as H bonding or electrostatic interactions, or by an external host. Further standardization of such attempts to make stable and tunable nanostructures using CT supra-amphiphiles will bring new opportunities for supramolecular biomaterials and electronic materials.

References

1. X. Zhang and C. Wang, *Chem. Soc. Rev.*, 2011, **40**, 94.
2. Y. P. Wang, H. P. Xu and X. Zhang, *Adv. Mater.*, 2009, **21**, 2849.
3. Y. Kang, K. Liu and X. Zhang, *Langmuir*, 2014, **30**, 5989.
4. C. Wang, Z. Wang and X. Zhang, *Acc. Chem. Res.*, 2012, **45**, 608.
5. H. Ringsdorf, B. Schlarb and J. Venzmer, *Angew. Chem., Int. Ed.*, 1988, **27**, 113.
6. R. Foster, *Organic Charge-Transfer Complex*, Academic Press, London, 1969.
7. A. Das and S. Ghosh, *Angew. Chem., Int. Ed.*, 2014, **53**, 2038.
8. M. Kumar, K. V. Rao and S. J. George, *Phys. Chem. Chem. Phys.*, 2014, **16**, 1300.
9. T. Murata, Y. Morita, Y. Yakiyama, K. Fukui, H. Yamochi, G. Saito and K. Nakasuji, *J. Am. Chem. Soc.*, 2007, **129**, 10837.
10. K. Tahara, T. Fujita, M. Sonoda, M. Shiro and Y. Tobe, *J. Am. Chem. Soc.*, 2008, **130**, 14339.
11. C. Wang, Q. Chen, Z. Wang and X. Zhang, *Angew. Chem., Int. Ed.*, 2010, **49**, 8612.
12. S. S. Babu, S. Prasanthkumar and A. Ajayaghosh, *Angew. Chem., Int. Ed.*, 2012, **51**, 1766.
13. J. Luo, L. Chen, J. Y. Wang, T. Lei, L. Y. Li, J. Pei and Y. Song, *New J. Chem.*, 2010, **34**, 2530.
14. S. Horiuchi and Y. Tokura, *Nat. Mater.*, 2008, **7**, 357.
15. M. L. Saha, S. De, S. Pramanik and M. Schmittel, *Chem. Soc. Rev.*, 2013, **42**, 6860.
16. R. Foster, *J. Chem. Soc.*, 1960, 1075.
17. M. S. Cubberley and B. L. Iverson, *J. Am. Chem. Soc.*, 2001, **123**, 7560.

18. D. B. Smithrud and F. Diederich, *J. Am. Chem. Soc.*, 1990, **112**, 339.
19. Z. Chen, B. Fimmela and F. Würthner, *Org. Biomol. Chem.*, 2012, **10**, 5845.
20. C. Wang, S. Yin, S. Chen, H. Xu, Z. Wang and X. Zhang, *Angew. Chem., Int. Ed.*, 2008, **47**, 9049.
21. C. Wang, Y. Guo, Y. Wang, H. Xu and X. Zhang, *Chem. Commun.*, 2009, **36**, 5380.
22. C. Wang, Y. Guo, Y. Wang, H. Xu, R. Wang and X. Zhang, *Angew. Chem., Int. Ed.*, 2009, **48**, 8962.
23. C. Wang, Y. Guo, Z. Wang and X. Zhang, *Langmuir*, 2010, **26**, 14509.
24. F. Li, Q. Song, L. Yang, G. Wu and X. Zhang, *Chem. Commun.*, 2013, **49**, 1808.
25. K. Liu, Y. Yao, C. Wang, Y. Liu, Z. Li and X. Zhang, *Chem.–Eur. J.*, 2012, **18**, 8622.
26. K. Liu, Y. Yao, Y. Liu, C. Wang, Z. Li and X. Zhang, *Langmuir*, 2012, **28**, 10697.
27. K. V. Rao, K. Jayaramulu, T. K. Maji and S. J. George, *Angew. Chem., Int. Ed.*, 2010, **49**, 4218.
28. K. V. Rao and S. J. George, *Chem.–Eur. J.*, 2012, **18**, 14286.
29. K. Liu, C. Wang, Z. Li and X. Zhang, *Angew. Chem., Int. Ed.*, 2011, **50**, 4952.
30. M. R. Molla and S. Ghosh, *Chem.–Eur. J.*, 2012, **18**, 9860.
31. H. J. Kim, J. Heo, W. S. Jeon, E. Lee, J. Kim, S. Sakamoto, K. Yamaguchi and K. Kim, *Angew. Chem., Int. Ed.*, 2001, **40**, 1526.
32. Y. J. Jeon, P. K. Bharadwaj, S. W. Choi, J. W. Lee and K. Kim, *Angew. Chem., Int. Ed.*, 2002, **41**, 4612.
33. L. Yang, H. Yang, F. Li and X. Zhang, *Langmuir*, 2013, **29**, 12375.
34. Y. Liu, Y. Yu, J. Gao, Z. Wang and X. Zhang, *Angew. Chem., Int. Ed.*, 2010, **49**, 6576.
35. C. Wang, D. Zhang and D. Zhu, *J. Am. Chem. Soc.*, 2005, **127**, 16372.
36. A. Das, M. R. Molla, A. Banerjee, A. Paul and S. Ghosh, *Chem.–Eur. J.*, 2011, **17**, 6061.
37. A. Das, M. R. Molla, B. Maity, D. Koley and S. Ghosh, *Chem.–Eur. J.*, 2012, **18**, 9849.
38. M. R. Molla, A. Das and S. Ghosh, *Chem.–Eur. J.*, 2010, **16**, 10084.
39. A. Sikder, B. Ghosh, S. Chakraborty, A. Paul and S. Ghosh, *Chem.–Eur. J.*, 2016, **22**, 1908.
40. A. Das and S. Ghosh, *Chem. Commun.*, 2014, **50**, 11657.
41. J. Boekhoven, P. van Rijn and J. H. van Esch, Self-Assembly of Facial Amphiphiles in Water, in *Supramolecular Chemistry: From Molecules to Nanomaterials*, ed. P. Gale and J. Steed, Wiley, vol. 7, 2012.
42. A. Klaikherd, B. S. Sandanaraj, D. R. Vutukuri and S. Thayumanavan, *J. Am. Chem. Soc.*, 2006, **128**, 9231.
43. A. Das and S. Ghosh, *Angew. Chem., Int. Ed.*, 2014, **53**, 1092.
44. G. J. Gabriel and B. L. Iverson, *J. Am. Chem. Soc.*, 2002, **124**, 15174.
45. S. De and S. Ramakrishnan, *Macromolecules*, 2009, **22**, 42.
46. S. Amemori, K. Kokado and K. Sada, *Angew. Chem., Int. Ed.*, 2013, **52**, 4174.

CHAPTER 6

Supra-Amphiphiles Based on Coordination Bonds

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6.1 Introduction

In addition to supra-amphiphiles formed by hydrogen bonding, electrostatic attraction, host–guest recognition, charge transfer interactions, hydrophobic–hydrophilic interactions and π–π stacking interactions, there is also a type of supramolecular amphiphile driven by coordination bonds (also known as metal–ligand interactions).[1] Metal–ligand interactions are unique noncovalent interactions formed between a metal ion (known as the coordination center) and its surrounding array of organic molecules (known as the ligand). Such interactions are highly tunable in strength. With different combinations of metal ions and ligands, the bond strength can be readily adjusted in a broad range from about 25 to 95% of a covalent C–C bond (with a bond energy of about 350 kJ mol^{-1}). As a result, chemists can take advantage of the abundant well-studied metal–ligand combinations to

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construct supramolecular amphiphiles with various topologies, structures and functions.

Specifically, supra-amphiphiles based on metal–ligand coordination refer to amphiphiles that are composed of a hydrophilic group, a hydrophobic group and a coordination complex as a linker (Figure 6.1). The coordination complex can be hydrophilic (when it carries a charge) or hydrophobic (when neutral). This results in additional tunability in the design of the supra-amphiphiles. For examples, the topology could also be a linear hydrophobic group connected to a hydrophilic metal–ligand complex, or a linear hydrophilic group connected to a hydrophobic metal–ligand complex. Supra-amphiphiles based on metal–ligand interactions can also be polymers in which the metal–ligand complex functions as a linker between a hydrophilic polymer (or oligomer) and a hydrophobic polymer (or oligomer).

Compared with other noncovalent interactions, metal–ligand interactions offer many unique advantages in the construction of supra-amphiphiles. As a result of their tunable binding geometry and strength, the metal–ligand interactions allow facile control over the molecular topology and self-assembly behavior. The presence of a metal complex in the copolymer structure introduces unique functionalities—including electrochemical, photochemical and redox properties—that are not observed in the covalent or noncovalent counterpart. The presence of active metal complexes in micellar systems is interesting for applications in supported catalysis and nanotechnology.

This chapter reviews supra-amphiphiles based on metal–ligand interactions. We first focus on the topology and self-assembly of supra-amphiphiles with different levels of complexity. The different metal–ligand coordination geometries facilitate the fabrication of supra-amphiphiles with various topologies, whereas the self-assembly of supra-amphiphiles provides new building blocks for complex structures. We then summarize the functions and applications of coordination supra-amphiphiles. The dynamic nature of metal–ligand interactions endows the assemblies of supra-amphiphiles with

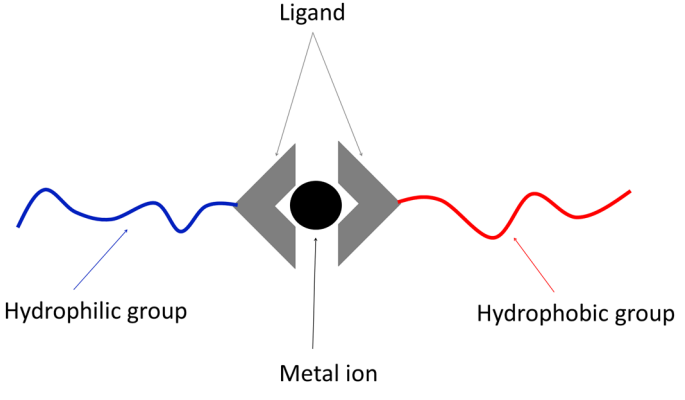

Figure 6.1 Schematic representation of the structure of coordination supra-amphiphiles.

stimuli-responsive functions, while the presence of metal ions introduces additional chemical and physical properties, such as luminescence, magnetism, redox and catalytic properties.

6.2 Topology and Self-Assembly Behavior

The topology and self-assembly behavior of coordination supra-amphiphiles are highly dependent on the geometries of the core coordination complex as well as the architecture of the supra-amphiphile.[2] In general, the topologies of conventional amphiphiles and supra-amphiphiles formed by other types of noncovalent interactions can also be realized in coordination supra-amphiphiles. Compared with hydrogen bonds or other noncovalent interactions, metal–ligand coordinations offer greater tunability in terms of binding strength, coordination number and binding geometry.

The geometry of the coordination center is mainly determined by the coordination number of the metal ions (defined as the number of donor atoms attached to the metal ion), which is dependent on the size, charge and electron configuration of the metal ion and the ligands. Typical geometries observed are: (1) linear for two coordination; (2) tetrahedral or square planar for four coordination; and (3) octahedral (orthogonal) or trigonal prismatic for six coordination. The architectures of supra-amphiphiles are correlated with the modes of connection between the hydrophilic/hydrophobic groups and coordination complexes. By combining these features with different hydrophilic or hydrophobic groups, we can obtain supra-amphiphiles with the traditional topological structures of covalent amphiphiles and also realize new topological structures. Supra-amphiphiles with single-tail, double-tail, multi-tail, bola-form, gemini-form and polymer-type topologies can be readily obtained.

Supra-amphiphiles are able to self-assemble in selective solvents to form various well-defined higher order molecular assemblies, such as micelles and vesicles. The structure and properties of the assemblies are closely related to the architecture of the supra-amphiphiles. Therefore even two amphiphiles with a similar molecular structure and chemical components can have distinct physical properties if their topologies are different. Through precise control of the architecture of supra-amphiphiles, different self-assembly behaviors can be obtained. We can design amphiphiles with different topologies to produce self-assemblies with different purposes.

6.2.1 Small Molecular Supra-Amphiphiles Based on Coordination Bonds

6.2.1.1 Single-Tail Supra-Amphiphiles

Supra-amphiphiles with a single-tail topology can be obtained by capping a hydrophilic or hydrophobic group with a metal–ligand complex (Figure 6.2a). The metal–ligand complex can function as either a hydrophilic or a

hydrophobic moiety, thus forming amphiphilic supramolecules. Metal–ligand coordination complexes are generally slightly hydrophilic because they contain charges. Therefore they can be directly used as hydrophilic heads, which are attached with hydrophobic chains to construct a supra-amphiphile. Arunachalam and coworkers developed a series of amphiphilic cobalt(III) complexes of the type *cis*-$[Co(en)_2(A)X]^{2+}$, *cis*-$[Co(bpy)_2(A)X]^{2+}$ and *cis*-α-[Co(trien) $(A)X]^{2+}$ (A = dodecyl or cetylamine, X = Cl^-, Br^-, NO_2^-) *via* the ligand substitution method (Figure 6.2b).[3,4]

By choosing suitable metal ions and ligands, the metal coordination complex can also be neutral. In this way, the metal–ligand coordination complex behaves more hydrophobically. If such metal–ligand coordination complexes are connected with hydrophilic chains, coordination supra-amphiphiles can be readily obtained. De Cola and coworkers demonstrated a neutral metal–ligand coordination complex using platinum complexes bearing a N^C^N cyclometallated 1,3-di(2-pyridyl)-benzene. These metal–ligand coordination complexes were then attached with a variety of hydrophilic ethylene glycol chains to obtain a supra-amphiphile (Figure 6.2c).[5]

Single-tail coordination supra-amphiphiles show good solubility in common solvents. When dissolved in water, these amphiphiles tend to "hide" their hydrophobic moiety from the surrounding water molecules to self-assemble into micellar structures (Figure 6.2d). De Cola and coworkers demonstrated a supra-amphiphile based on neutral rhenium complexes and

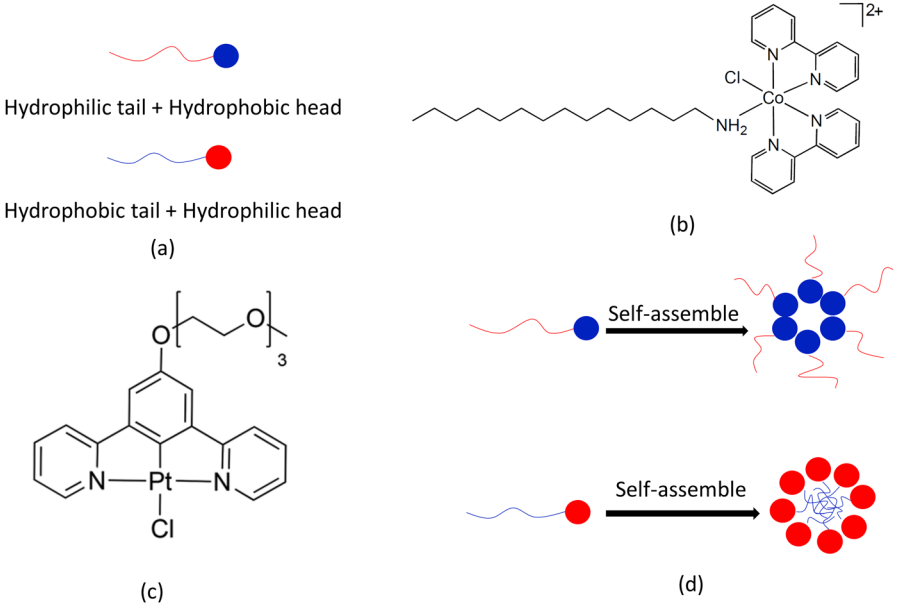

Figure 6.2 (a) Topology, (b,c) examples and (d) self-assembly of single-tail supra-amphiphiles based on coordination bonds. Reproduced from ref. 5 with permission from the Royal Society of Chemistry.

ethylene glycol chains. The aggregation properties were thoroughly investigated in dioxane–water mixtures, where all the complexes assembled in globular-like supramolecular architectures with a well-defined size (hydrodynamic diameter 200–400 nm).[6]

6.2.1.2 *Double-Tail Supra-Amphiphiles*

The double-tail topology of supra-amphiphiles can be realized in many different ways (Figure 6.3a). First, it can be formed by connecting a hydrophobic block and a hydrophilic block with a metal–ligand complex. In this way, the metal–ligand complex functions only as a linker. Alternatively, double-tail supra-amphiphiles can be obtained by connecting two hydrophilic blocks with a hydrophobic metal–ligand complex, or connecting two hydrophobic

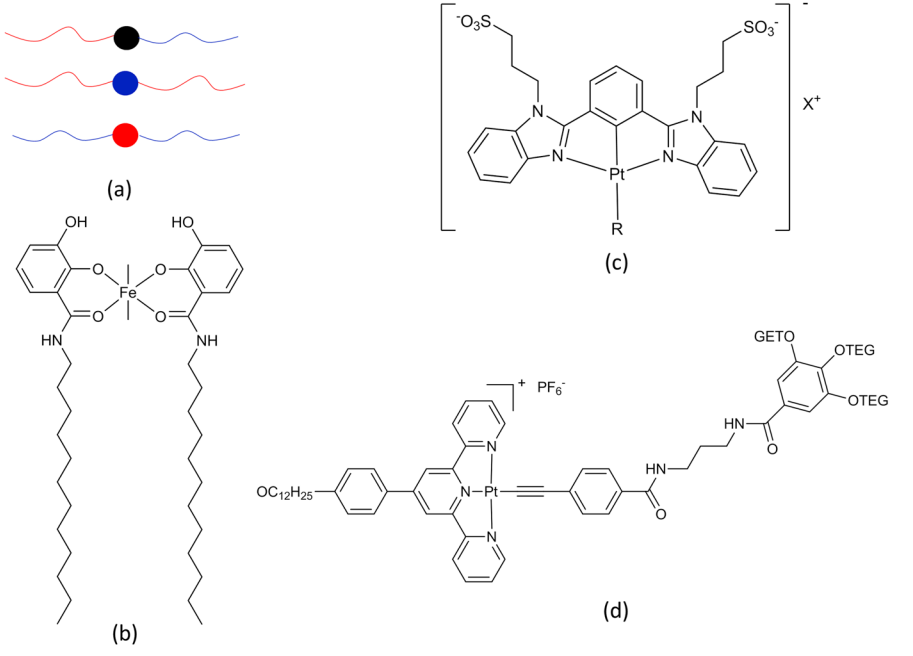

Figure 6.3 Topology (a) and examples (b–d) of multi-tail supra-amphiphiles based on coordination bonds. Image (b) reproduced from M. Apostol, P. Baret, G. Serratrice, J. Desbrières, J.-L. Putaux, M.-J. Stébé, D. Expert and J.-L. Pierre, Self-assembly of an amphiphilic iron(III) chelator: mimicking iron acquistion in marine bactiera, *Angew. Chem. Int. Ed.*, 2005, **44**, 2580. Copyright © 2005 Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim. Image (c) reproduced from C. Po, A. Y.-Y. Tam, K. M.-C. Wong and V. W.-W. Yam, Supramolecular self-assembly of amphiphilic anionic platinum(II) complexes: a correlation between spectroscopic and morphological properties, *J. Am. Chem. Soc.*, 2011, **133**, 12136. Copyright (2011) American Chemical Society. Image (d) reproduced from ref. 9 with permission from the Royal Society of Chemistry.

blocks with a hydrophilic metal–ligand complex. Such supra-amphiphiles show good amphiphilicity and can self-assemble into spherical structures. The self-assembly behavior will be dependent on the position of the hydrophilic/hydrophobic blocks in the supra-amphiphile.

By using catecholate ligands attached with fatty acid tails as the building block, Pierre and coworkers showed that a double-tail supra-amphiphile can be made on the addition of iron(III) ions due to the formation of an iron–catehcholate coordination complex (Figure 6.3b). This supra-amphiphile can self-assemble into vesicular structures in water.[7]

A double-tail topology can also be obtained by using metal–ligand coordination based on platinum ions. Yam and coworkers demonstrated a series of amphiphilic anionic platinum(II)bzimpy complexes containing a hydrophilic anionic sulfonate head and a hydrophobic Pt(bzimpy) complex. The hydrophilic moieties were connected through an alkynyl chain (Figure 6.3c). Such supra-amphiphiles showed aggregation behavior in water through Pt ⋯ Pt and π ⋯ π stacking interactions. An interesting aggregation–partial deaggregation–aggregation process and a morphological transformation from vesicles to nanofibers were observed on increasing the content of nonaqueous solvent. These changes can be systematically controlled by a variation in solvent composition and can be readily probed by UV–visible absorption and emission spectrometry, nuclear magnetic resonance spectrometry, transmission electron microscopy and even with the naked eye.[8] Wu and coworkers reported an amphiphilic cationic platinum(II) terpyridyl complex bearing a platinum(II) complex with a ferrocene unit as a hydrophobic moiety and three triethylene glycol (TEG) monomethyl ether chains as hydrophilic tails (Figure 6.3d). Such an amphiphile can self-assemble in water to form vesicular aggregates with diameters of about 100 nm and an average thickness of the wall of about 6–8 nm.[9]

6.2.1.3 Multi-Tail Supra-Amphiphiles

In addition to single- and double-tail topologies, supra-amphiphiles with multi-tail topologies can also be realized (Figure 6.4a). A tri-tail topology of supra-amphiphiles can be built by combining a three-coordinated metal ion with a monodentate ligand, a six-coordinated metal ion with a bidentate ligand or a nine-coordinated metal ion with a tridentate ligand (Figure 6.4b and c). Alternatively, if the ligand contains multiple hydrophilic/hydrophobic tails, multi-tail coordination supra-amphiphiles can be achieved in coordination complexes with a metal-to-ligand ratio of 1 : 1. Ghadiri *et al.* designed and synthesized a peptide terminated with a bipyridine group at one end, thus forming a tri-tail coordination supra-amphiphile when bound with six-coordinated metal ions. In the presence of metal ions such as Ni^{2+} or Ru^{2+}, the peptide self-assembled into a triple helical coiled shape. This triple-coil topology was further supported by computer modeling results.[10] Uozumi and coworkers reported an amphiphilic pincer palladium complex bearing hydrophobic side-chains to form a tetra-arm supra-amphiphile, which self-assembled in aqueous media to provide bilayer vesicles (Figure 6.5(a) and (b)).[11]

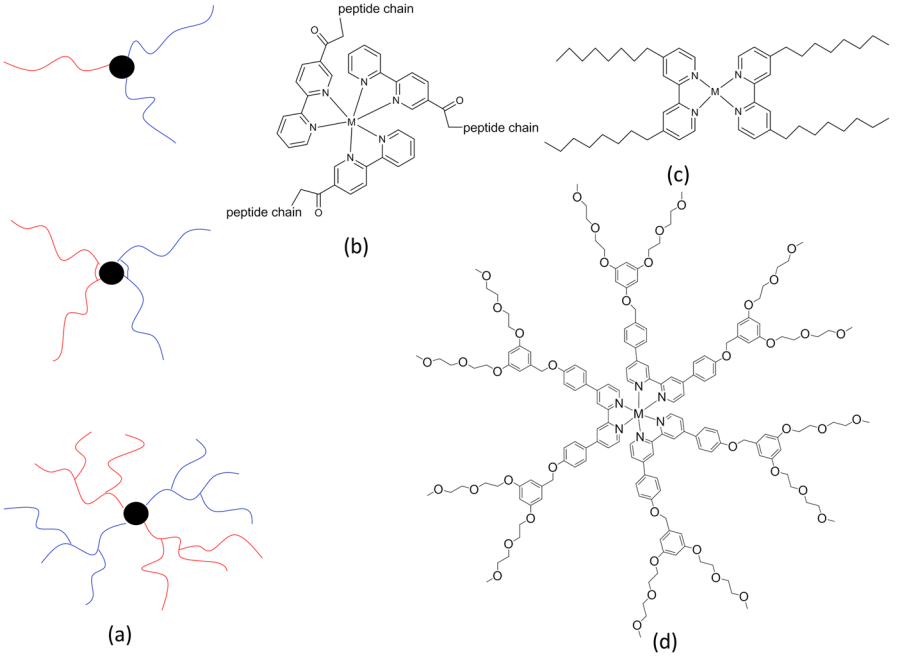

Figure 6.4 Topology (a) and proposed examples (b–d) of multi-tail supra-amphiphiles based on coordination bonds.

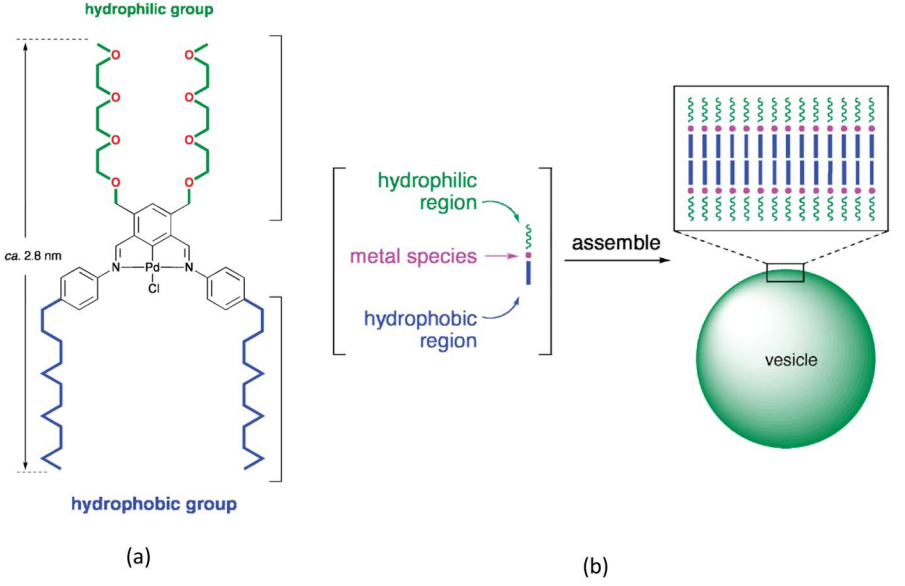

Figure 6.5 Chemical structure (a) and self-assembly (b) of tetra-arm amphiphilic pincer palladium complex. Reproduced from ref. 11 with permission from the Royal Society of Chemistry.

When ligands terminated with dendritic hydrophobic chains are chosen, a dendritic supra-amphiphile can be obtained (Figure 6.4d). As demonstrated by De Cola and coworkers, a dendritic topology supra-amphiphile was realized by the complexation of ruthenium ions with dendritically modified bathophenanthroline ligands, which were attached with ethylene glycol chains. The presence of hydrophilic oligo(ethylene glycol) groups on the surface of the monodispersed metal complexes enabled solubilization of all the fractal species in a wide range of solvents, including water. The encapsulation of the highly luminescent $[Ru(dpp)_3]^{2+}$-type (dpp = 4,7-diphenyl-1, 10-phenanthroline) core unit within a dendritic microenvironment created a powerful means of shielding the center from dioxygen quenching. This shielding effect, as exerted on the phosphorescent ruthenium-derived center, is reflected by enhanced emission intensities and extended excited state lifetimes close to the highest reported values, even in an air-equilibrated aqueous medium.[12]

6.2.1.4 Bola-Form Supra-Amphiphiles

A bola-amphiphile is a surfactant molecule that contains two hydrophilic heads on one hydrophobic chain (Figure 6.6(a)). The bola-form topology can provide the amphiphile with a much higher thermal stability than conventional surfactants. Using metal–ligand coordination, we can construct a supra-amphiphile with a bola-form structure. Figure 6.6(b) and (c) show that the incorporation of bipyridine groups in the hydrophobic alkyl chain allows the amphiphile to bind with a copper ion to give a bola-form supra-amphiphile. The bipyrimidine

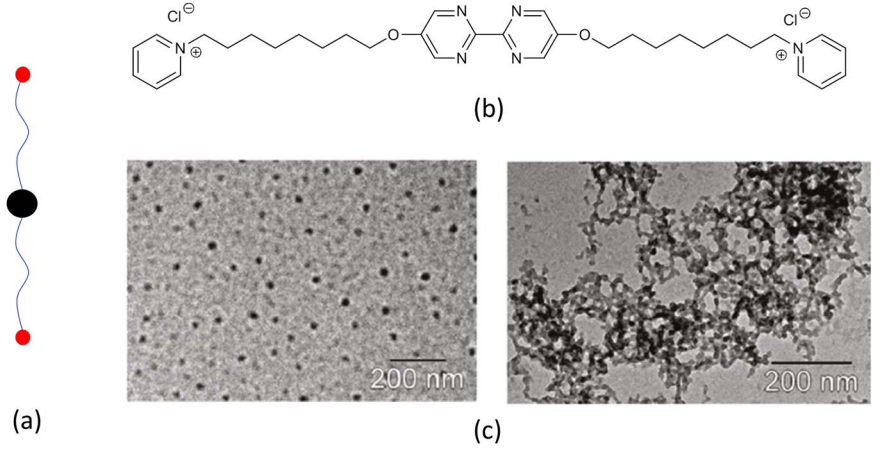

Figure 6.6 (a) Topology, (b) examples and (c) self-assembled nanostructure of bola-form supraamphiphile based on Cu^{II}-bipyrimidine coordination complex. Panel (b) is reproduced with permission from B. Song, G. Wu, Z. Wang, X. Zhang, M. Smet and W. Dehaen, Metal–ligand coordination-induced self-assembly of bolaamphophiles bearing bipyrimidine, *Langmuir*, 2009, **25**, 13306. Copyright (2009) American Chemical Society.

moiety allows metal–ligand coordination, thereby influencing the self-assembly of the bola-amphiphile. Before coordination, bpym-8 self-assembles in water to form spherical aggregates. An interesting finding is that the coordination of the Cu^{II} ion with bipyrimidine can induce the assembly of bpym-8 to change from spheres to clustered aggregates. The assembly of bpym-8 can be reversibly converted back by removing the Cu^{II} ion from the coordination. This study presents a new type of bola-amphiphile that is able to coordinate with metal ions, which may provide a new clue to fabricating reversibly tunable supramolecular nanomaterials.[13]

6.2.1.5 Gemini-Form Supra-Amphiphiles

A gemini-form coordination supra-amphiphile has, in sequence, a long hydrophobic chain, an ionic group, a coordination complex as the linker, a second ionic group and another hydrophobic chain (Figure 6.7(a)). Compared with conventional supra-amphiphiles, the gemini topology provides the supra-amphiphile with better surface-active properties. Again, we can use metal–ligand coordination to realize this topology. Nolte and coworkers synthesized a supra-amphiphile terminated with an imidazole group and used it as the building block. On the addition of copper ions, each copper binds with two imidazole groups (Figure 6.7(b)). In this way, a gemini-type supra-amphiphile can be obtained by adding the imidazole surfactant and copper ions at a molar ratio of 2 : 1. This coordination may force the imidazole groups to become more parallel to the bilayer plane, increasing the effective headgroup area and favoring a vesicle morphology over the original planar lipid bilayer.[14]

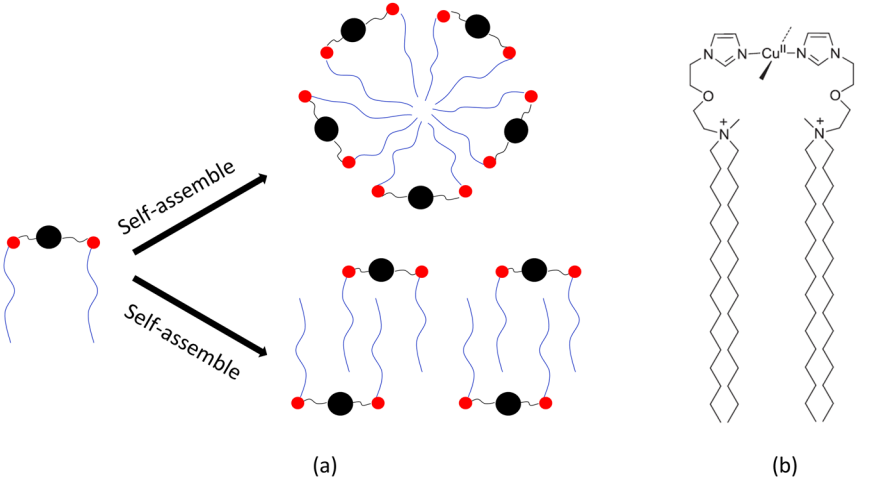

Figure 6.7 (a) Topology and self-assembly, and (b) example of gemini-form supra-amphiphile based on coordination bonds. Panel (b) is reproduced from ref. 14 with permission from the Royal Society of Chemistry.

6.2.2 Polymer-Type Supra-Amphiphiles Based on Coordination Bonds

Metal–ligand coordination bonds can also be utilized to make polymer-type supra-amphiphiles. Three types of polymeric supra-amphiphiles can be obtained. Linear polymeric supra-amphiphiles are formed when hydrophilic/hydrophobic polymers are connected by a coordination complex. In some cases, when metal ions with high coordination numbers are combined with low-dentate polymer ligands, multi-tail or star-type polymeric supra-amphiphiles can be obtained. If linear hydrophilic/hydrophobic polymers are functionalized with pendent ligands and then coordinated to metal ions, brush-type supra-amphiphiles can be readily formed.

6.2.2.1 Linear-Type Polymer Supra-Amphiphiles

Linear-type polymer supra-amphiphiles can be formed by connecting a hydrophobic block and a hydrophilic block with a metal–ligand complex. Alternatively, they can be obtained by connecting two hydrophilic blocks with a hydrophobic metal–ligand complex, or connecting two hydrophobic blocks with a hydrophilic metal–ligand complex (Figure 6.8a).

Early examples of linear-type polymer supra-amphiphiles were reported by Schubert and coworkers. They demonstrated a series of coordination supra-amphiphiles by connecting hydrophilic and hydrophobic blocks with

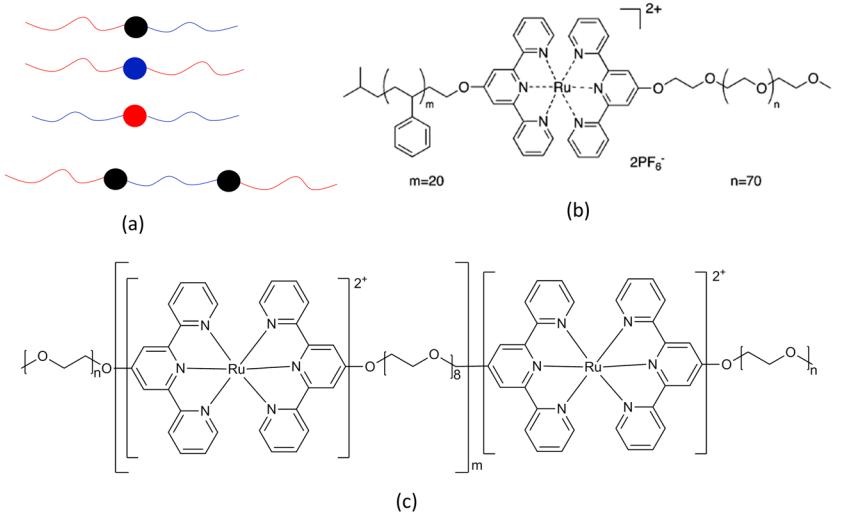

Figure 6.8 (a) Topology and (b–c) examples of linear-type polymer supra-amphiphiles. Panels (b) and (c) are reproduced with permission from M. A. R. Meier, D. Wouters, C. Ott, P. Guillet, C.-A. Fustin, J.-F. Gohy and U. S. Schubert, Supramolecular ABA triblock copolymers *via* a polycondensation approach: synthesis, characterization, and micelle formation, *Macromolecules*, 2006, **39**, 1569. Coyright (2006) American Chemical Society.

coordination complexes. The ligand they used was 2,2′:6′,2″-terpyridine. The most studied system, poly(styrene)-[Ru]-poly(ethylene oxide) (PS_{20}-[Ru]-PEO_{70}) was prepared from the macro-ligands of poly(ethylene oxide) (PEO) and polystyrene (PS), both of which have a terpyridine terminal unit (Figure 6.8b). When water was added to an initial dimethylformamide solution of the PS_{20}-[Ru]-PEO_{70} supra-amphiphiles, well-defined micelles were observed. In such micelles, the core and shell are connected only by ligand–metal interactions rather than by chemical bonds.[15–17] They also studied an A–b–B–b–A-type supramolecular triblock copolymer, where two hydrophilic terpyridine end-functionalized poly(ethylene oxide) polymers were connected by a hydrophobic α-terpyridine-ω-methyl-poly(ethylene glycol) polymer (Figure 6.8c). The resulting triblock copolymer was able to form micelles in water, as investigated by dynamic light scattering, atomic force microscopy and transmission electron microscopy.[18]

Another linear polymer supra-amphiphile system was developed by Moughton and O'Reilly.[19] In this system, the hydrophobic PS block and hydrophilic poly(acrylic acid) (PAA) block had a relatively weak coordinating pyridine ligand and a strong S^C^S (S^C^S = 1,3-benzenedicarbothioamide) pincer ligand connected to the Pd^{II} metal center, respectively. As expected, this PS-[Pd}-PAA, where [and } refer to different ligands, formed well-defined micelles in water with a PS core and a PAA shell. Following crosslinking of the PAA shell, selective cleavage of the pyridine–Pd complex of the PS blocks was easily realized by simply adjusting the acidity of the medium to pH 5. Under this acidic condition, the pyridine ligand was protonated and lost its ability to form a complex with Pd^{II}. The released hydrophobic PS was removed by dialysis against THF–water. Thus metal functionalized nanocages of crosslinked PAA were obtained (Figure 6.9). Compared with the block copolymers with the terpyridine–Ru linkage, this block copolymer with asymmetrical ligand–metal bonds shows a great advantage in its readiness to realize the selective cleavage of the complexes.[19]

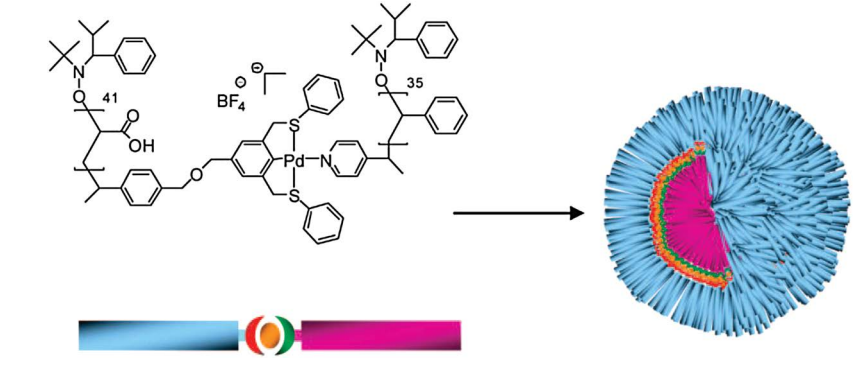

Figure 6.9 Chemical structure and self-assembly of PAA-[Pd}-PS. Reproduced with permission from A. O. Moughton and R. K. O'Reilly, Noncovalently connected micelles, nanoparticles, and metal-functionalized nanocages using supramolecular self-assembly, *J. Am. Chem. Soc.*, 2008, **130**, 8714. Copyright (2008) American Chemical Society.

6.2.2.2 Star-Type Polymer Supra-Amphiphiles

Star-type supra-amphiphiles can also be obtained using metal–ligand coordination. Harruna and coworkers demonstrated a star-shaped tri-tail coordination supra-amphiphile by linking one hydrophobic PS chain with 55 repeating units and two hydrophilic poly(*N*-isopropylacrylamide) chains with 108 or 63 repeating units to one Fe^{3+} ion using and iron–bipyridine complex. This star-shaped supra-amphiphile self-assembled in water to form micelle structures, as evidenced by transmission electron microscopy. The dynamic light scattering results showed that the apparent hydrodynamic diameter of the PS_{55}bpy-Ru-$(bpyPNIPAM_{63})_2$ micelle is about 107 nm, whereas that of PS_{55}bpy-Ru-$(bpyPNIPAM_{108})_2$ is 237 nm (Figure 6.10).[20]

Another example was reported by Schubert and coworkers, who synthesized rod–coil tri- and tetra-arm star metallo-supramolecular block copolymers through bis-complex formation between an ω-terpyridine ruthenium(II) monocomplex poly(ethylene glycol) (PEG) and either a tris-terpyridine or a tetra-terpyridine functionalized conjugated rigid core. The tri-arm star supra-amphiphiles did not self-assemble following the common bilayer structure found in vesicular walls because of steric constraints resulting from their peculiar shape. The vesicular wall was formed by rigid cores and both its inner and outer surfaces were decorated with the PEG blocks. Such vesicles were found to be stable after the addition of 5 wt% water and kept the same structure as in pure acetone. The formation of vesicles was attributed to the stacking of the tri-arm cores.[21]

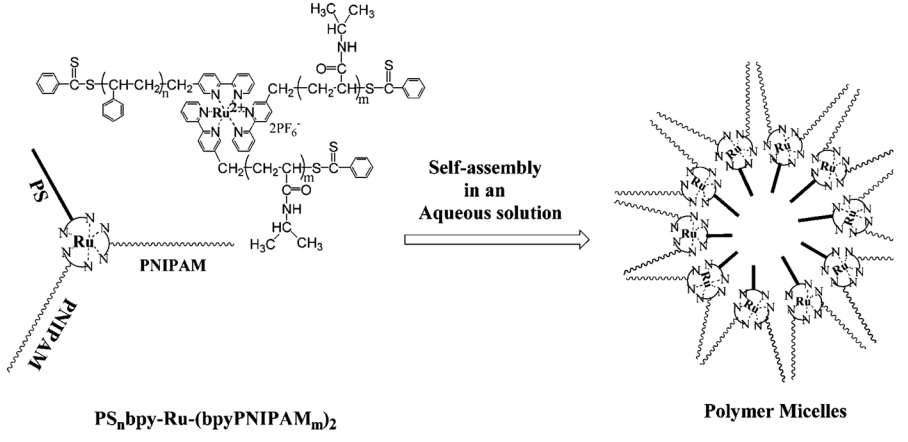

Figure 6.10 Structure and self-assembly of tri-tail coordination supra-amphiphile PS_nbpy-Ru-$(bpyPNIPAM_m)_2$. Reproduced with permission from U. Hahn, H. Luelf, H. D. F. Winkler, C. A. Schalley, F. Vögtle and L. De Cola, Encapsulation of luminescent homoleptic $[Ru(dpp)_3]^{2+}$- type chromophores within an amphiphilic dendritic environment, *Chem. Eur. J.*, 2012, **18**, 15424. Copyright © 2012 Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim.

6.2.2.3 *Brush-Type Supra-Amphiphiles*

Brush-type topology can be realized by incorporating hydrophilic and/or hydrophobic pendent groups on a polymeric main chain through the formation of coordination complexes. Manners and coworkers reported an amphiphilic linear brush block copolymer based on poly(ferrocenyldimethylsilane)-*b*-poly(allylglycidyl ether) (PFS-*b*-PAGE) decorated with TEG, abbreviated as PFS-*b*-(PEO-*g*-TEG) (Figure 6.11). Cylindrical micelles of controlled length with low polydispersities were obtained in *N*,*N*-dimethylformamide using small seed initiators *via* living crystallization-driven self-assembly. Successful dispersion of these micelles into aqueous media was achieved by dialysis against deionized water. B–A–B amphiphilic triblock co-micelles with PFS-*b*-poly(2-vinylpyridine) (P2VP) as the hydrophobic B blocks and hydrophilic PFS-*b*-(PEO-*g*-TEG) A segments were prepared and their hierarchical self-assembly in aqueous media studied. It was found that the superstructures formed were dependent on the length of the hydrophobic blocks. Quaternization of P2VP was shown to cause the disassembly of the superstructures, resulting in the first examples of water-soluble cylindrical multi-block co-micelles. They also demonstrated the ability of the triblock co-micelles with quaternized terminal segments to complex DNA and therefore to potentially function as gene vectors.[22]

Brush-type supra-amphiphiles can also be obtained by the combination of metal–ligand coordination and other noncovalent interactions. For example,

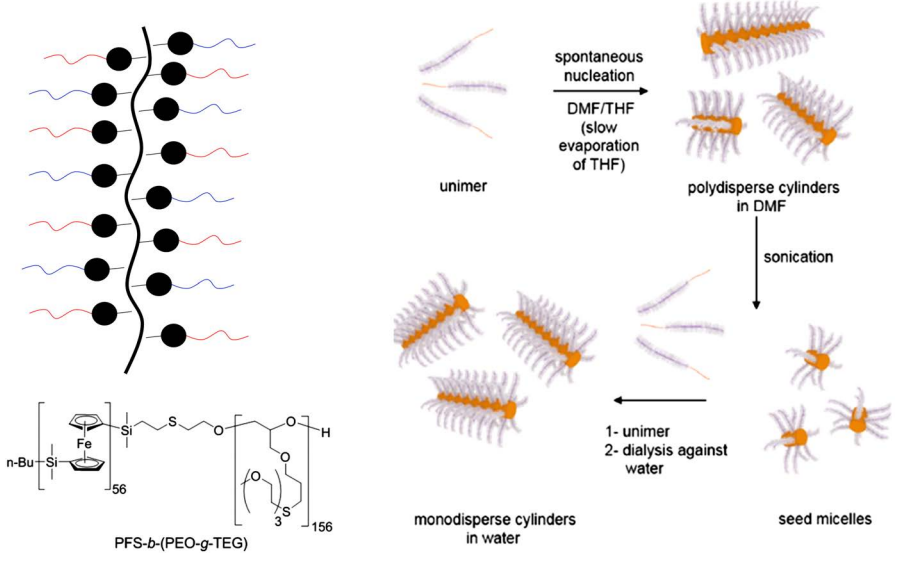

Figure 6.11 Topology and self-assembly of brush-type coordination supra-amphiphile. Reproduced with permission from J.-F. Gohy, B. G. G. Lohmeijer and U. S. Schubert, From supramolecular block copolymers to advanced nano-objects, *Chem. Eur. J.*, 2003, **9**, 3472. Copyright © 2003 Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim.

Gohy and coworkers described an amphiphilic brush consisting of a polystyrene block linked to a PEO block *via* a charged bis-terpyridine ruthenium(II) complex (PS-[Ru]-PEO). The initial hexafluorophosphate counter ions associated with the complex were exchanged for poly(styrenesulfonate) (PSS) anions. In dimethylformamide, flexible amphiphilic brushes were observed in which PS-[Ru]-PEO chains decorated the PSS main chain. These systems have been further transferred into pure water, resulting in the collapse of the PS chains into hydrophobic cores. Spherical or worm-like micelles have been observed in water, depending on the length of the PSS chain.[23]

A brush-type supra-amphiphile based on metal–ligand coordination using a hierarchical strategy was demonstrated by Kurth and coworkers. First, they synthesized a supramolecular polymer electrolyte based on the complexation between Fe^{3+} ions and a terpyridyl ligand. As a second step, they added sodium di-hexyl(2-ethyl)phosphate, which is a surfactant containing two hydrophobic chains and one negative charge. The surfactant bonded to the polyelectrolyte to form a brush-type supra-amphiphile driven by electrostatic attraction. The resulting supra-amphiphile was soluble in common organic solvents, formed Langmuir monolayers at the air–water interface and was readily transferred onto solid substrates.[24,25]

6.3 Functional Supra-Amphiphiles Based on Coordination Bonds

Supra-amphiphiles can have many functions due to the presence of metal ions. By careful selection of the combination of ligand and metal ion, it is possible to tune the reversibility and dynamic properties of the bond. Such systems can be used to make stimuli-responsive supra-amphiphiles. For example, bola-type supra-amphiphiles can reversibly self-assemble into different structures on the addition and removal of copper ions. The occurrence of semi-occupied d-orbitals gives rise to some of the most prominent properties, including strong absorption, highly efficient emission and tunable redox states. The splitting of the d-orbitals in a ligand field of appropriate symmetry and strength can give rise to thermally or photo-induced spin transition and spin crossover phenomena. The metal ions in the coordination supra-amphiphile can function as catalytic centers, which may lead to an unexpected catalytic performance.

6.3.1 Stimuli-Responsive Properties

Metal–ligand coordination is sensitive to the external environment, which provides an effective approach to making stimuli-responsive supra-amphiphiles. Manipulation of the metal–ligand interactions has resulted in stimuli-responsive metallo-supramolecular polymers and metallo-supramolecular gels, which can be utilized in different applications. The stimuli-responsive properties can be chemically responsive, thermally responsive, light-responsive, redox-responsive or multi-stimuli-responsive.

Chemically responsive coordination supra-amphiphiles undergo reversible transformations in their chemical, physical or mechanical properties on the addition of a chemical species. Schubert and coworkers studied the chemically responsive properties of an amphiphilic poly(ethylene-*co*-butylene)-[Ru]-PEO diblock copolymer. Although bis-2,2′:6′,2″-terpyridine-ruthenium(II) complexes have proved to be extremely stable in various environments, they showed that the addition of a large excess of a competing ligand (hydroxyethyl ethylenediaminetriaceticacid, trisodic salt, HEEDTA) allowed cleavage of the initial bis-2,2′:6′,2″-terpyridine-ruthenium(II) complex. Therefore the addition of a large excess of HEEDTA followed by dialysis can remove the detached coronal PEO polymer chains, yielding spherical, nanosized particles surface coated with vacant terpyridine ligands. The availability for monocomplexation with other suitable transition metal ions was demonstrated by complexing with iron(II), giving a characteristic violet-colored solution.[16] They also prepared core–shell corona micelles consisting of a PS core, a P2VP shell and a PEO corona. This kind of micelle has the capability to respond to pH *via* protonation/deprotonation of the P2VP shell. The pH responsiveness of these micelles can be used advantageously for the encapsulation and controllable release of active species reversibly trapped in the P2VP shell. The P2VP shell can serve as a nanoreactor for the production of metal nanocapsules (Figure 6.12(a) and Figure 6.12(b)).[26]

Some coordination bonds are relatively weak in strength. Therefore thermal energy from irradiation with UV or visible light is strong enough to dissociate the coordinative links between the metal ions and the hydrophilic/hydrophobic groups, leading to dissociation of the supra-amphiphiles. Removal of the radiation can lead to the re-formation of the coordination supra-amphiphile. Thus light-responsive coordination supra-amphiphiles are expected. Lu and coworkers synthesized an amphiphilic block copolymer, polystyrene-*block*-poly(2-hydroxy-5-vinylbenzaldehyde) (PS-*b*-PHVB), by the reversible addition–fragmentation chain transfer polymerization of HVB using a trithiocarbonate-terminated polystyrene macro-chain transfer agent. Subsequent grafting of monoamine-terminated PEG (PEG–NH_2) and 2-(2-aminoethoxy) ethanol (AME) onto the HVB blocks of PS-*b*-PHVB *via* aldehyde–amine condensation yielded an amphiphilic block copolymer PS-*b*-(PHVB-*g*-PEG-and-AME) bearing a pendant salicylidene Schiff base. PS-*b*-(PHVB-*g*-PEG-and-AME) in ethanol self-assembled into micelles with salicylidene Schiff base groups at the core–shell interface. The addition of Zn^{2+} ions to the resulting micellar solution not only endowed the micelles with fluorescent features, but also stabilized the luminescent micelles through ionic crosslinking because of the formation of salicylaldimine–Zn^{2+} complexation. The obtained fluorescent crosslinked micelles were "light-controllable" in terms of their fluorescence emission and crosslinking structure due to the reversibility of the salicylaldimine–Zn^{2+} coordinative bond in response to light stimuli. The reversible decrease and recovery of fluorescence could be achieved periodically by switching the 254 nm UV irradiation on and off (Figure 6.13).[27]

Some metal ions have multiple valence states and can therefore undergo multiple stages of reversible transition on the addition of redox reagents.

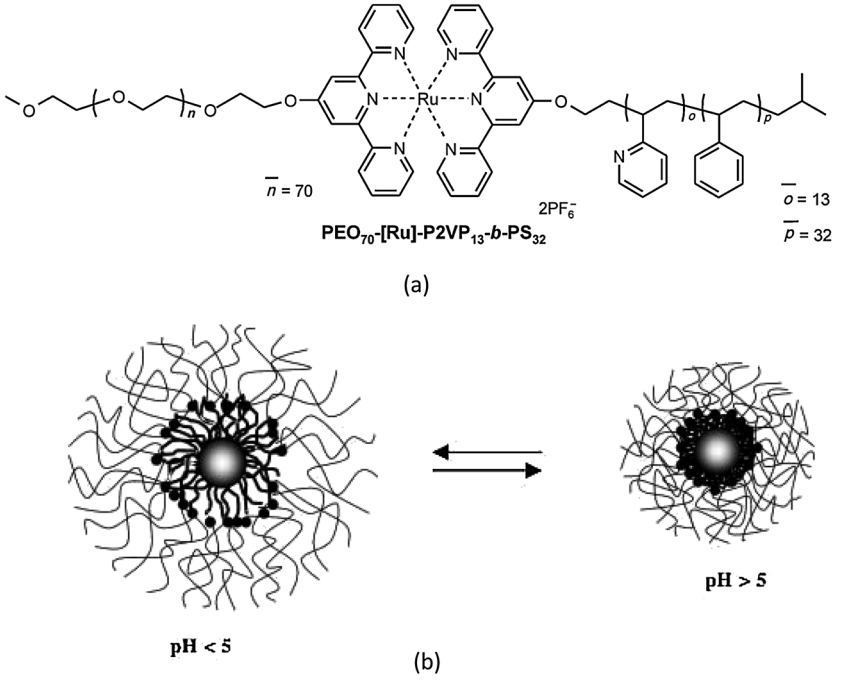

Figure 6.12 (a) Structure and (b) pH-induced reversible transformation of self-assembled amphiphilic PEO_{70}-[Ru]-$P2VP_{13}$-*b*-PS_{32}. Reproduced with permission from J.-F. Gohy, B. G. G. Lohmeijer and U. S. Schubert, from supramolecular block copolymers to advanced nano-objects, *Chem. Eur. J.*, 2003, **9**, 3472. Copyright © 2003 Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim.

Zhang and coworkers reported a redox-responsive ferrocene-containing amphiphilic block copolymer PEG-*b*-PMAEFc, which was synthesized by atom transfer radical polymerization (ATRP) of 2-(methacryloyloxy) ethyl ferrocene-carboxylate (MAEFc) using a PEG-based macro-ATRP agent. In aqueous solution, these block-type PEG-*b*-PMAEFc amphiphiles self-assembled into various interesting nanostructures, which disassembled with external redox stimuli, such as H_2O_2 (Figure 6.14). Such a redox-responsive polymeric system can be utilized for the controlled release of a hydrophilic payload such as Rhodamine B on oxidation with H_2O_2. This feature could be important in the controlled release of drugs because, in some specific cases, tumor cells are slightly more oxidative than normal cells.[28]

Some supra-amphiphiles based on metal–ligand coordination can also show multi-stimuli-responsive properties. Ge and Liu fabricated crosslinked micelles from amphiphilic poly(2-(2-methoxyethoxy)ethylmethacrylate)-*b*-poly(2-(diethylamino)ethyl methacrylate-*co*-4′-(6-methacryloxyhexyloxy)-2,2′:6′,2″-terpyridine) [$PMEO_2MA$-*b*-(PDEA-co-TPHMA)] *via* the formation of bis(terpyridine) ruthenium(II) complexes. In aqueous solution, these supra-amphiphiles showed multi-stimuli responsiveness due to the presence of pH-responsive PDEA cores, thermo-responsive $PMEO_2MA$

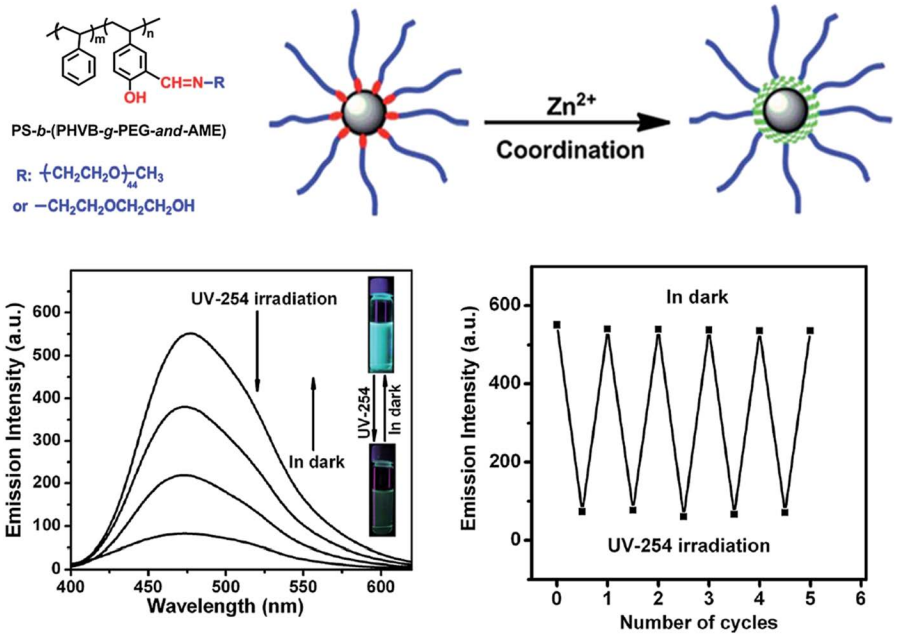

Figure 6.13 Light-responsive coordination supra-amphiphiles of PS-*b*-(PHVB-*g*-PEG-and-AME) coordinated with Zn^{2+}. Reproduced from ref. 27 with permission from the Royal Society of Chemistry.

shells and dissociable bis(2,2′:6′,2″-terpyridine)ruthenium(II) complex crosslinkers.[29] The amphiphilic platinum(II) complex reported by Wu and coworkers can self-assemble in water to form vesicular aggregates that can be disrupted either by an oxidant [$Fe(ClO_4)_3$] or a host molecule (cucurbituril) as a result of the redox properties of the ferrocene group. The well-defined architectures can be reversibly switched by *in situ* electrochemistry (Figure 6.15).[9]

6.3.2 Magnetic Properties

Spin crossover, sometimes referred to as spin transition or spin equilibrium behavior, is a phenomenon that occurs in some metal complexes when the spin state of the complex changes due to external stimuli, such as a variation in temperature, pressure, light irradiation or magnetic field. The presence of two different stable electronic or magnetic states plays a key part in the development of storage media for signal processing and transduction. The conversion between a low-spin and a high-spin state is typically observed in transition metal ion compounds with a $3d^n$ ($4 \leq n \leq 7$) electronic configuration, the most extensively studied element being the Fe^{II} ion. In a ligand field of octahedral symmetry, the d-orbitals split into low-lying t_{2g} and high-lying e_g subsets. In the case of the Fe^{II} ion, the low-spin state arises from a closed shell t_{2g}^6 electronic configuration and the high-spin state from a $t_{2g}^4 e_g^2$

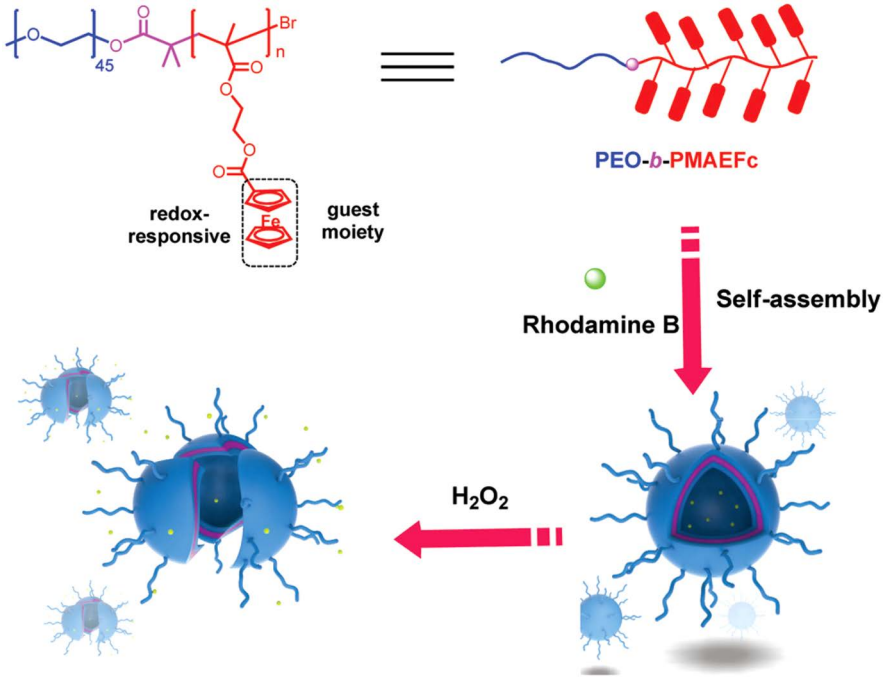

Figure 6.14 Structure and redox-responsive self-assembly of ferrocene-containing block copolymers PEG-*b*-PMAEFc. Reproduced from ref. 28 with permission from the Royal Society of Chemistry.

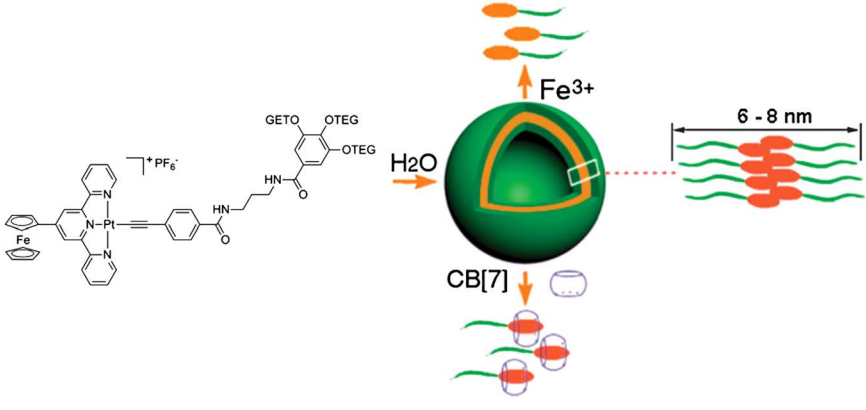

Figure 6.15 Multi-stimuli-responsive supra-amphiphiles based on platinum(II) terpyridyl complex with ferrocene units. Reproduced from ref. 9 with permission from the Royal Society of Chemistry.

electronic configuration. The spin crossover is generally accompanied by a change in the optical and magnetic properties, as well as a lengthening of the metal ion–ligand bond due to the occupation of the anti-bonding e_g subset.

Amphiphilic groups have multiple effects on the properties of spin crossover metal complexes. First, spin crossover materials based on coordination supra-amphiphiles generally have good solubility in common solvents, which make it possible to fabricate devices through solution casting methods or the Langmuir–Blodgett (LB) technique. Mingotaud and coworkers demonstrated an amphiphilic iron(II) complex $[Fe^{II}L_2(NCS)_2$, where L was a substituted bipyridine, which formed a perfectly stable LB film when formamide–water mixtures were used as a subphase. After transfer onto a solid substrate, a well-defined LB film was obtained. The LB film exhibited a thermal spin crossover phenomenon around room temperature.[30] Second, the amphiphilic group induced significant changes in the spin crossover behavior. Morgan and coworkers showed that the spin crossover profile was responsive to chain length in $[Fe(sal)_2trien]^+$ complexes functionalized with an alkyl chain. Partial crossover was observed with C6 alkylation and full transition was observed on lengthening to C12. No crossover was observed when the backbone was unfunctionalized.[31]

The most important effect of supra-amphiphiles on the properties of spin crossover metal complexes is the intriguing amphiphilic phase transition induced spin crossover. Kurth and coworkers proposed that a phase transition in an amphiphilic mesophase can induce sufficient (mechanical) strain to distort the coordination sphere of the tightly coupled Fe^{II} centers in metallo-supramolecular polyelectrolytes. They fabricated LB multilayers of polyelectrolyte–amphiphile complexes through the self-assembly of 1,4-bis(2,2′:6′,2″-terpyridine-4′-yl)benzene, Fe^{2+} ions and dihexadecyl phosphate with a metal ion to dihexadecyl phosphate stoichiometry of 1:6. LB transfers result in a polyelectrolyte–amphiphile complex architecture in which the amphiphilic molecules are arranged in double layers with opposing alkyl chains. The interstitial space is occupied by the rigid rod-like metallo-supramolecular polyelectrolyte, which is formed through coordinative interaction between the terpyridine ligands and the Fe^{2+} ions. Melting of the amphiphiles induces a reversible, but partial, spin crossover slightly above room temperature caused by a distortion of the coordination geometry around the central Fe^{2+} ions. The distortion is strong enough to reduce the strength of the ligand field, giving rise to spin transition from a low- to a high-spin state (Figure 6.16).[24,25]

6.3.3 Luminescent Properties

Luminescent materials have attracted much attention because they can be utilized for a variety of applications such as optical sensors and light-emitting diodes. The emission behavior provides a probe for the investigation of photoreactions, such as artificial photosynthesis. The photoluminescence of metal complexes is particularly interesting due to their diversified excited

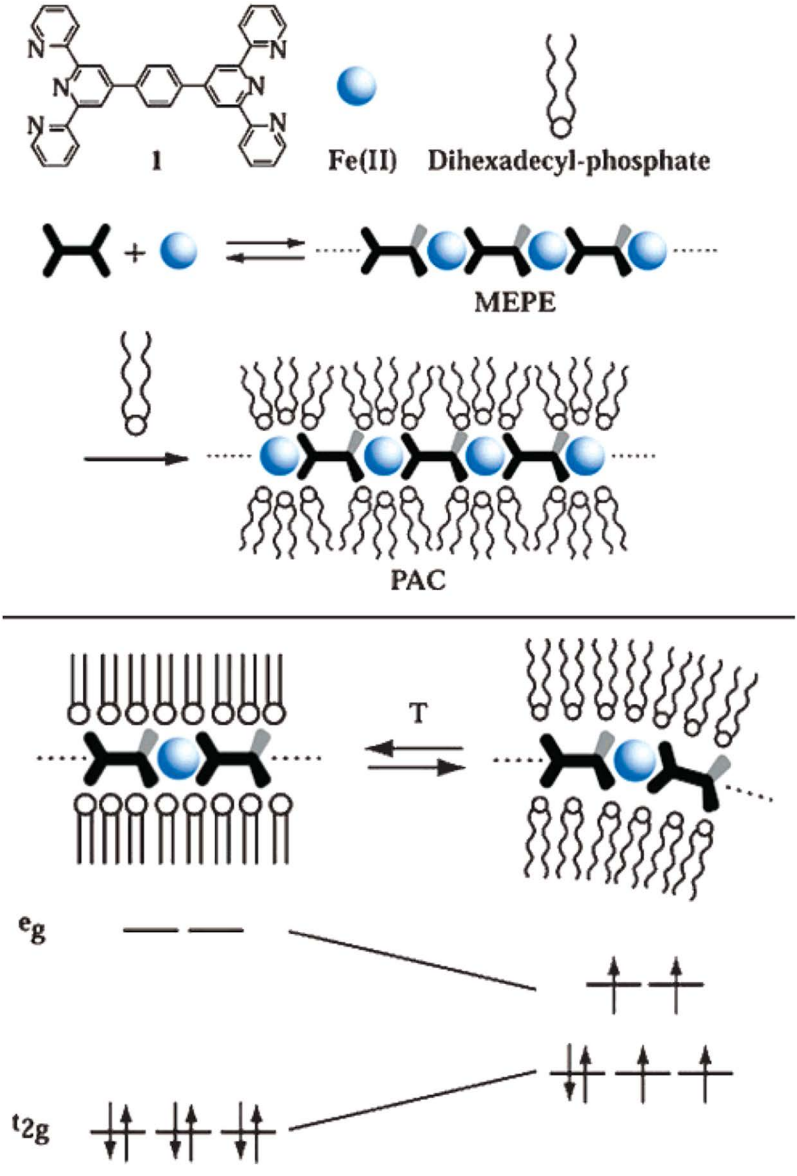

Figure 6.16 Self-assembly and amphiphilic phase transition induced spin crossover in metallo-supramolecular polyelectrolyte. Reproduced with permission from Y. Bodenthin, U. Pietsch, H. Möhwald and D. G. Kurth, Inducing spin crossover in metallo-supramolecular polyelectrolytes through an amphiphilic phase transition, *J. Am. Chem. Soc.*, 2005, **127**, 3110. Copyright (2005) American Chemical Society.

states, including metal-centered, ligand-to-metal charge transfer, metal-to-ligand charge transfer, ligand-to-ligand charge transfer, metal-to-metal charge transfer, and ligand-centered (or intra-ligand) and intra-ligand charge transfer excited states. Recent research efforts aim to develop luminescent metal complexes with high emission quantum yields, long emission lifetimes and good stability.

Supra-amphiphiles based on coordination bonds have significant advantages in these fields of research. First, the hydrophilic or hydrophilic group in the coordination supra-amphiphiles can encapsulate the luminescent metal complex inside as a functional core, which stabilizes the luminescent center from quenching. Hahn *et al.* synthesized a series of monodispersed homoleptic metallo-dendrimers through ruthenium complexation by dendritically modified bathophenanthroline ligands. The luminescent $[Ru(dpp)_3]^{2+}$-type chromophore was thus encapsulated within an amphiphilic core–shell environment created by a lipophilic interior and a hydrophilic oligo(ethylene glycol) outer layer. As a result of the presence of hydrophilic surface moieties, elongated excited state lifetimes and improved emission quantum yields were obtained compared with the bare $[Ru(dpp)_3]^{2+}$ core. This supra-amphiphile structure also showed efficient protection of the central ruthenium-derived chromophore against dioxygen quenching, as deduced from the luminescence lifetimes of several microseconds in aerated solutions, even at room temperature (Figure 6.17(a) and (b)).[12]

The presence of a hydrophilic or hydrophilic group in coordination supra-amphiphiles can effectively avoid aggregate formation. It is known

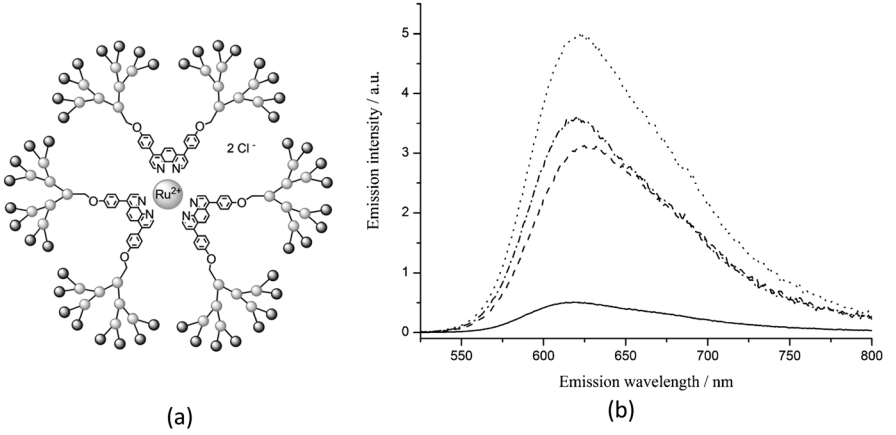

Figure 6.17 Chemical structures of $[Ru(dpp)_3]^{2+}$-derived metallo-dendrimers and their emission spectra. Reproduced with permission from U. Hahn, H. Luelf, H. D. F. Winkler, C. A. Schalley, F. Vögtle and L. De Cola, Encapsulation of luminescent homoleptic $[Ru(dpp)_3]^{2+}$-type chromophores within an amphiphilic dendritic environment, *Chem. Eur. J.*, 2012, **18**, 15424. Copyright © 2012 Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim.

that aggregate formation will result in intermolecular energy transfer or non-radiative decay pathways, thus reducing the electron injection efficiency and/or emission quantum yields. By designing supra-amphiphile structures with metal–ligand complexes linked by alkyl chains, the coordination cores can always remain at a sufficient distance from each other, avoiding the aggregation-induced quenching effect. This is particularly unfavorable for photosensitizers in photo-to-electric conversion devices such as dye-sensitized solar cells, as aggregate formation results in a decreased performance of dye-sensitized solar cells by increasing both the short-circuit photocurrent density (J_{sc}) and the open-circuit voltage (V_{oc}). Han and coworkers reported a series of amphiphilic ruthenium(II) terpyridine sensitizers with long alkyl chain substituted β-diketonato ligands. As a result of decreased aggregate formation because of the supra-amphiphile structure, these dyes showed an enhanced photovoltaic performance.[32]

Another advantage of luminescent coordination supra-amphiphiles is their facilitation of the formation of uniform films. The development of optical devices always requires luminescent compounds to be processed into solid films. The amphiphilic properties of coordination supra-amphiphiles allow the formation of thin luminescent films by the LB technique. This approach can be easily applied to photoluminescent films, organic light-emitting diodes, waveguides and other devices that require highly ordered molecular packing. Neri and coworkers reported an amphiphilic 3-hexadecylpentane-2,4-dione ligand and its rare earth element metal complexes. The obtained rare earth element metal complexes were satisfactorily miscible in hexane. As a result of its amphiphilic properties, the ligand was able to introduce metallic cations into non-polar ambients, which enabled the use of these complexes to form ordered thin films ranging from one molecule thick up to several nanometers (many layers) using the LB technique.[33]

6.3.4 Electrochemical Properties

The metal ions in coordination supra-amphiphiles typically have multiple valence states. Therefore coordination supra-amphiphiles containing variable valence metal ions can exhibit interesting redox properties. Verani and coworkers synthesized a series of amphiphilic salycilaldimine-copper(II) soft materials (**1**, **3**, **3′** and **4** in Figure 6.18), which consisted of hydrophilic copper-containing headgroups and hydrophobic alkyl oralkoxo tails. The amphiphilic properties depended on the ratios between the hydrophobic and hydrophilic groups. They demonstrated that there is a balance between amphiphilicity and the redox response in these complexes. In complex **3**, an apparent redox reversibility was obfuscated by a complete lack of amphiphilic behavior. The inclusion of three alkoxy groups per ligand in **4** improved the amphiphilic properties. The redox response was seriously compromised by an increased separation between the cathodic and anodic peaks in the first phenolate/phenoxyl process. Increased flexibility of the core in **3′** resulted in an improved amphiphilicity and excellent redox reversibility.[34]

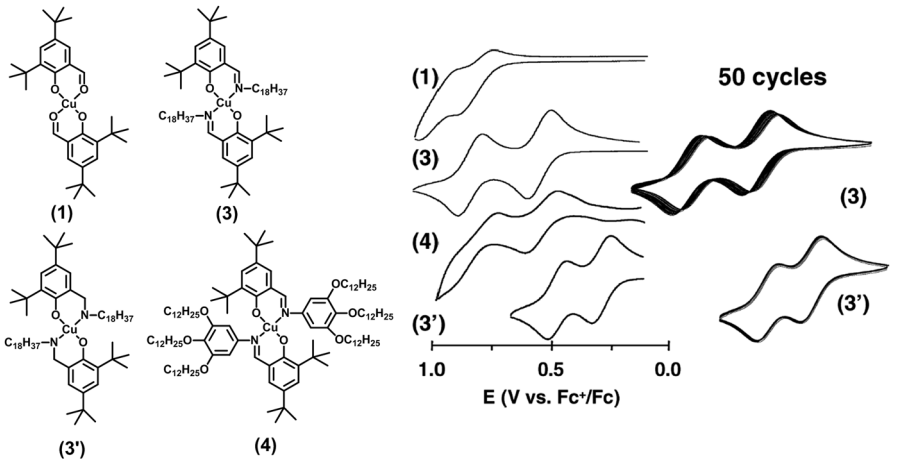

Figure 6.18 Structures and cyclic voltammetry of 1.0×10^{-3} M CH_2Cl_2 solutions of **1**, **3**, **3′** and **4**. Reproduced with permission from S. S. Hindo, R. Shakya, N. S. Rannulu, M. M. Allard, M. J. Heeg, M. T. Rodgers, S. R. P. da Rocha and C. N. Verani, Synthesis, redox, and amphiphilic properties of responsive salycilaldimine-copper(II) soft materials, *Inorg. Chem.*, 2008, **47**, 3119. Copyright (2008) American Chemical Society.

6.3.5 Catalytic Properties

The presence of metal ions in coordination supra-amphiphiles integrates interesting catalytic properties into the assembly structures. Supra-amphiphiles based on coordination bonds and aggregated in particular micelles can be used as nanosized molecular containers to capture and concentrate lipophilic and ionic species. The unique features of metallo-micelles can be exploited in many kinds of catalytic reactions.

For example, the supra-amphiphile design can greatly enhance the catalytic efficiency of the hydrolysis of carboxylate or phosphate esters. Tonellato and coworkers investigated the catalytic properties of a series of hydroxy-functionalized lipophilic pyridine-based ligands. After investigating a number of activated esters of carboxylic or phosphoric acids as substrates, the most impressive results were obtained for α-amino acid esters and the substrate of choice for the assessment of the efficacy of the systems was *p*-nitrophenylpicolinate. The pseudo-first-order rate constants measured were, in some cases, over a million-fold larger than those observed in the pure buffer. Such accelerations are remarkable compared with those observed in the presence of the Cu^{2+} ion alone, which is a good catalyst for this reaction. The most likely reason for the improvement might be the template effect in the cleavage of amino acid esters. In a ternary complex, the metal ion brings the two reactants together with the correct geometry and activates the nucleophile for the *trans*-acylation process (Figure 6.19(a)–(c)). The micellar aggregates ensure further kinetic benefits.[35,36]

Palladium complexes are efficient catalysts for many organic reactions. Therefore coordination supra-amphiphiles based on palladium complexes

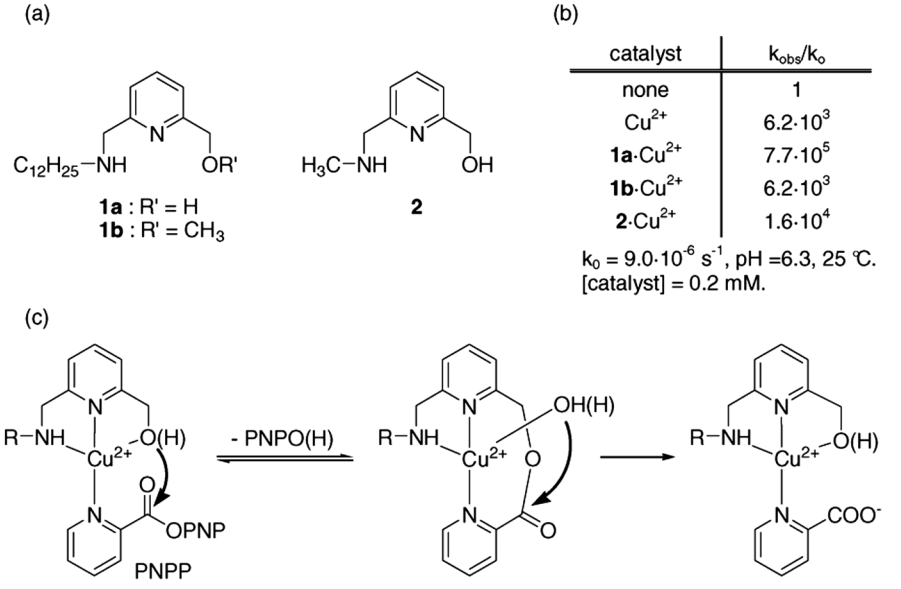

Figure 6.19 The reaction acceleration observed for the cleavage of *p*-nitrophenyl picolinate (PNPP) in the presence of amphiphilic copper complexes and proposed mechanism. (a) Example of a lipophilic ligand and its models. (b) Acceleration observed for the cleavage of PNPP in the presence of the copper complexes of ligands 1 and 2. (c) Proposed mechanism for the cleavage of PNPP promoted by the copper complexes of ligands 1 and 2. Reproduced with permission from P. Scrimin, P. Tecilla and U. Tonellato, Metallomicelles as catalysts of the hydrolysis of carboxylic and phosphoric acid esters, *J. Org. Chem.* 1991, **56**, 161. Copyright (1991) American Chemical Society.

can also have interesting catalytic properties. Uozumi and coworkers explored the catalytic potential of vesicles formed by an amphiphilic pincer palladium complex for the Miyaura–Michael reaction of 2-cyclohexene-1-one with sodium tetraphenylborate. The reaction proceeded in the presence of vesicles provided a yield of 83% with 98% reaction selectivity. By contrast, only a 7% yield of the product was obtained when a monomer of the pincer palladium complex was used as the catalyst. Significant acceleration of the Miyaura–Michael reaction was observed by the formation of vesicles.[11]

6.4 Conclusions and Outlook

This chapter has briefly described the topology, self-assembly behavior, function and potential applications of supra-amphiphiles based on coordination bonds. From the selected examples, it is clear that the presence of metal–ligand complexes can give supra-amphiphiles many unique features. The different metal–ligand coordination geometries make it easy to construct supra-amphiphiles with rich topologies, leading to various self-assembly structures. The dynamic nature of the metal–ligand interactions gives assemblies of supra-amphiphiles with stimuli-responsive functions. The presence

of metal ions introduces additional chemical and physical properties, such as luminescence, magnetism, redox and catalytic properties.

It is evident that increasing effort has been devoted to supra-amphiphiles based on coordination bonds during recent decades. However, the field is still far from a stage of maturity. Although the control of self-assembly process has been extensively studied, the specific properties and functions of supra-amphiphiles based on coordination bonds remain underexplored. Further development of these systems with catalytic, photo-physical and magnetic properties into functional materials for real applications is still a major challenge.

References

1. X. Zhang and C. Wang, *Chem. Soc. Rev.*, 2011, **40**, 94.
2. C. Wang, Z. Wang and X. Zhang, *Acc. Chem. Res.*, 2012, **45**, 608.
3. R. S. Kumar and S. Arunachalam, *Biophys. Chem.*, 2008, **136**, 136.
4. K. Santhakumar, N. Kumaraguru, M. N. Arumugham and S. Arunachalam, *Polyhedron*, 2006, **25**, 1507.
5. A. Colombo, F. Fiorini, D. Septiadi, C. Dragonetti, F. Nisic, A. Valore, D. Roberto, M. Mauro and L. De Cola, *Dalton Trans.*, 2015, **44**, 8478.
6. C. Cebrian, M. Natali, D. Villa, M. Panigati, M. Mauro, G. D'Alfonso and L. De Cola, *Nanoscale*, 2015, **7**, 12000.
7. M. Apostol, P. Baret, G. Serratrice, J. Desbrières, J.-L. Putaux, M.-J. Stébé, D. Expert and J.-L. Pierre, *Angew. Chem., Int. Ed.*, 2005, **44**, 2580.
8. C. Po, A. Y.-Y. Tam, K. M.-C. Wong and V. W.-W. Yam, *J. Am. Chem. Soc.*, 2011, **133**, 12136.
9. L.-B. Xing, S. Yu, X.-J. Wang, G.-X. Wang, B. Chen, L.-P. Zhang, C.-H. Tung and L.-Z. Wu, *Chem. Commun.*, 2012, **48**, 10886.
10. M. R. Ghadiri, C. Soares and C. Choi, *J. Am. Chem. Soc.*, 1992, **114**, 825.
11. G. Hamasaka, T. Muto and Y. Uozumi, *Dalton Trans.*, 2011, **40**, 8859.
12. U. Hahn, H. Luelf, H. D. F. Winkler, C. A. Schalley, F. Vögtle and L. De Cola, *Chem.–Eur. J.*, 2012, **18**, 15424.
13. B. Song, G. Wu, Z. Wang, X. Zhang, M. Smet and W. Dehaen, *Langmuir*, 2009, **25**, 13306.
14. J. H. van Esch, A. L. H. Stols and R. J. M. Nolte, *J. Chem. Soc., Chem. Commun.*, 1990, 1658.
15. C. A. Fustin, P. Guillet, U. S. Schubert and J. F. Gohy, *Adv. Mater.*, 2007, **19**, 1665.
16. J.-F. Gohy, B. G. G. Lohmeijer and U. S. Schubert, *Chem.–Eur. J.*, 2003, **9**, 3472.
17. J.-F. Gohy, B. G. G. Lohmeijer and U. S. Schubert, *Macromol. Rapid Commun.*, 2002, **23**, 555.
18. M. A. R. Meier, D. Wouters, C. Ott, P. Guillet, C.-A. Fustin, J.-F. Gohy and U. S. Schubert, *Macromolecules*, 2006, **39**, 1569.
19. A. O. Moughton and R. K. O'Reilly, *J. Am. Chem. Soc.*, 2008, **130**, 8714.
20. G. Zhou, J. He and I. I. Harruna, *J. Polym. Sci., Part A: Polym. Chem.*, 2007, **45**, 4204.

21. J.-F. Gohy, M. Chiper, P. Guillet, C.-A. Fustin, S. Hoeppener, A. Winter, R. Hoogenboom and U. S. Schubert, *Soft Matter*, 2009, **5**, 2954.
22. A. Nazemi, C. E. Boott, D. J. Lunn, J. Gwyther, D. W. Hayward, R. M. Richardson, M. A. Winnik and I. Manners, *J. Am. Chem. Soc.*, 2016, **138**, 4484.
23. P. Guillet, C.-A. Fustin, D. Wouters, S. Hoeppener, U. S. Schubert and J.-F. Gohy, *Soft Matter*, 2009, **5**, 1460.
24. G. Schwarz, Y. Bodenthin, Z. Tomkowicz, W. Haase, T. Geue, J. Kohlbrecher, U. Pietsch and D. G. Kurth, *J. Am. Chem. Soc.*, 2011, **133**, 547.
25. Y. Bodenthin, U. Pietsch, H. Möhwald and D. G. Kurth, *J. Am. Chem. Soc.*, 2005, **127**, 3110.
26. J.-F. Gohy, B. G. G. Lohmeijer, S. K. Varshney, B. Décamps, E. Leroy, S. Boileau and U. S. Schubert, *Macromolecules*, 2002, **35**, 9748.
27. Q. He, J. Huang, H. Liang and J. Lu, *Polym. Chem.*, 2014, **5**, 4348.
28. L. Liu, L. Rui, Y. Gao and W. Zhang, *Polym. Chem.*, 2014, **6**, 1817.
29. Z. Ge and S. Liu, *Macromol. Rapid Commun.*, 2013, **34**, 922.
30. H. Soyer, C. Mingotaud, M. L. Boillot and P. Delhaes, *Langmuir*, 1998, **14**, 5890.
31. P. N. Martinho, C. J. Harding, H. Müller-Bunz, M. Albrecht and G. G. Morgan, *Eur. J. Inorg. Chem.*, 2010, **2010**, 675.
32. A. Islam, S. P. Singh, M. Yanagida, M. R. Karim and L. Han, *Int. J. Photoenergy*, 2011, **2011**, 757421.
33. L. F. Gomes, K. T. de Oliveira, C. R. Neri, P. C. de Sousa Filho, M. J. Dal Bianco, A. P. Ramos, M. E. D. Zaniquelli and O. A. Serra, *J. Lumin.*, 2008, **128**, 1339.
34. S. S. Hindo, R. Shakya, N. S. Rannulu, M. M. Allard, M. J. Heeg, M. T. Rodgers, S. R. P. da Rocha and C. N. Verani, *Inorg. Chem.*, 2008, **47**, 3119.
35. F. Mancin, P. Scrimin, P. Tecilla and U. Tonellato, *Coord. Chem. Rev.*, 2009, **253**, 2150.
36. P. Scrimin, P. Tecilla and U. Tonellato, *J. Org. Chem.*, 1991, **56**, 161.

CHAPTER 7

Dynamic Covalent Surfactants and Amphiphiles

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7.1 Introduction

The ability of amphiphilic molecules to self-assemble into ordered supramolecular aggregates such as micelles and vesicles are incredibly well studied and exploited.[1,2] In a drive to develop ever smarter aggregates, chemists have recently turned to supramolecular chemistry for inspiration. Supramolecular interactions can be modulated in very controlled ways, imparting dynamic properties that allow features such as self-assembly, error correction and self-repair. As skilfully and comprehensively documented in the other chapters within this book, the incorporation of supramolecular bonds into amphiphilic molecules[3] allows the formation of aggregates that express unique properties imparted by the special nature of their supramolecular bonds.

The last 20 years or so have seen a resurgence of interest from the supramolecular chemistry community in what is often called dynamic covalent chemistry,[4,5] which has developed to become a formidable tool in any supramolecular chemist's repertoire. Dynamic covalent chemistry relates to chemical reactions carried out under conditions of equilibrium control

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and exploits dynamic covalent bonds (DCBs), which, in a similar manner to non-covalent bonds, display a dynamic nature, but which also possess the chemical robustness associated with all covalent bonds. The term DCB simply describes any covalent chemical bond that has the capacity to be formed and broken under equilibrium control. It encompasses many of the organic functional groups taught in any good undergraduate chemistry programme. As Stoddart and coworkers[4] pointed out in their landmark review in 2002, dynamic covalent chemistry is nothing new; DCBs have been studied and exploited, particularly in carbohydrate and polymer chemistry, since the early days of the discipline of organic chemistry. But by thinking about these bonds in a different way, supramolecular chemists have taken them very much to heart with a vigour and passion which has seen the emergence of whole new sub-fields of supramolecular chemistry, such as dynamic combinatorial chemistry[6,7] and constitutionally adaptive materials.[8–14]

This chapter focuses on dynamic covalent surfactants and amphiphiles, ranging from small molecule examples through to macromolecules, where DCBs are used to link the hydrophilic and hydrophobic moieties. It examines how the properties of DCBs are exploited to endow the self-assembled aggregates formed by these molecules with unique, interesting and, ultimately, useful properties, and concludes with some thoughts on the future prospects of this particular area within the field of supramolecular amphiphiles.

7.2 Dynamic Covalent Bonds

To better understand the interesting properties of DCBs, we use, for illustrative purposes, the imine bond (Figure 7.1),[15–17] which is formed from the condensation of carbonyls with amines, also producing a molecule of water. This condensation reaction is an equilibrium process and its position is affected by factors such as temperature, pH and the concentration of reaction partners. Lehn and coworkers performed[18] an in-depth investigation of the pH sensitivity of the imine bond, which showed that the position

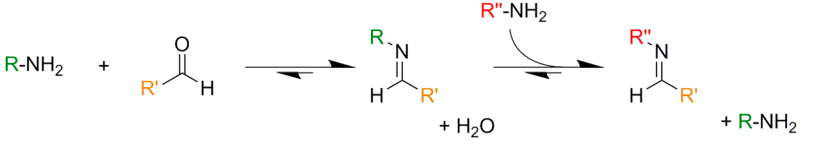

Figure 7.1 The features of DCBs that make them of interest are highlighted using the imine bond as an example. The condensation of an amine with a carbonyl (in this instance an aldehyde) proceeds to form an imine bond and a molecule of water. The position of this equilibrium is sensitive to environmental conditions such as temperature, concentration and pH. DCBs can also undergo component-exchange processes, illustrated here with the reaction of the imine bond with another amine to afford a new imine bond. Exchange processes allow polymers to reshuffle or incorporate/unincorporate their components, changing their structures and thus their properties and function.

of equilibrium can be shifted from almost complete imine to the starting materials over about three pH units. It is possible to control the precise pH at which these processes occur by tuning the electronics of the reaction partners. This ability to modulate the position of equilibrium is particularly powerful because it presents a way to join together two chemical entities through an imine bond. When we no longer wish these chemical entities to be connected, we can simply change the reaction conditions in a way that no longer favours imine bond formation, causing the chemical entities to dissociate and, in principle, this process can be cycled many times.

Another important feature of DCBs is their capacity to undergo component-exchange processes involving the exchange of one reaction partner for another, which can also be illustrated by using the imine bond as an example (Figure 7.1). An imine bond can react with an amine to produce a different imine and amine (transimination) and this component-exchange feature can present amphiphilic molecules opportunities to modify their structures by reshuffling, incorporating or releasing components, and thus changing their structures, properties and functions.

Another important feature of DCBs is that their dynamic nature can often be switched-off by kinetically fixing the bond, an option that is not usually available with non-covalent supramolecular interactions. A chemical process can be used to facilitate this chemical fixing. For example, reduction of the imine bond with hydride reducing agents affords a secondary amine, which does not display any dynamic covalent nature. Another well-known DCB—the hydrazone bond—requires a catalyst to display its dynamic nature, operating with optimum kinetics at pH 4.5.[6] Increasing the pH to 7.0 greatly reduces the kinetics to such an extent that the bond becomes, in effect, kinetically fixed. Many non-covalent supramolecular interactions are inherently dynamic in nature, but their non-covalent nature can present an Achilles heel in that their relative weakness in strength, when compared with covalent chemical bonds, can reduce the stability and robustness of the supramolecular assemblies that rely on them for their structure and function. DCBs, possessing the robustness of covalent bonds, present an appealing approach to overcome this weakness. Another important issue when considering DCBs is, of course, that the kinetics of bond-forming, breaking and component-exchange processes are considerably slower than their non-covalent counterparts, reflecting the fact that covalent bonds rather than non-covalent bonds have to be broken and reformed. This feature is by no means a significant weakness—slower kinetics can sometimes be advantageous, allowing processes to be studies on an experimentally more convenient timeframe, but we must always consider this point carefully when designing dynamic covalent systems.

There is an extensive range of DCBs and some of the more commonly used DCBs utilized in dynamic covalent chemistry are highlighted in Figure 7.2. Almost all of the work described in this chapter utilized only a relatively small selection of the available reactions and thus many still remain unexplored within the context of dynamic covalent surfactants and amphiphiles. It is also

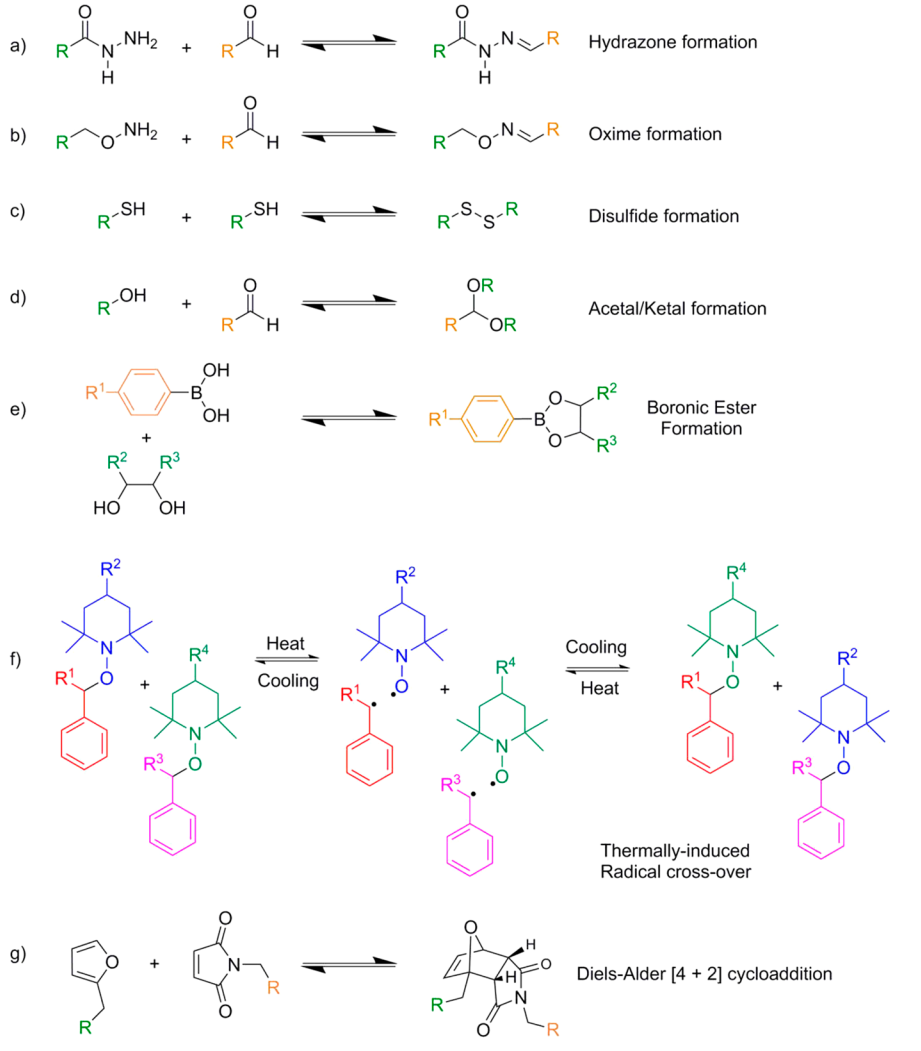

Figure 7.2 Examples of commonly used DCBs. (a) Hydrazone formation; (b) oxime formation; (c) disulfide formation; (d) acetal/ketal formation; (e) boronic ester formation; (f) thermally induced radical cross-over reactions; and (g) Diels–Alder [4+2] cycloadditions.

worthwhile noting that, in the opinion of this author, the field of dynamic covalent chemistry would benefit from an expanded palette of DCBs and better methods to enhance the dynamic nature of covalent bonds, suggesting there are many opportunities for research chemists. Recent progress on this front has seen work to exploit the dynamic nature of selenium–selenium and selenium–nitrogen bonds[19] and there has been seminal work to develop organocatalysts that allow acylhydrazone bonds to display their dynamic nature at neutral pH,[20,21] increasing the biocompatibility of this chemistry.

As the field of dynamic covalent chemistry continues to grow, there will no doubt be some exciting new developments that increase the potential of dynamic covalent chemistry to add value to surfactants and amphiphiles.

7.3 Small Molecule Amphiphiles

The utilization of one or more DCBs to link together hydrophilic and hydrophobic moieties to form a new class of small molecule amphiphiles presents a method to introduce new properties into the resultant supramolecular aggregate formed by the amphiphilic molecules. In effect, the dynamic nature of the DCB is imparted into the supramolecular structure, presenting it with possibilities that would not be found in their non-dynamic counterparts.

The imine bond has found favour as a DCB on account of the ease by which the position of its equilibrium can be controlled by changes in pH or temperature. It is reasonably stable in water (especially when aromatic aldehyde reaction partners are used) and the position of the equilibrium can be easily monitored by ^{1}H nuclear magnetic resonance (NMR) spectrometry. These features were exploited by van Esch and coworkers to show that the micellization of dynamic covalent surfactants could be controlled by modulating the pH and temperature.[22] The condensation (Figure 7.3A) of aromatic aldehyde **1** with the alkyl amine **2** formed the dynamic covalent surfactant **3**. Components **1** and **2** are not themselves surface active, but surfactant **3** predictably forms micelles with diameters of about 4–6 nm depending on the length of the alkyl chains utilized. The dynamic covalent imine bond is stable under mildly alkaline conditions, but undergoes hydrolysis under neutral to mildly acidic conditions to form the amine and aldehyde precursors, inducing micelle disassembly. This process is completely reversible and increasing the pH leads to re-formation of the surfactant imine bonds and subsequent re-micellization. The exploitation of temperature sensitivity to modulate equilibrium is far less explored in dynamic covalent chemistry, but in this work the Dutch group showed that at mildly elevated temperatures (>55 °C) the imine equilibrium can be shifted far enough to the side of the precursors to cause micelle decomposition, a process which is again completely reversible. This remarkably simple, yet elegant, work highlights how the assembly and disassembly of supramolecular species can be triggered in response to pH or temperature and the authors suggest that this work may lead to future applications in smart delivery or switchable bilayers and polyelectrolytes.

Vesicles are another class of supramolecular aggregate of great interest and can be accessed using double-chain surfactant building blocks. Vesicles tend to be very static in nature and so to translate the success of their micellar system into vesicles, van Esch and coworkers have developed[23] double-chain surfactant building blocks with dynamic covalent imine bonds. This system utilizes the cationic *bis*-aldehyde **4**, which condenses with the aliphatic amine **2** to form the single-tailed and double-tailed surfactants **5** and **6**, which are in equilibrium with each other (Figure 7.3B). Components

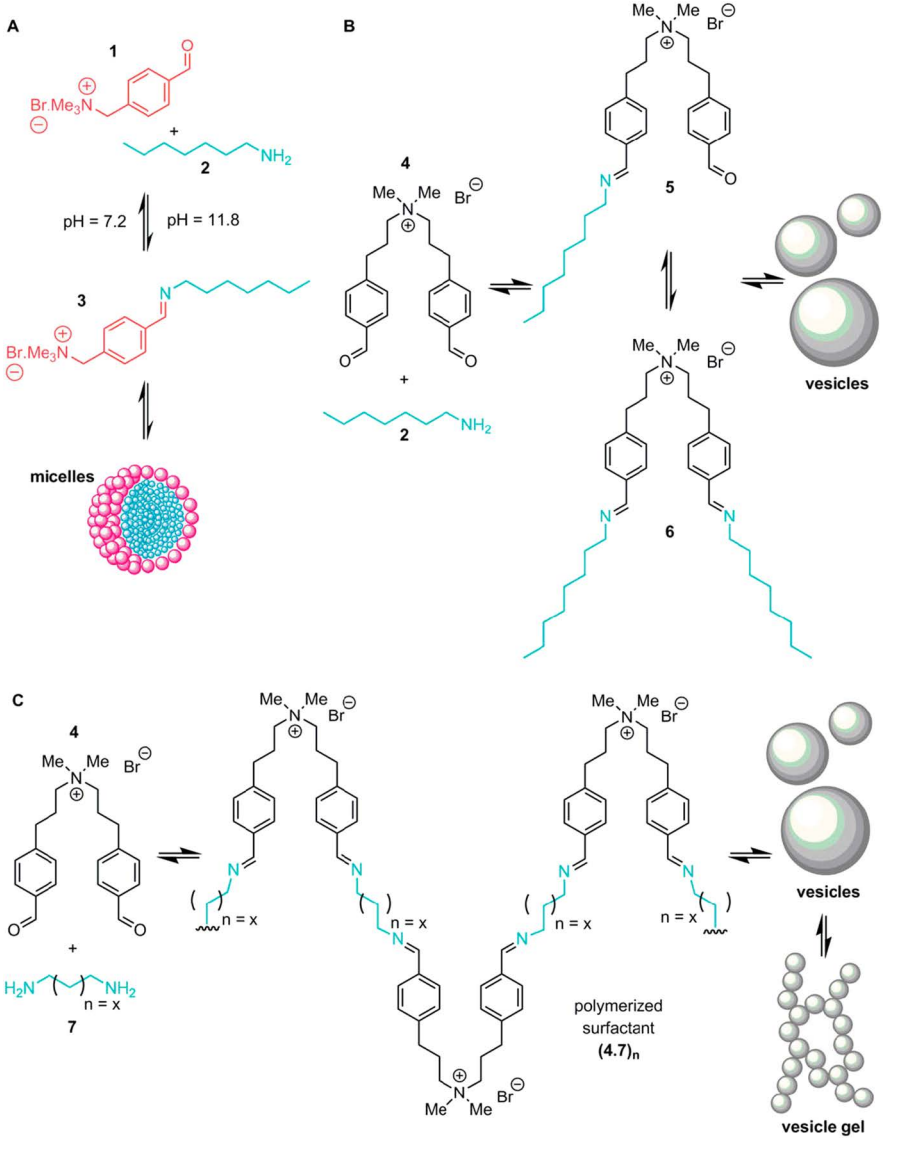

Figure 7.3 (A) Condensation of aldehyde **1** with amine **2** forms the dynamic covalent amphiphile **3**, which is able to form micellar assemblies. The assembly and disassembly of these can be modulated by changing the equilibrium position of the imine bond within **3**. (B). Condensation of the *bis*-aldehyde **4** with amine **2** forms amphiphiles **5** and **6**, which are able to form vesicles whose assembly and disassembly can also be modulated by changing the equilibrium position of the imine bond. (C). Condensation of diamine **7** with **4** forms a polymerized surfactant that is able to self-assemble into vesicles, which themselves self-assemble into higher order vesicle gels.

2 and **4** possess good water solubility. When mixed in water, the components spontaneously react and the resulting amphiphiles form a mixed population of vesicles with two size ranges (2–5 μm vesicles and 50–100 nm unilamellar vesicles). As with the micelle system highlighted in Figure 7.3A, it is possible to trigger vesicle formation and disassembly simply by modulating the pH. Thus at pH > 7.1, vesicle formation is favoured, but at pH < 4 the imine bonds are completely hydrolysed and the vesicles disassemble completely. This work also demonstrates exploitation of the concentration-dependence of the imine bond formation, with amphiphile formation favoured at higher concentrations, and vesicles are thus observed. A hundred-fold dilution pushes the imine equilibrium to the left; amine and aldehyde are thus favoured and the vesicles quickly dissociate into their components.

This Dutch group has expanded further the dynamic covalent surfactant idea using molecular building blocks, including the *bis*-amine **7**, which can easily condense with *bis*-aldehyde **4** to access polymerized surfactants $(\mathbf{4.7})_n$ (Figure 7.3C).[24] These species self-assemble into so-called vesicle gels, a three-dimensional network of connected vesicles that can display the properties of viscoelastic hydrogels, potentially making them useful in cell culture and tissue growth applications. When the aldehyde and amine components are mixed, the resultant amphiphiles begin to self-assemble into vesicles (<5 min), which then grow and cluster over 5–20 min. At 50–60 min after initial mixing, the vesicle clusters have cross-linked to form percolating vesicle gel networks, which behave as relatively weak viscoelastic gels. To determine the nature of the molecular species that constitute these gels, the imine bonds were kinetically fixed through $NaBH_4$ reduction and the species were analysed by liquid chromatography–mass spectrometry to reveal a complex mix of $(\mathbf{4.7})_n$ polymers, oligomers, macrocycles and single-tailed surfactants in addition to *bis*-amine **7**. The group demonstrated that the gels are responsive to pH and temperature, the latter relying on the tendency of the imine bond to dissociate as the temperature is increased. It would have been interesting to see these materials evaluated for their potential in biomedical applications, but at the time of writing no further development has been reported.

Further structural adaptations, this time utilizing dynamic covalent gemini surfactants (Figure 7.4) incorporating two positive charges, allows access to worm-like micelles, which display responsive behaviours imparted by imine bonds.[25] Mixing the *bis*-aldehyde **8** with primary amines, both of which are readily soluble in water, affords the dynamic covalent surfactants **9** and **10**, which self-assemble into worm-like micelles. Evidence from NMR spectroscopic studies suggests that there is an aggregation-induced stabilization of the imine bonds and, consequently, the double-tailed surfactant dominates. As with their previous systems, the authors exploited the dynamic nature of the imine bond to impart responsiveness into the micellar aggregates and demonstrated how the modulation of pH and temperature can reversibly switch self-assembly on and off. Dispersions of worm-like micelles prepared from conventional surfactants often display highly viscous solutions; however, in this case the small length and large flexibility of the dynamic covalent

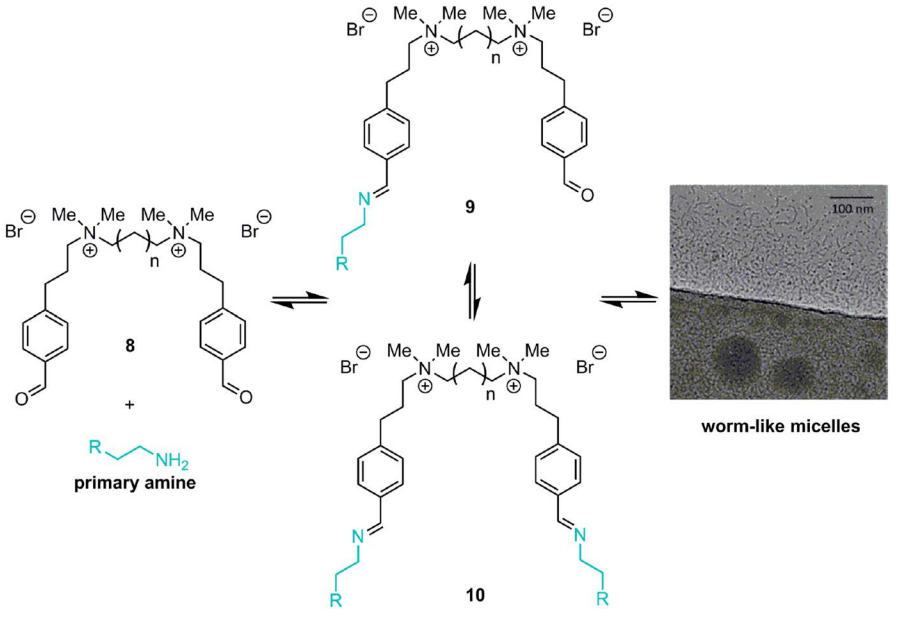

Figure 7.4 Condensation of *bis*-aldehyde **8** with primary amines affords a mixture of surfactants that can self-assemble into work-like micelles, as seen in a transmission electron micrograph. Reproduced with permission from C. B. Minkenberg, B. Homan, J. Boekhoven, B. Norder, G. J. M. Koper, R. Eelkema and J. H. van Esch, Responsive wormlike micelles from dynamic covalent surfactants, *Langmuir*, 2012, **28**, 13570. Copyright (2012) American Chemical Society.

worm-like micelles imparts their aqueous dispersions with little in the way of viscoelastic properties—crucial features of hydrogel materials. This inability to modulate the viscoelastic properties of worm-like micelle dispersions may limit their potential applications, but with adjustments to the surfactant structure it may be possible to address this deficiency.

The group of Xi Zhang at Tsinghua University in Beijing has studied a series of dynamic covalent amphiphiles that possess pH responsiveness on account of the dynamic imine bonds that link their hydrophilic and hydrophobic moieties. By systematically increasing the structural complexity of the amphiphiles, they have gained an understanding of how the responsive properties of the supramolecular micelles formed from these amphiphiles are altered by their molecular features.

Their initial work reports[26] the bola-form amphiphile **11** (Figure 7.5), which has a single dynamic covalent imine bond. The pH sensitivity of this imine bond allows its hydrolysis at low pH and re-formation at higher values. The group showed that this amphiphile forms micellar aggregates in the size range 4–5 nm, which disassemble at lower pH values because the hydrolysis of the imine bond causes the amphiphiles to dissemble into their components.

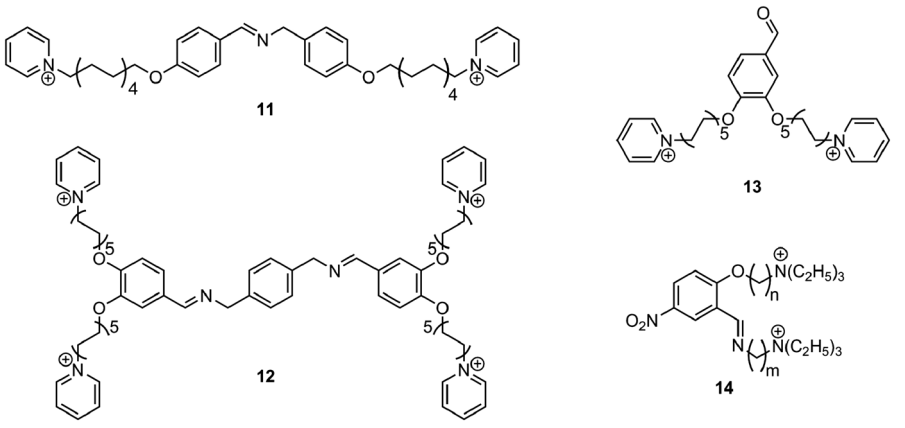

Figure 7.5 Structures of a series of bola-form amphiphiles developed by Xi Zhang and coworkers to explore the potential of incorporating dynamic covalent imine bonds to reversibly connect hydrophobic and hydrophilic moieties.[26–28]

Zhang and coworkers also investigated how the nature of the micelle may affect its pH responsiveness. Throughout this work,[26–28] the electronics of the surfactant imine bonds were maintained to be essentially identical and thus it would be anticipated that the pH responsiveness of the resulting micelles would also be very similar. However, the Tsinghua group found that the pH-responsive nature of the imine bonds was influenced by the nature of the micelles formed by the amphiphile. For instance, the H-shaped amphiphile **12** (Figure 7.5) displays[27] a more confined shape and its resulting micellar assemblies are more stable than those formed from its component aldehyde **13**. This is itself a bola-amphiphile, a fact which is reflected in the imine bonds within **12** being less prone to hydrolysis at lower pH. There is a correlation between the experimentally determined critical micelle concentrations (CMCs) and the ease with which the imine bonds are hydrolysed. These observations suggest that it is easier for protons and water to infiltrate into the hydrophobic cores of micelles that display lower stabilities (and thus higher CMCs), triggering imine hydrolysis at lower than expected pH values. Similar findings are reported[28] in work with amphiphile **14**, where it was observed that those amphiphiles displaying an asymmetrical nature (possessing hydrocarbon tails of differing lengths, *i.e.* $m \neq n$) tend to hydrolyse more at lower pH values than their more symmetrical counterparts, presumably because asymmetrical amphiphiles form less stable micelles. This work presents another fine example of how the nature of a supramolecular assembly can influence molecular processes in ways that are not immediately obvious.

With small molecule dynamic covalent surfactants, the amine and aldehyde components themselves can also self-assemble into micellar structures, depending on the precise concentrations under study. This phenomena was

observed throughout the work of Zhang and coworkers,[26–28] who worked at intermediate CMCs to encourage the aggregation of only the dynamic covalent amphiphiles. An identical situation was present in the work of Chen and coworkers,[29] who described amphiphiles **i-FDI** and **i-FDP** (Figure 7.6) containing dynamic covalent benzoic imine bonds with the ability to self-assemble into vesicles with diameters in the range 70–110 nm depending on the exact polar headgroup used. The imine bonds are stable at pH 11.8 and hydrolyse at lower pH values, triggering vesicle disassembly into the component amines and aldehydes, which, of course, have their own amphiphilic nature and can, at the correct concentration and pH, self-assemble into micelles. The authors present evidence that these micelles consist of both the (protonated) amine and aldehydes. Increasing the pH triggers re-formation of the dynamic covalent amphiphile, which can, of course, self-assemble into vesicles. As with the work of Zhang and coworkers, there is strong evidence to support the fact that the nature of the supramolecular structure formed affects the ease with which the imine bonds are hydrolysed. This feature is manifest in the rates of release of hydrophobic guests (the authors use the dye Nile Red) encapsulated within the vesicles' bilayers. The guest release profiles are shown to very much depend on the nature of the headgroup, which probably contributes towards vesicle stability and thus influences the rate of guest release. This work is another example of how DCBs can introduce responsive natures into supramolecular assemblies and also highlights how the nature of the supramolecular assembly can subtlety influence the properties of the DCBs.

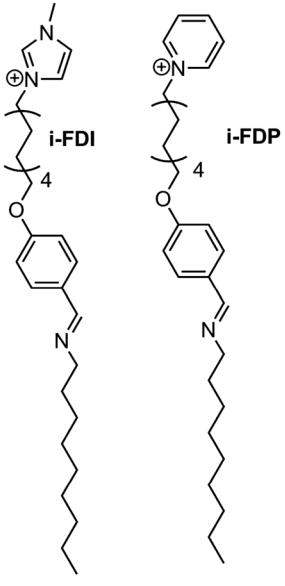

Figure 7.6 Amphiphiles with dynamic covalent imine bonds prepared by Chen and coworkers.[29]

7.4 Macromolecular Amphiphiles

The surfactants discussed so far are small molecule in nature, but macromolecular amphiphiles are also very well known. Just like small molecule amphiphiles, their macromolecular counterparts can self-assemble into a variety of supramolecular architectures[3] and in recent years chemists have begun to investigate how the incorporation of DCBs into these building blocks can endow added function into their resultant supramolecular aggregates.

He and coworkers[30] have described dynamic diblock copolymers **15** (Figure 7.7A) in which the hydrophobic block is conjugated to the hydrophilic block through a dynamic covalent acyl hydrazone linker. As expected, these diblocks self-assemble into a range of morphologies, including micelles and vesicles (Figure 7.7B), with the hydrophilic to hydrophobic ratio determining the nature of the self-assembled morphology obtained. As with dynamic covalent imine bonds, acylhydrazones also possess acid sensitivity, with the electronics of this bond tuned so that the bond hydrolyses at mildly acidic pH. By working with a relatively electron-rich aldehyde component, this research group has managed to obtain dynamic bonds that can hydrolyse at pH 4, causing the self-assembled morphologies to shed their hydrophilic corona to reveal what are probably kinetically stable aggregates of hydrophobic

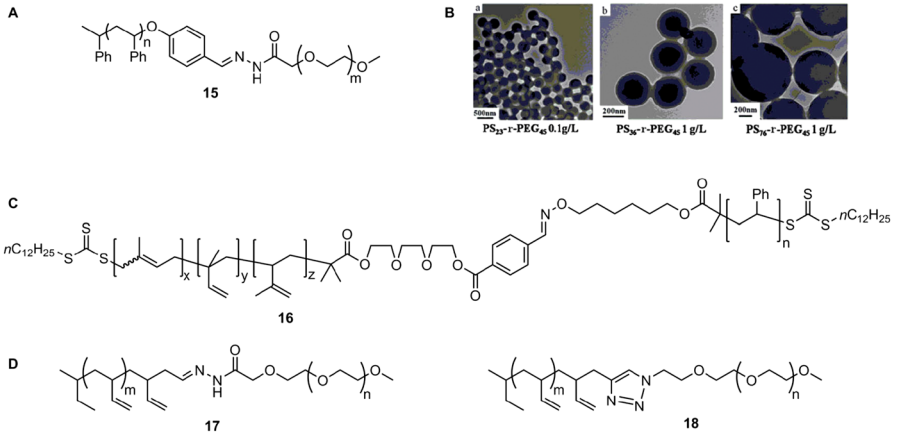

Figure 7.7 (A) Macromolecular amphiphile prepared by He and coworkers.[30] (B) Transmission electron micrographs of the supramolecular aggregates prepared from amphiphile **15** with different degrees of polymerization of the hydrophilic and hydrophobic blocks. Reproduced from ref. 30 with permission from the Royal Society of Chemistry. (C) Macromolecular amphiphile prepared by Fulton and Jackson.[31] (D) Macromolecular amphiphiles prepared by Brinkhuis and coworkers.[32] Amphiphile **17** has a dynamic covalent acylhydrazone bond that links the hydrophilic and hydrophobic moieties, whereas **18** has a non-dynamic triazole linkage.

polymer chains, or perhaps even whole hydrophobic cores, as suggested by dynamic light scattering measurements. The propensity of the hydrophobic chains to remain aggregated even after the hydrophilic blocks have been lost probably explains the slow release profile of an encapsulated guest (methyl porphyrin), which takes about 10 h to achieve 80% release.

This author's own laboratory at Newcastle University also investigated dynamic diblock copolymers **16** (Figure 7.7C) where the blocks were linked through oxime linkages.[31] By working with poly(isoprene) and poly(styrene) blocks, our group was able to form diblock copolymers that self-assemble into micellar aggregates in dimethylformamide, a selective solvent for the polystyrene block. By adding an excess of a small molecule alkoxyamine, we were able to invoke a component-exchange process, which in effect caused cleavage of the diblock copolymer, inducing micellar disassembly. Interestingly, dynamic light scattering and gel-permeation chromatography studies suggested that the polyisoprene cores remained to some degree intact, an observation similar to that made by He and coworkers[30] in their water-compatible system.

Just how many coronal chains can a supramolecular assembly loose and still remain intact? Brinkhuis *et al.*[32] used dynamic covalent diblock copolymers to answer this question. The Dutch group linked a hydrophobic poly(isoprene) block to a poly(ethylene glycol) (PEG) block using an acid-sensitive acylhydrazone linker and mixed the resulting amphiphile **17** (Figure 7.7D) with varying amounts of a fixed diblock (**18**) of identical block compositions and molecular weights linked through an inert triazole linker. After extruding the mixtures to form polymersomes—a term that describes vesicles consisting of macromolecular amphiphiles—and then lowering the pH, thus hydrolysing the hydrazone bonds and causing the PEG chains to fall off, the group were able to estimate just how little PEG is required for the polymersome to maintain its stability, an amount that is as low as 5%. These observations are in agreement with PEGylated liposomes, where it has been shown that only 5–10% PEGylation is required to shield cationic liposomes from their surroundings.

Brinkhuis *et al.*[33] have also exploited the potential of the same dynamic covalent polymer-based amphiphile to undergo component-exchange processes in an ingenious strategy to decorate the outer surfaces of polymersomes. After polymersome formation, the groups were able to exchange (Figure 7.8A) the outer PEGylated block with other acylhydrazide-functionalized polymers labelled with fluorescent dyes. The group also showed that polymersomes can exchange their surface components with one another (Figure 7.8B). This work presents a beautiful example of how hydrazone exchange chemistry can be used to decorate selectively the outer layer of polymersomes and to make compositionally adaptive supramolecular assemblies. It will be particularly interesting to see how these ideas are developed in future years.

Imine bonds hydrolyse over about three pH units, meaning that these bonds exist in some state of partial hydrolysis over a wide range of pH values. This feature may be considered disadvantageous should a more digital

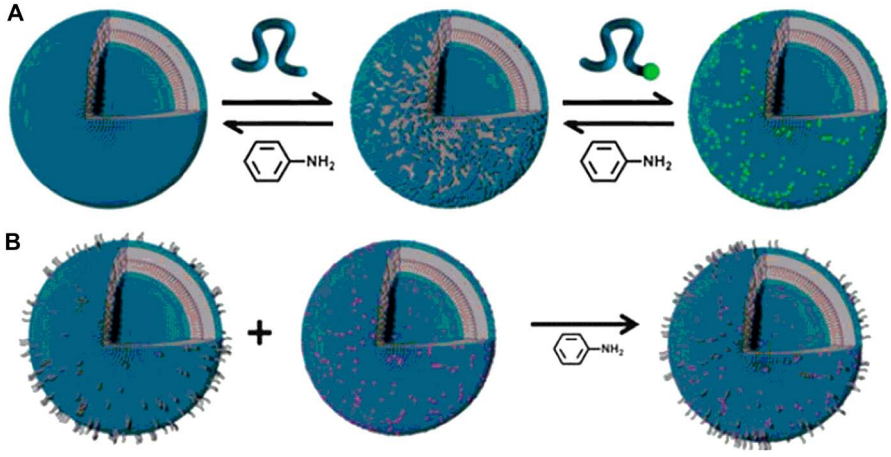

Figure 7.8 (A) Polymersome structures formed from the self-assembly of **17** can lose surface hydrophilic blocks, which can be replaced with other types of hydrophilic block. In effect, there is a mechanism to allow the polymersomes to reshuffle their outer leaf chains while maintaining the structure of the inner leaf. (B) When polymersomes displaying different outer-leaf compositions are mixed, dynamic component-exchange processes lead to a mixing of components. Reproduced from ref. 33 with permission from the Royal Society of Chemistry.

response be required. Zhang and coworkers[34] have cleverly circumvented this issue, developing a novel toothbrush-like macromolecular amphiphile that is able to convert a broad range response into a sharp response. The doubly hydrophilic polymer **19** (Figure 7.9) with a polylysine block is transformed into amphiphile **21** through condensation with many molecules of the small hydrophobic molecule 4-(decyloxy)benzaldehyde **20** at pH 7.4. The amphiphile aggregates to form micellar assemblies with hydrodynamic diameters of 70 nm. It was demonstrated that the assembly and disassembly of the micelle can be triggered by exploiting the pH sensitivity of the imine bonds. Thus at pH 6.5 a sufficient fraction of the imine bonds is hydrolysed to cause **21** to lose its amphiphilicity, triggering disassembly of the micelle. Experiments with the hydrophobic guest molecule Nile Red indicate that its release from the hydrophobic micelle core can occur within 20 min. Increasing the pH to 7.4 drives a sufficiently high fraction of imine bond formation, allowing the polymer to regain its amphiphilicity and inducing micelle formation. Thus this system responds over a relatively small pH range, with only a small decrease in pH from 7.4 to 6.5 required to trigger micelle decomposition. In effect, this system is exploiting the pH to modulate the hydrophobic–hydrophilic balance of the polymer building blocks—as imine bonds are partially hydrolysed the polymer becomes increasingly hydrophilic. Presumably a well-defined tipping

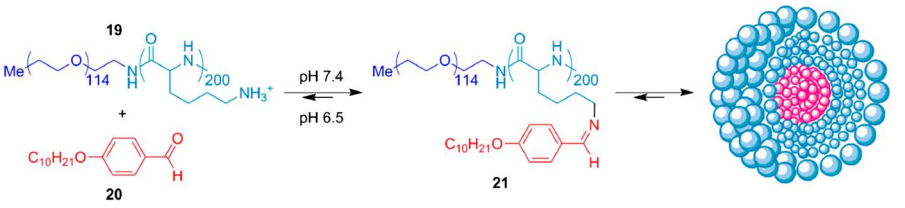

Figure 7.9 Multiple hydrophobic aldehyde units **20** conjugate onto a polylysine diblock copolymer **19** to prepare amphiphile **21**, which spontaneously self-assembles into a micelle. Lowering the pH to 6.5 causes partial hydrolysis of the imine linkages, reducing the amphiphilicity of the diblock copolymers and triggering micelle disassembly.

point is reached and the polymer no longer possesses the required degree of hydrophobicity to remain within a supramolecular assembly. This is a particularly ingenious trick and worthy of further development.

Although many researchers have speculated that DCBs may endow supramolecular assemblies with responsive behaviours that may enhance their potential as candidates for drug delivery, there have been surprisingly few *in vitro* studies to actually investigate this possibility. Zhu and coworkers[35] developed an amphiphilic triblock copolymer system consisting of a central poly(caprolactone block), the termini of which are conjugated to PEG blocks through oxime linkages. This triblock was shown to self-assemble into micelles with diameters of about 250 nm, which were able to encapsulate the relatively hydrophobic anticancer drug doxorubicin (DOX) within their hydrophobic cores. The group showed that the rate of release of DOX from these micelles was much faster at pH 5 than at pH 7.4, an observation which supports the idea that the oximes are (at least partially) hydrolysed at mildly acidic pH values, destabilizing the micelles and triggering DOX release. Studies with HeLa cells, a robust cancer cell line that is easy to work with, showed that the DOX-loaded micelles are internalized and display a cytotoxic effect. Somewhat frustratingly, the authors did not report a model study investigating the effects of pH on the equilibrium position of the oxime bond, which would have been helpful in better understanding the pH responsiveness of the amphiphiles and their resulting supramolecular assemblies.

It is not surprising to see that researchers have been quick to investigate the possibilities arising when DCBs are included within macromolecular amphiphiles and the work we will now describe has a very different flavour to most of the work already highlighted. Giuseppone and coworkers have performed some notable work,[36–38] but to truly appreciate the underlying science it is first necessary to revisit some work from the 1990s of Bachmann *et al.*,[39] which reported micelles that can catalyse their own replication. This work exploits the hydrolysis of ethyl-caprylate to afford the simple amphiphile sodium caprylate, which can form micellar assemblies above its CMC. The rate of hydrolysis of ethyl-caprylate is about 900 times faster within the

interior of micelles that on the outside. This feature manifests itself in an initially slow rate of ethyl-caprylate hydrolysis, but, as soon as sufficient sodium caprylate is available to allow the formation of micelles, the rate of hydrolysis increases exponentially and thus the population of micelles also increases exponentially. Thus the micelles are able to catalyse their own formation, a process termed autopoiesis, a term stemming from the Greek 'auto' (self) and 'poiesis' (formation).

Taking inspiration from this earlier work, Giuseppone and coworkers[36–38] used dynamic covalent imine bonds to join a hydrophobic aldehyde **22** (Figure 7.10) with a selection of amines based on hydrophilic poly(ethylene oxide) such as **23a** and **23b** to afford a number of dynamic amphiphilic blocks such as **24a** and **24b**, which the group termed "dynablocks". These dynablocks self-assemble into higher order structures, the nature of which is determined by the hydrophilic to hydrophobic ratio of the dynablocks. ^{1}H NMR spectroscopic studies reveal that a high degree of condensation occurs in D_2O relative to acetonitrile, observations suggesting that the imine bond is stabilized within the inner hydrophobic environment of the micelles. Crucially, the kinetics of imine bond formation are also faster within the hydrophobic inner core. When the kinetics of imine bond formation are measured, the resulting concentration–time profile reveals a sigmoidal shape, a tell-tale characteristic of an autocatalytic system; clearly, the micelles that form from the dynablocks catalyse further imine bond formation, leading to an exponential growth in the micelle population. The size of the micellar structures constantly decreased until reaching a plateau, an observation that can be attributed to a growth/division cycle of the micellar structures until a constant average size is observed. A contributing factor to this autocatalytic behaviour is almost certainly the poor water solubility of aldehyde **22**, which provides considerable encouragement for the aldehyde to localize within the hydrophobic interiors of any nearby micelles, where it can more readily react with amines.

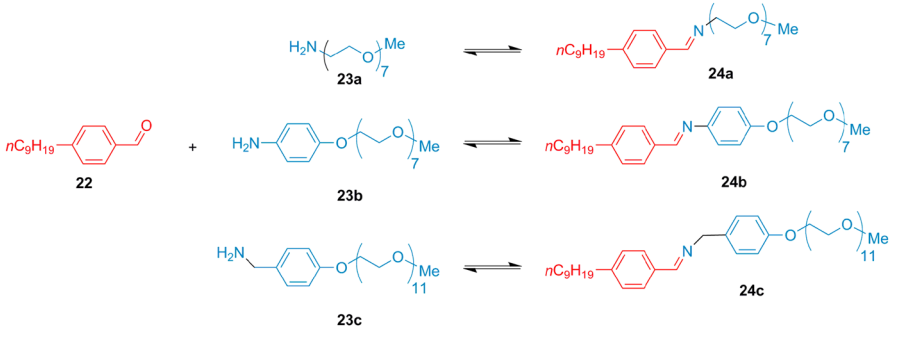

Figure 7.10 Condensation of hydrophobic aldehyde **22** with hydrophilic amines **23a–c** affords the amphiphiles **24a–c**, which are able to self-assemble into micellar architectures.

Expanding the scope of this work, Giuseppone and coworkers investigated a competition experiment using the hydrophilic amines **23a** and **23b**, allowing them to compete with one another for aldehyde **22**. The dynablock that won, *i.e.* had the greater concentration, was dictated by the relative thermodynamic stabilities of the resultant micellar assemblies. When the components were mixed in D_2O, dynablock **24b** formed faster than **24a** as its micellar assembly was, relatively speaking, more stable than that formed by **24a**, and was thus able to act as a more effective catalyst for the formation of **24b**. In a second experiment, when the components were mixed in CD_3CN, dynablock **24a** formed faster than **24b** and when equilibrium was reached the higher concentration of imine within **24a** suggested that its micelle population was greater than the population of the micelle formed from **24b**. This latter observation is to be anticipated as this micelle is expected to be relatively more stable in CD_3CN than the micelle made from **24b**. When CD_3CN was exchanged for D_2O, the micelle made from **24b** was thermodynamically more favoured and the system re-equilibrated to favour this species at the expense of the micelle derived from **24a**.

Extending this work further, Giuseppone and coworkers[38] took aldehyde **22** and mixed it with hydrophilic amines **23b** and **23c** to afford a mixture of amphiphiles **24b** and **24c**. The ratio of these two amphiphiles in solution was determined by pH; at higher pH values **24c** was formed as amine **23c** is more nucleophile than **23b**, whereas at lower pH **24b** was formed as amine **24c** was trapped by protonation and was thus unable to condense with **22**. By changing the pD between 6.3 and 12, it was possible to reversibly change the composition of **24b** and **24c**. This change in composition affected the nature of the supramolecular structures observed in solution, with small-angle neutron scattering studies utilized to probe the nature of the self-assembled species. The amphiphiles were shown to self-assemble into cylindrical micelles over all pH ranges, but the nature of the micellar structures is pH dependent with their lengths, masses, aggregation numbers and structural parameters all dependent on the micellar composition. At lower pD values, where amphiphile **24b** predominates, the cylindrical micelles have a larger diameter (as given by the radius of gyration) and linear mass density (suggesting they are longer and denser), whereas at higher pD values, where amphiphile **24c** predominates, the cylinders are shorter and have lower linear mass densities. Solutions of amphiphile **24b** on its own self-assemble into spherical micelles and so, as the concentration of **24b** in a mixed amphiphile solution decreases, it could be the case that the system is headed towards a spherical micellar structure. The group have also shown that small-angle neutron scattering, small-angle X-ray scattering and light scattering methods can be applied to quantify the different types of micellar architectures available in solution; however, it would have been interesting to utilize transmission electron microscopy to further verify the nature of the self-assembled structures. Nevertheless, the work does again demonstrate how modulation of the position of equilibrium of a dynamic covalent bond can affect the architecture of supramolecular species.

7.5 Conclusions and Outlook

It is hoped that the work highlighted here has given the reader an introduction to the basics and a taste of progress made within this sub-field of supramolecular amphiphiles. Since the first report[22] of dynamic covalent surfactants by van Esch and coworkers in 2009, there has clearly been much activity in this area. Work to date has increased our understanding of what might be possible with this new class of amphiphile. Controlled delivery is clearly an area of great interest, yet there remains much scope for developing this work further. Progress will require chemists to work with pharmacists, pharmacologists and other biomedical scientists to identify real-world problems in drug delivery that might benefit from the unique properties with which DCBs can endow micellar supramolecular assemblies. We also should turn our attention to other controlled delivery issues of commercial interest, such as fragrance delivery, where opportunities are certain to exist.

The work highlighted also suggests that the inclusion of DCBs within amphiphiles allows the development of rich and interesting chemical systems that can begin to display emergent behaviours and, beyond the work of Giuseppone and coworkers,[36–38] it is surprising that more has not been done in this area. It is very much the opinion of this author that dynamic covalent amphiphiles will have an important part to play as the field of systems chemistry continues to develop. Much of the work described in this chapter relies heavily on the dynamic nature of the carbon–nitrogen double bond, but there is much scope for other well-known dynamic DCBs to be utilized. There has been a strong emphasis on exploiting the controlled formation and cleavage of DCBs and relatively little on utilizing component-exchange process, but, as the work of Brinkhuis and coworkers shows,[32,33] this aspect of dynamic covalent chemistry introduces some powerful features into supramolecular assemblies formed from dynamic covalent amphiphiles. Over the coming years chemists will also develop new DCBs and it will be important to consider the potential opportunities that arise as and when these are reported. At the time of writing, this subfield of supramolecular amphiphiles is only seven years old, but it is very much the opinion of this author that this body of early work will only be the starting point and the very best is yet to come.

References

1. D. Myers, *Surfactant Science and Technology*, VCH, New York, 1992.
2. J. H. Fuhrhop and T. Y. Wang, *Chem. Rev.*, 2004, **104**, 2901.
3. C. Wang, Z. Wang and X. Zhang, *Acc. Chem. Res.*, 2012, **45**, 608.
4. S. J. Rowan, S. J. Cantrill, G. R. L. Cousins, J. K. M. Sanders and J. F. Stoddart, *Angew. Chem., Int. Ed.*, 2002, **41**, 898.
5. Y. Jin, C. Yu, R. J. Denman and W. Zhang, *Chem. Soc. Rev.*, 2013, **42**, 6634.

6. P. T. Corbett, J. Leclaire, L. Vial, K. R. West, J. L. Wietor, J. K. M. Sanders and S. Otto, *Chem. Rev.*, 2006, **106**, 3652.
7. J. Li, P. Nowak and S. Otto, *J. Am. Chem. Soc.*, 2013, **135**, 9222.
8. J.-M. Lehn, *Aust. J. Chem.*, 2010, **63**, 611.
9. J.-M. Lehn, *Chem. Soc. Rev.*, 2007, **37**, 151.
10. J.-M. Lehn, *Prog. Polym. Sci.*, 2005, **30**, 814.
11. R. J. Wojtecki, M. A. Meador and S. J. Rowan, *Nat. Mater.*, 2011, **10**, 14.
12. C. J. Kloxin, T. F. Scott, B. J. Adzima and C. N. Bowman, *Macromolecules*, 2010, **43**, 2643.
13. T. Maeda, H. Otsuka and A. Takahara, *Prog. Polym. Sci.*, 2009, **34**, 581.
14. Y. Zhang and M. Barboiu, *Chem. Rev.*, 2016, **116**, 809.
15. S. Patai, *The Chemistry of the Carbon–Nitrogen Double Bond*, Interscience, London, 1968.
16. C. D. Meyer, C. S. Joiner and J. F. Stoddart, *Chem. Soc. Rev.*, 2007, **36**, 1705.
17. M. E. Belowich and J. F. Stoddart, *Chem. Soc. Rev.*, 2012, **41**, 2003.
18. C. Godoy-Alcántar, A. K. Yatsimirsky and J.-M. Lehn, *J. Phys. Org. Chem.*, 2005, **18**, 979.
19. S. Ji, J. Xia and H. Xu, *ACS Macro Lett.*, 2016, **5**, 78.
20. A. Dirksen, S. Dirksen, T. M. Hackeng and P. E. Dawson, *J. Am. Chem. Soc.*, 2006, **128**, 15602.
21. A. Dirksen, S. Yegneswaran and P. E. Dawson, *Angew. Chem., Int. Ed.*, 2010, **49**, 2033.
22. C. B. Minkenberg, L. Florusse, R. Eelkema, G. J. M. Koper and J. H. van Esch, *J. Am. Chem. Soc.*, 2009, **131**, 11274.
23. C. B. Minkenberg, F. Li, P. van Rijn, L. Florusse, J. Boekhoven, M. C. A. Stuart, G. J. M. Koper, R. Eelkema and J. H. van Esch, *Angew. Chem., Int. Ed.*, 2011, **50**, 3421.
24. C. B. Minkenberg, W. E. Hendriksen, F. Li, E. Mendes, R. Eelkema and J. H. van Esch, *Chem. Commun.*, 2012, **48**, 9837.
25. C. B. Minkenberg, B. Homan, J. Boekhoven, B. Norder, G. J. M. Koper, R. Eelkema and J. H. van Esch, *Langmuir*, 2012, **28**, 13570.
26. G. Wang, C. Wang, Z. Wang and X. Zhang, *Langmuir*, 2011, **27**, 12375.
27. G. Wang, C. Wang, Z. Wang and X. Zhang, *Langmuir*, 2012, **28**, 14567.
28. G. Wang, C. Wang, Z. Wang and X. Zhang, *Langmuir*, 2014, **30**, 1531.
29. J. Wang, X. Chen, W. Cui and S. Yi, *Colloids Surf., A*, 2015, **484**, 28.
30. L. He, Y. Jiang, C. Tu, G. Li, B. Zhu, C. Jin, Q. Zhu, D. Yan and X. Zhu, *Chem. Commun.*, 2010, **46**, 7569–7571.
31. A. W. Jackson and D. A. Fulton, *Macromolecules*, 2010, **43**, 1069.
32. R. P. Brinkhuis, T. R. Visser, F. P. J. T. Rutjes and J. C. M. van Hest, *Chem. Commun.*, 2011, **2**, 550.
33. R. P. Brinkhuis, F. de Graaf, M. B. Hansen, T. R. Visser, F. P. J. T. Rutjes and J. C. M. van Hest, *Polym. Chem.*, 2013, **4**, 1345–1350.
34. C. Wang, G. Wang, Z. Wang and X. Zhang, *Chem.–Eur. J.*, 2011, **17**, 3322.
35. Y. Jin, L. Song, Y. Su, L. Zhu, Y. Pang, F. Qiu, G. Tong, D. Yan, B. Zhu and X. Zhu, *Biomacromolecules*, 2011, **12**, 3460.

36. R. Nguyen, L. Allouche, E. Buhler and N. Giuseppone, *Angew. Chem., Int. Ed.*, 2009, **48**, 1093.
37. R. Nguyen, E. Buhler and N. Giuseppone, *Macromolecules*, 2009, **42**, 5913.
38. N. Jouault, R. Nguyen, M. Rawiso, N. Giuseppone and E. Buhler, *Soft Matter*, 2011, **7**, 4787.
39. P. A. Bachmann, P. L. Luisi and J. Lang, *Nature*, 1992, **357**, 57.

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