

Dynamic Supramolecular Complexes Constructed by Orthogonal Self-Assembly

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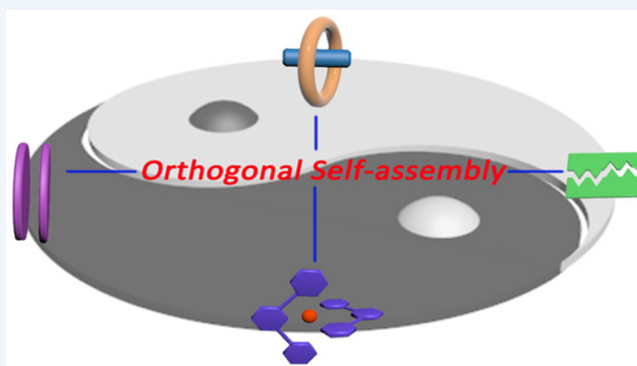
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CONSPECTUS: Supramolecular complexes, including various low-molecular-mass structures and large molecular aggregates that are assembled by reversible and highly directional noncovalent interactions, have attracted more and more attention due to their fascinating and unconventional chemical and physical properties that are different from those of traditional architectures encountered by covalently linked backbones. Supramolecular complexes are by nature dynamic architectures considering the reversibility of noncovalent interactions by which small molecular monomers can assemble into specific architectures that are able to be repeatably reorganized through the assembly/disassembly processes under certain environmental factors such as temperature, concentration, and solvent conditions. The construction of

supramolecular complexes by orthogonal self-assembly with different types of highly specific, noninterfering interactions is currently attracting considerable interest since they not only can dynamically self-assemble, but also can be tuned by various external stimuli through addressing each type of noncovalent interaction separately. Therefore, these dynamic supramolecular complexes, especially with external responsiveness, represent the most outstanding candidates for the future development of functional and smart materials, and even mimic the assembling process of natural systems.

In this Account, we will summarize the recent advances of dynamic supramolecular complexes constructed by orthogonal self-assembly in solution in two sections: (1) Construction strategies for supramolecular complexes based on orthogonal self-assembly, whose dynamic behaviors with external responsiveness were not experimentally investigated but potentially existed due to the intrinsic reversibility of noncovalent bonds; (2) dynamic behaviors of multiresponsive supramolecular complexes, which were experimentally reported to exhibit reversible multi-responsiveness to external stimuli. Dynamic nature is one of intrinsic properties of supramolecular complexes constructed by self-assembly. Therefore, in the first section, we will describe the dynamic self-assembly in the construction of supramolecular complexes, but will focus on their external responsive dynamic behaviors in the second section. In addition, considering that an increasing number of supramolecular complexes constructed by biological building blocks through bio-orthogonal assembly as mimics of biological systems have been reported in recent years, in the second section we will also present some typical examples on such special dynamic biological supramolecular complexes. The final part of this Account is devoted to foreseeing the rapid development of dynamic supramolecular complexes toward applications in functional and smart materials and fundamental questions facing dynamic supramolecular complexes in the future.



1. INTRODUCTION

Supramolecular chemistry, defined as chemistry beyond the molecule,¹ is intrinsically a dynamic chemistry in view of the reversibility of noncovalent interactions which connect the molecular components into a supramolecular entity. The goal of supramolecular chemistry is to gain progressive control of the structural and dynamic features of architectures through self-organization in the development of highly complicated and adaptive chemical systems based on noncovalent interactions. As a result, chemists have explored different aspects of the field of supramolecular chemistry by applying noncovalent interactions for the construction of well-defined structures from simple molecules.

Noncovalent interactions endow molecular species with the ability to undergo similar dynamic exchange and reorganization processes by virtue of the reversible assembly/disassembly processes in specific conditions. Just as Lehn said “the third feature of supramolecular chemistry resides in its dynamic nature that was always implicit and operating in all processes investigated,”² supramolecular complexes intrinsically possess dynamic behaviors due to the intrinsic reversibility of noncovalent interactions applied for the construction of supramolecular backbones. The

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future development of successful dynamic complexes requires the precise control of the reversible self-assembly processes to generate adaptive smart materials.

In supramolecular systems, “orthogonal” was defined as “two (or more) non-covalent interactions occur without crosstalk”.³ Early in 1997, Reinhoudt reported the first divergent nanostructure assembled by two different types of compatible noncovalent interactions, in which the importance of the orthogonality between the metal–ligand coordination and hydrogen bonding was explicitly recognized.⁴ In recent years, the principles of orthogonality have been exploited in synthetic organic chemistry, coupling chemistry to obtain complicated polymers, supramolecular chemistry to elaborately fabricate well-defined supramolecular architectures, and biochemistry to label biomolecules in living cells.

In 2005, Hofmeier and Schubert presented the highlights of the polymeric architectures with the combination of orthogonal supramolecular interactions.⁵ Recently, we have published a tutorial review, where we summarized the reported supramolecular polymers constructed from the combination of multiple noncovalent binding interactions, mainly of two kinds, in the orthogonal way.⁶ In 2013, Schmittel and Zimmerman and their colleagues further emphasized the highly useful concept of orthogonality in organic chemistry, materials, and supramolecular chemistry.^{3,7} Since dynamic characteristics represent the most distinguishing features of supramolecular complexes and provide an extremely important key to realize the intelligent function of novel “smart materials”, we would like to present this Account herein to summarize the recent progress of dynamic supramolecular complexes that were orthogonally constructed by the combination of noncovalent interactions, and their emerging applications as “smart materials” are also briefly discussed. Since the combination of hydrophilic and hydrophobic interactions with other noncovalent interactions for the construction of dynamic supramolecular complexes has been reviewed recently,⁸ it will not be discussed in this Account.

2. CONSTRUCTION STRATEGIES FOR SUPRAMOLECULAR COMPLEXES BASED ON ORTHOGONAL SELF-ASSEMBLY

Noncovalent interactions can be different in type and strength, ranging from weak dipole–dipole interactions to strong metal–ligand coordination or ion–ion interactions, and they are widely involved in the binding interactions of building blocks for the construction of a number of supramolecular complexes. Among various supramolecular architectures, some of them are constructed by the same type of noncovalent interactions (homogeneous interactions), while others are formed by different types of such interactions (heterogeneous interactions). Orthogonal combination of these noncovalent binding interactions provides a very useful strategy for the construction of supramolecular complexes with interesting structures and functions. In this section, the construction strategies for supramolecular complexes based on orthogonal self-assembly will be summarized, whose dynamic nature with external responsiveness was not experimentally reported in literature but potentially existed due to the intrinsic reversibility of noncovalent bonds.

2.1. Supramolecular Self-Assembly Driven by Orthogonal Homogeneous Interactions

2.1.1. Metal–Ligand Coordination Interactions. Metal–ligand coordination is highly directional with high association

constant and reversible properties, which could be easily well-tuned by appropriate metal ions or ligands. For example, Schmittel and co-workers presented a bis-porphyrinic supramolecular rectangle via a double self-assembly algorithm based on two orthogonal metal–ligand coordination themes.⁹ Subsequently, they further developed a facile synthetic procedure in which the supramolecular double-porphyrin tweezer was further assembled into a dynamic five-component structure by four orthogonal metal–ligand coordination interactions.¹⁰ Recently, using a heterometallic coordination-driven hierarchical self-assembly strategy, a supramolecular polymer network was fabricated through a two-step self-assembly pathway,¹¹ where a linear supramolecular polymer **2** was initially constructed, and then its 1,2,3-triazole unit could efficiently coordinate with $\text{PdCl}_2(\text{PhCN})_2$, resulting in the formation of supramolecular polymer network **3** (Figure 1).

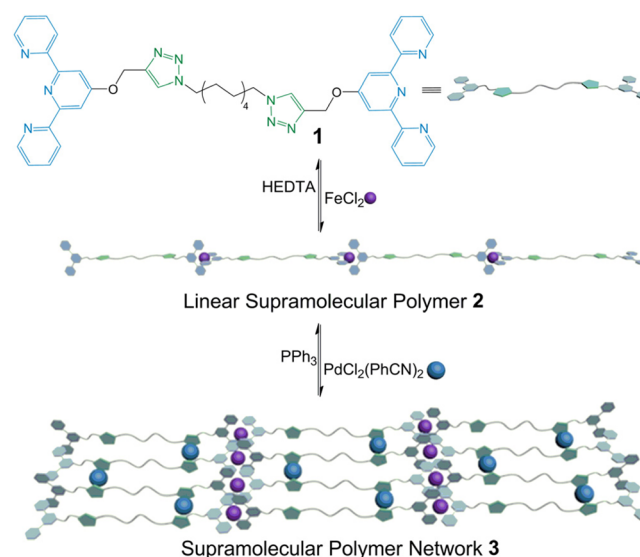


Figure 1. Representation of the hierarchical self-assembly of supramolecular polymer network from homoditopic monomer **1**. Reproduced with permission from ref 11. Copyright 2013 The Royal Society of Chemistry.

2.1.2. Host–Guest Recognitions. Host–guest recognition has been widely used as driving force to create a variety of self-assembled supramolecular structures. Based on the self-sorting organization of two kinds of crown-ether-based host–guest interactions, Huang and co-workers elaborately designed two heteroditopic crown-ether-based monomers **4** and **5**, by which a supramolecular alternating copolymer **6** was constructed through an orthogonal self-assembling process (Figure 2).¹² In this alternating copolymer, two types of heteroditopic crown-



Figure 2. Formation of supramolecular alternating copolymers from self-sorting organization of heteroditopic monomers.

ether-based monomers were alternatively linked due to their different binding constants. Subsequently, they also successfully introduced this strategy to construct a linear main-chain pseudopolyrotaxane based on two orthogonal host–guest interactions, which represents a more effective method for the construction of polypseudorotaxanes.¹³

2.1.3. Hydrogen Bonding Interactions. Hydrogen bonds are very attractive for their directionality and the possibility to tune the dynamics, and they have been proven to be especially suitable as noncovalent interactions for supramolecular assembly. As an elaborate work for investigating the stepwise and one-pot orthogonal self-assembly of complementary hydrogen-bonding motifs, Weck et al. utilized three different covalent polymer blocks to construct a supramolecular ABC triblock copolymer by linking each block with the Hamilton receptor cyanuric acid (CA) and 2,7-diamido-1,8-naphthyridine (DAN)-ureidoguanosine (UG), which was based on two distinct and orthogonal hydrogen-bonding receptor pairs (Figure 3).¹⁴ Such

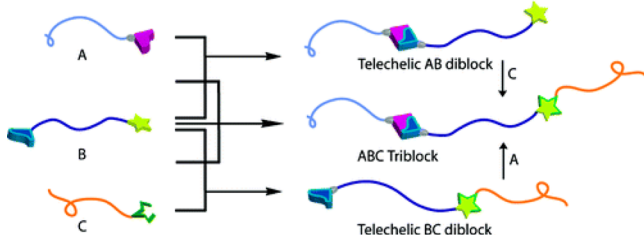


Figure 3. Schematic representation of a library of AB, BC, and ABC block copolymers from mono- and heterotelechelic polymers. Reproduced with permission from ref 14. Copyright 2010 American Chemical Society.

heterotelechelic polymer of the ABC copolymer possessing two different hydrogen-bonding units at the chain-ends is a useful

building block for the construction of higher order supramolecular copolymers with novel architectures.

2.2. Supramolecular Self-Assembly Driven by Orthogonal Heterogeneous Interactions

The introduction of different types of highly specific, non-interfering noncovalent interactions into one supramolecular system is currently attracting more considerable interest than homogeneous interactions, because such a system based on the different characteristics of interactions can be better tuned by different external stimuli through addressing the target interaction separately.

2.2.1. Hydrogen Bonding and Host–Guest Interactions. Well-defined artificial supramolecular heterodimers with unique pseudo[2]rotaxane structures were prepared in orthogonal fashion based on the intermolecular quadruple hydrogen-bonding and host–guest interactions in 2003.¹⁵ Recently, we designed and synthesized two heteroditopic monomers: one is a ureidopyrimidinone (UPy) based monomer with paraquat moiety (M1), and the other is a UPy-based monomer with crown ether moiety (N1). They were exploited to construct supramolecular aggregates by UPy dimerization and crown-ether–paraquat recognition (Figure 4).¹⁶ Furthermore, we developed crown-ether–paraquat supramolecular polypseudorotaxane networks with the hydrogen bonded linear supramolecular polymer as the polymeric framework as well as crown-ether–paraquat motif as a cross-linker.¹⁷

Then to follow this idea, we obtained a novel type of supramolecular aggregates bearing pillararene moieties.¹⁸ In this system, we introduced one UPy group into two rims of pillar[5]arenes, respectively, and found that such a bifunctional UPy pillar[5]arene with the addition of appropriate diamine guests could form a linear supramolecular polypseudorotaxane at high concentration based on the orthogonal quadruple hydrogen bonding and pillararene-based host–guest interactions. Sub-

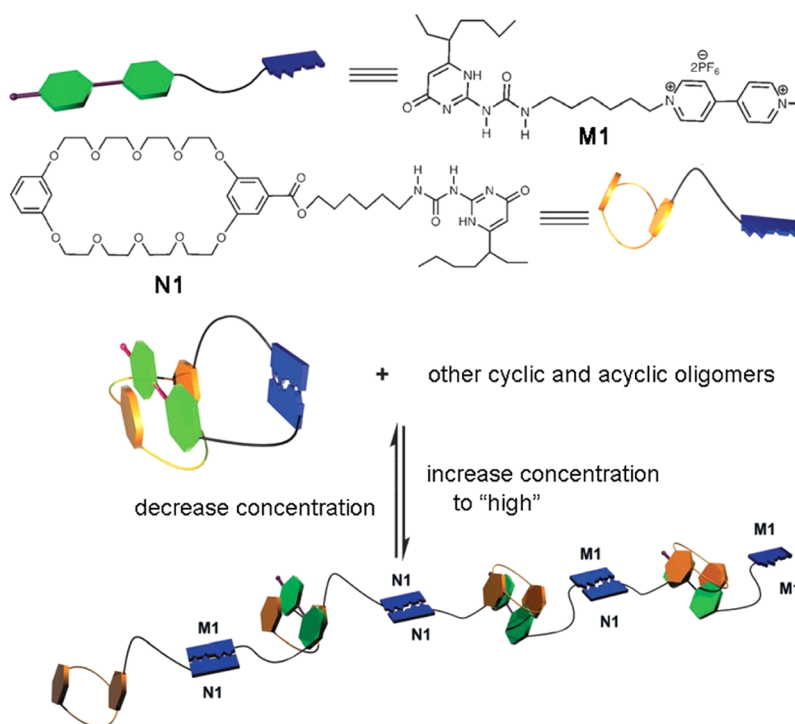


Figure 4. Graphical representation of the construction of supramolecular polymers from monomers M1 and N1.

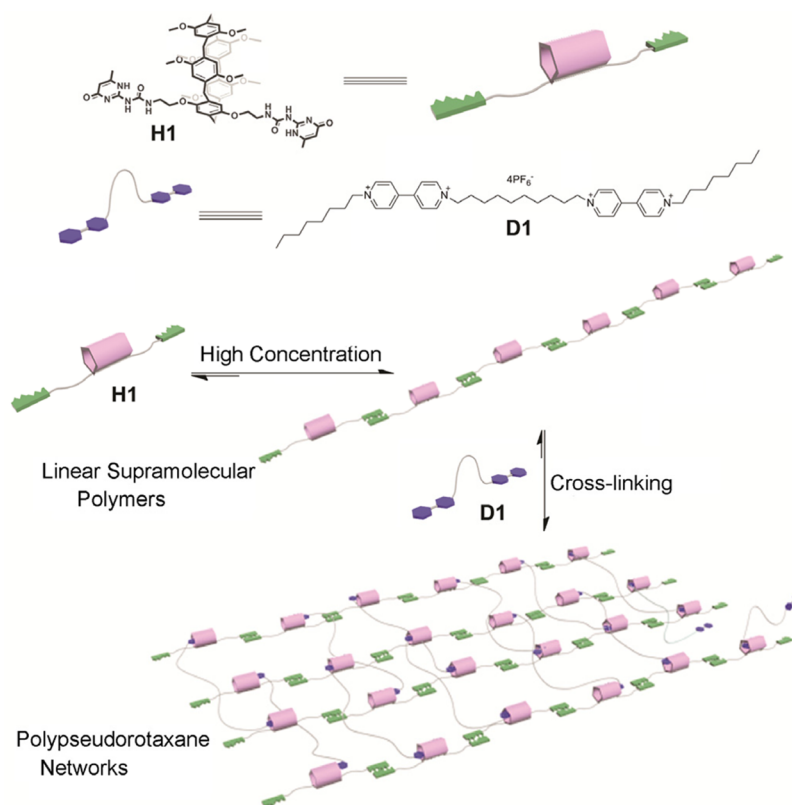


Figure 5. Graphical representation of the construction of a polypseudorotaxane network from monomer **H1** and cross-linker **D1**.

sequently, we developed more complicated linear pillararene-based supramolecular aggregates, where a bisparaquat guest and a mono-UPy modified pillar[5]arene (UPyP5) host were exploited.¹⁹

Very recently, continuously following the above work and with the idea that bisparaquat derivative (**D1**) as an appropriate guest can form a [3]pseudorotaxane with two molecules of bifunctional UPy pillar[5]arene (**H1**), we have fabricated pillar[5]arene-based supramolecular polypseudorotaxane networks, where linear quadruple hydrogen bonded supramolecular polymer backbones formed from **H1** bound with bisparaquat derivatives by the paraquat moiety threading into the cavity of the pillar[5]arene units (Figure 5).²⁰ Transmission electron microscopy observation showed that such supramolecular networks could further assemble to much bigger spherical aggregates, affording specific and tunable properties to form a translucent film with the combination of PEG-2000 as the polymer matrix.

2.2.2. Hydrogen Bonding and Metal–Ligand Interactions. The main chain of linear supramolecular polymers constructed by hydrogen bonding and metal–ligand interactions was first established by Schubert and co-workers,²¹ in which UPy unit and terpyridine (tpy) moieties were introduced to the two ends of a short spacer, respectively, and the resulting monomer with two binding sites could orthogonally self-organize into linear polymers with the addition of metal ions. Subsequently, to improve the poor solubility of the above system, they further developed telechelic polymers bearing both a tpy-ligand and a UPy motif at the ends of a variable-length chain.²² Recently, self-assembled molecular squares and triangles have been obtained via the combination of hydrogen bonding (UPy dimers) and metal–ligand coordination (Pd-pyridine).²³ More recently, an efficient method for the preparation of dendronized

organoplatinum(II) metallacyclic polymers was developed in orthogonal fashion through hierarchical self-assembly. In the first step, the rhomboidal metallodendrimers with pendant UPy groups at their vertices were obtained driven by metal–ligand coordination, and in the second step, supramolecular polymerization of these discrete metallodendrimers through intermolecular UPy H-bonding produced the target dendronized organo-Pt(II) metallacyclic polymers, which possessed the structural features of conventional dendronized polymers as well as the dynamic reversibility of supramolecular polymers.²⁴

2.2.3. Host–Guest and Metal–Ligand Interactions. Based on the combination of orthogonal host–guest and metal–ligand interactions, Huang and co-workers constructed cross-linked supramolecular polymer networks from heteroditopic monomers, which consisted of 1,2,3-triazole groups between the cryptand host and complementary paraquat guest.²⁵ Recently, cucurbit[8]uril-based supramolecular polymers have been fabricated in aqueous solution by employing cucurbit[8]uril-based host–guest interaction and terpyridine-Fe coordination as the driving force.²⁶ In this system, the rigid and bulky terpyridine-Fe linker could not only effectively suppress cyclization, thereby facilitating supramolecular polymerization, but also enable the monomer to become soluble in water.

2.2.4. Hydrogen Bonding with π – π Stacking Interactions. Hydrogen bonds with π – π stacking interactions are also applied for the construction of supramolecular architectures. For example, cross-linked polymeric materials based on self-assembly of benzene-1,3,5-tricarboxamide (BTA) and UPy motifs were prepared through the orthogonal quadruple hydrogen bonding and π – π stacking interactions.²⁷ This study was a prime example to demonstrate that utilizing the orthogonal blends as a supramolecular compatibilizer could greatly improve the bulk material properties. Recently, as a framework for

discussing the pathway complexity in orthogonal supramolecular polymerization, Meijer and co-workers for the first time reported the time-resolved observations of the formation of supramolecular assemblies with opposite helicity from π -conjugated oligomers via quadruple hydrogen bonding and π - π stacking interactions.²⁸ They further used a supramolecular chiral auxiliary to fully control the chirality in one-dimensional self-assembled stacks of achiral oligo(*p*-phenylenevinylene) ureido-triazine (AOPV3) monomers (Figure 6),²⁹ which represents a new tool to create helical one-dimensional self-assembled systems.

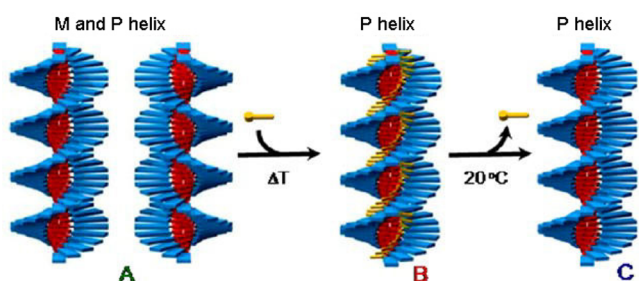


Figure 6. Schematic representation of the asymmetric synthesis of AOPV stacks having a *P*-helicity using a supramolecular chiral auxiliary approach. Reproduced with permission from ref 29. Copyright 2012 American Chemical Society.

3. DYNAMIC BEHAVIORS OF MULTIRESPONSIVE SUPRAMOLECULAR COMPLEXES

The most obvious benefits of noncovalent interactions for the construction of supramolecular complexes are their dynamic

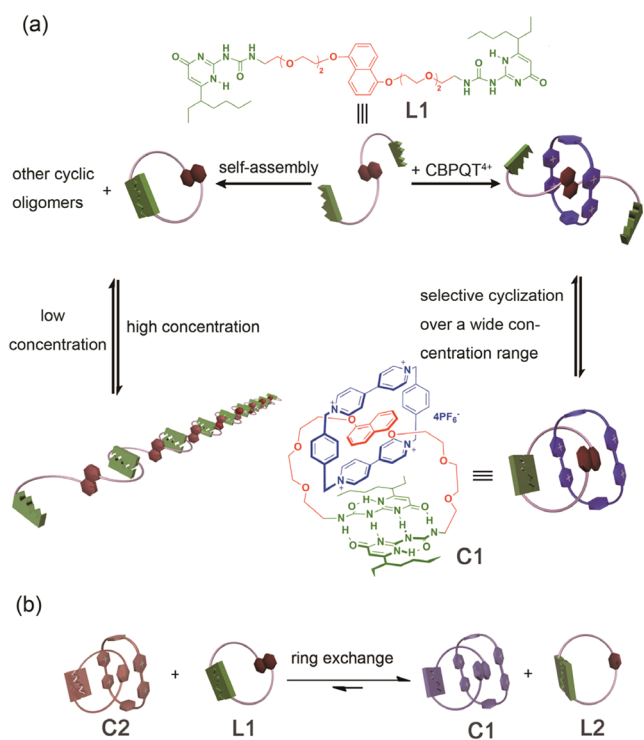


Figure 7. Graphical representation of the formation of the dynamic [2]catenane by the selective cyclization of the supramolecular polymer based on the UPy motif.

nature, which makes them possible to show reversible responsiveness to external factors such as temperature, concentration, pH value, and polarity of the medium. Therefore, it is highly desirable to demonstrate the dynamic behaviors of supramolecular complexes with multiresponsiveness, which is also the source of the considerable current interest in the development of adaptive smart materials. In this section, the dynamic behaviors of supramolecular complexes constructed by orthogonal self-assembly will be summarized, which were experimentally investigated with multiresponsive properties in literature and could be potentially applied for the development of smart supramolecular materials in future.

3.1. Dynamic Catenanes Driven by Orthogonal Self-Assembly

As mentioned in the section 2, employing the orthogonal quadruple hydrogen bonding and host–guest interactions, we have fabricated various simple or complicated supramolecular complexes that possess implicit dynamic behaviors with external responsiveness. Therefore, to further develop supramolecular complexes constructed by orthogonal interactions, especially experimentally proven to exhibit dynamic responsiveness, we achieved a novel type of dynamic [2]catenane, interlocked by the quadruple hydrogen bonding UPy motif,³⁰ where a bifunctional UPy compound (L1) bridged by 1,5-dioxynaphthalene (DNP) unit was designed as a monomer (Figure 7). This monomer proceeded a concentration-dependent ring-opening polymerization to linear supramolecular polymers, and with the addition of cyclobis(paraquat-*p*-phenylene) cyclophane (CBPQT⁴⁺), a dynamic donor–acceptor dynamic [2]catenane (C1) interlocked by quadruple hydrogen bonding interactions could be obtained selectively. Moreover, the dynamic properties of the [2]catenane were further demonstrated through a ring-exchange experiment based on the different strength of host–guest interactions within C1 and C2, another different [2]catenane which was composed of CBPQT⁴⁺ and a hydroquinone (HQ)-containing compound L2. This is the first example of noncovalent bonded catenane interlocked by quadruple hydrogen bonding interactions instead of metal–ligand interactions, especially with dynamic ring-exchange property.

Recently, driven by orthogonal pillar[5]arene-based and crown-ether-based molecular recognitions, Huang and coworkers presented a novel kind of self-assembled dynamic [1]catenane with pH responsiveness using a threading-followed-by-complexation methodology.³¹ They first synthesized a copillar[5]arene bearing two benzo-18-crown-6 (B18C6) units, which could recognize 1,8-diaminooctane to form a [2]pseudorotaxane based on pillararene-based host–guest interactions. And then acidification of the diamine guest led to the formation of B18C6-based host–guest complex, generating a dynamic [1]catenane, which could be tuned reversibly by changing the solution pH, providing a simple molecular on–off switch.

3.2. Dynamic Supramolecular Polymers with Multiresponsive Properties

3.2.1. Dynamic Linear Supramolecular Polymers.

Inspired by our previous work on supramolecular polypseudorotaxanes with alkyl diamine as the axle,²³ we designed a diamine guest using the strategy of “diamine threading followed by end-capping with UPy units” to achieve solvent-responsive dynamic supramolecular polyrotaxanes (Figure 8).³² The resulting dynamic polyrotaxanes constructed from pillar[5]arenes (7) as wheels and diamines (8 or 8′) as axles were interlocked by orthogonal quadruple hydrogen bonding and pillararene-based

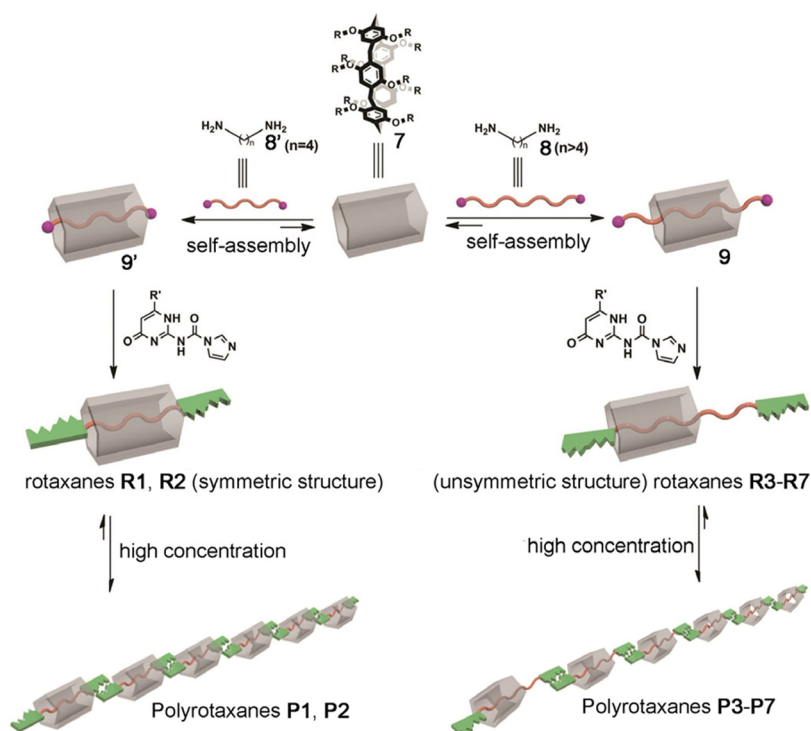


Figure 8. Graphical representation of the construction of dynamic polyrotaxanes.

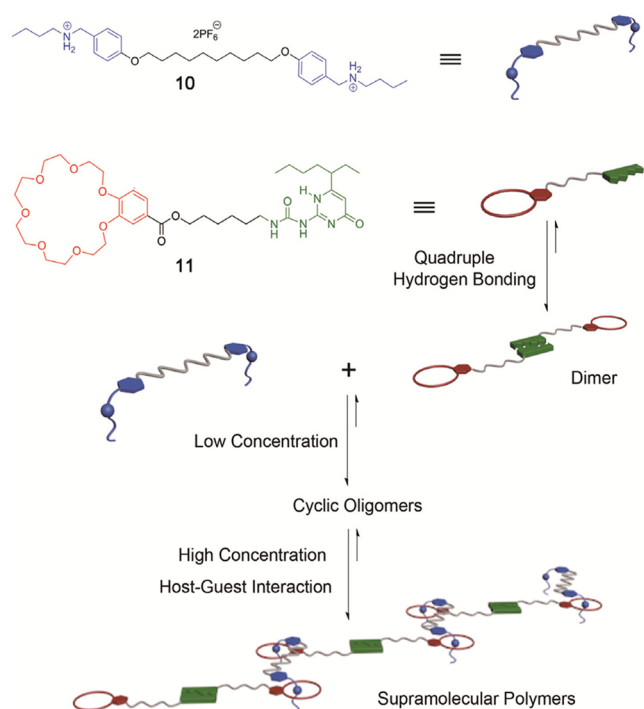


Figure 9. Graphical representation of the supramolecular polymers constructed from monomers 10 and 11 by orthogonal self-assembly.

host–guest interactions, in which the UPy motifs played a dual role, acting not only as a large end-capping group but also as a reversible linker to control the structure of the dynamic supramolecular polyrotaxanes. Consequently, the reversibility of main-chain backbones and the sliding process of the axle were achieved by changing the polarity of the solvent.

We further explored the fabrication of metal-ion-responsive dynamic linear supramolecular polymers constructed by orthogonal hydrogen bonding and crown-ether-based host–guest interactions.³³ We designed and synthesized two homoditopic monomers: **10** containing two symmetrical dialkylammonium groups and **11** bearing one B21C7 moiety and one UPy unit. As shown in Figure 9, linear supramolecular polymers were achieved, in which a supramolecular dimer from **11** was initially obtained followed by polymerization upon addition of **10**. The disassembly/assembly of supramolecular polymers could be reversibly switched by addition/removal of K^+ without interfering with UPy dimerization due to the stronger binding of K^+ with B21C7 moiety than dialkylammonium moiety.

Similar to the above example of using K^+ as a metal competitive guest, organic molecules have also been used as competitive guests in dynamic host–guest chemistry. Recently, novel supramolecular ternary linear polymers mediated by two different macrocyclic molecules cucurbit[8]uril (CB[8]) and β -cyclodextrin (β -CD) with competitive-guest responsiveness were constructed by using two orthogonal host–guest interactions, and their self-assembly process could be controlled by adding a competitive guest which was able to expel both viologen moiety and naphthol group from the cavity of CB[8], leading to the disassembly of such linear supramolecular polymer.³⁴

Recently, Stoddart and Bruns elaborately fabricated pH-switchable bistable [c2]daisy chains based on orthogonal host–guest interaction and terpyridine–Fe coordination.³⁵ Interestingly, these bistable [c2]daisy chains showed musclelike mechanical actuation by varying the pH value, which could amplify individual nanometric displacements (1 nm) up to the micrometer-length scale (6 μ m) when largely integrated into a microscopic polymer (Figure 10). Moreover, Sessler and co-workers synthesized a new flexible tetracationic macrocycle

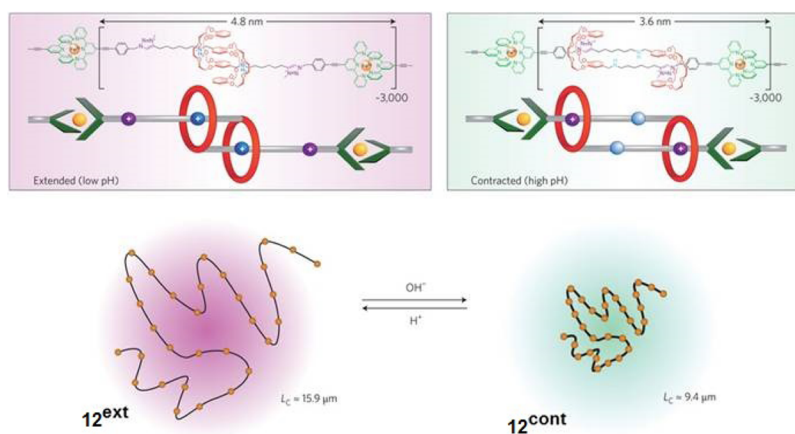


Figure 10. Amplification of muscle-like mechanical actuation within a [c2]daisy chain polymer **12**. Reproduced with permission from ref 35. Copyright 2013 Macmillan Publishers Limited.

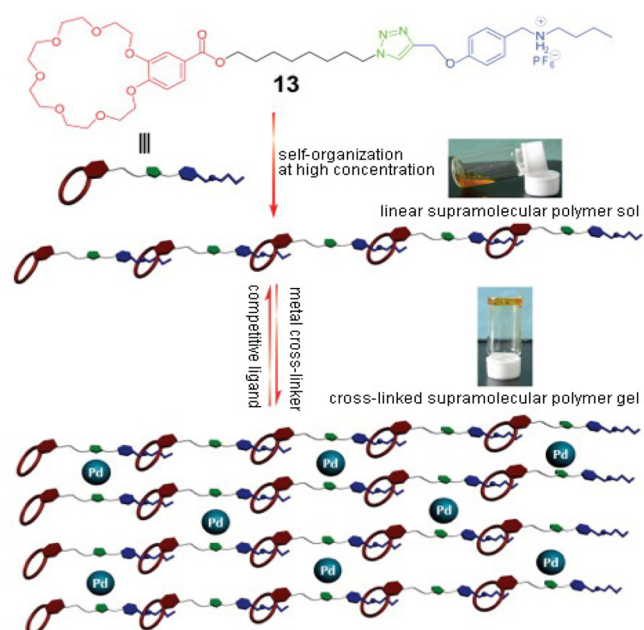


Figure 11. Schematic representation of controlling the topology and rheology of the supramolecular polymer prepared from heteroditopic monomer **13**.

named as “Texas-sized” molecular box, which could form a concentration- and temperature-responsive anion-induced supramolecular necklace with monoterphthalate anions based on hydrogen bonds and possible anion- π interactions.³⁶

A photoresponsive linear β -CD-based polypseudorotaxane was achieved by orthogonal self-assembly of azobenzene- β -CD host-guest interaction cooperating with the Pd-N metal-ligand coordination.³⁷ The assembly/disassembly behavior of its main chain with photoisomerization induced by azobenzene motifs was demonstrated using the specific viscosity measurement.

3.2.2. Dynamic Supramolecular Polymer Networks.

Huang and co-workers constructed a novel quadruple-responsive (pH-, metallo-, thermo-, and cation-responsive), shape-persistent, and elastic supramolecular polymer network gel, which was constructed by the orthogonal host-guest and metal-ligand interactions, introducing dynamic and smart properties into the supramolecular polymers.³⁸ The polymer network gel was

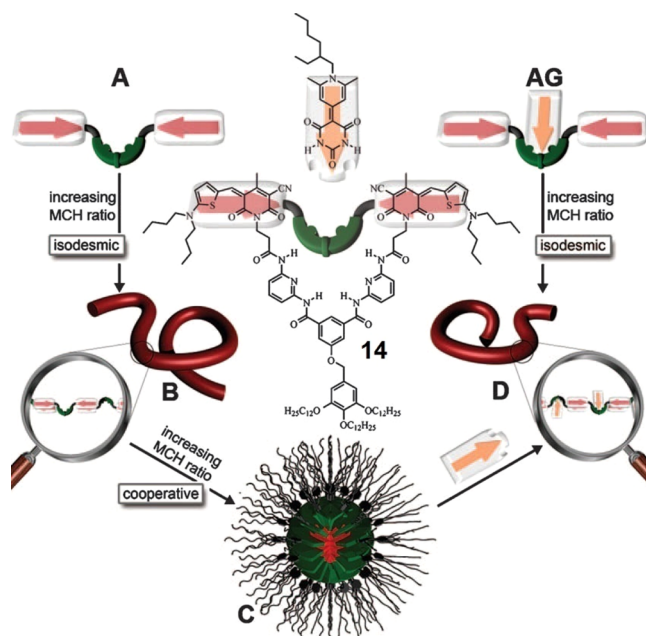


Figure 12. Schematic representation of the solvent- and guest-dependent self-assembly of Hamilton receptor tethered bis-merocyanine dyes **14**. Reproduced with permission from ref 40. Copyright 2010 Wiley Publishers.

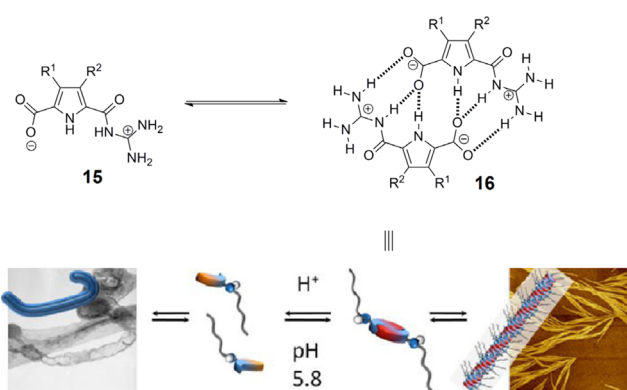


Figure 13. Switching the morphology of aggregates of zwitterion by reversible protonation and deprotonation. Reproduced with permission from ref 42. Copyright 2013 American Chemical Society.

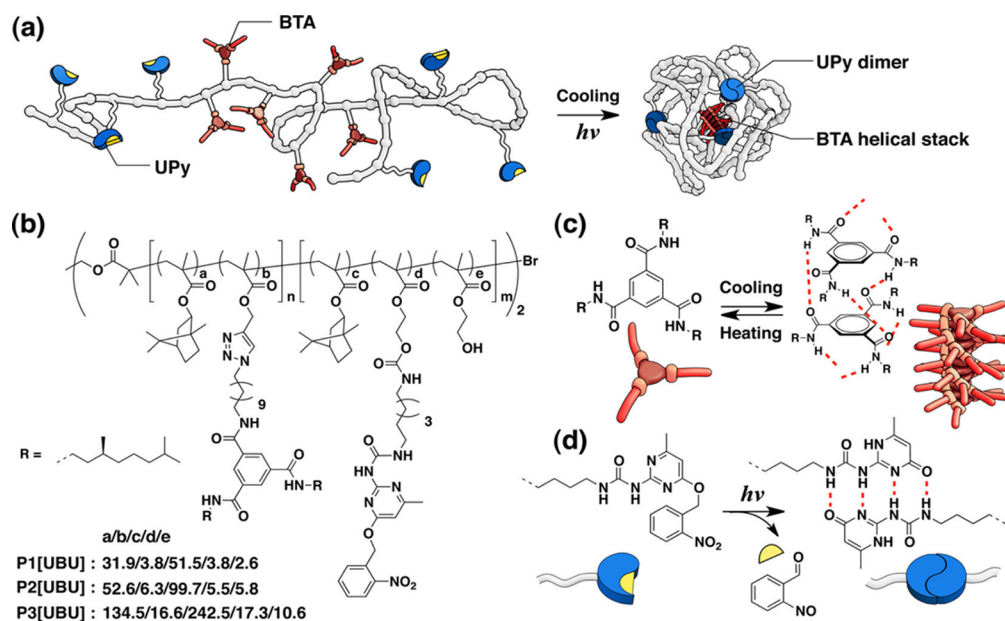


Figure 14. Schematic representation of orthogonal self-assembly in folding block copolymers. Reproduced with permission from ref 43. Copyright 2013 American Chemical Society.

formed by the combination of a heteroditopic monomer **13** with bridging ligand (1,2,3-triazole group) and the metallic cross-linker $[\text{PdCl}_2(\text{PhCN})_2]$ that could bind the 1,2,3-triazole motif, allowing a transition from linear supramolecular polymer to the cross-linked networks and resulting in the gelation (Figure 11). Multiresponsive properties as well as excellent mechanical properties were both realized in this supramolecular system, making it an ideal candidate of intelligent soft material.

Recently, Weng and co-workers have also reported the construction of multiresponsive supramolecular network gel systems constructed via orthogonal Eu–N metal–ligand coordination and hydrogen bonding interaction.³⁹ In particular, different gels showed different chemoresponsive properties based on the chemical stimulation test by using various chemicals with different polarity, pH, and chelating properties.

3.2.3. Highly Complicated Supramolecular Aggregates. For the construction of highly complicated supramolecular aggregates, Hamilton receptor tethered bis-(merocyanine) dye **14** that is responsive to solvent, concentration, and guest molecules was demonstrated to be a successful example to fabricate solvent- and guest-responsive supramolecular aggregates based on orthogonal hydrogen bonding and dipolar interactions.⁴⁰ As triggered by solvent polarity or concentration, different self-assembled species, such as oligomers, polymers, and inverted micelles, could be observed (Figure 12). Moreover, this system was also highly responsive toward the addition of guest molecules such as merocyanine, resulting in the transformation of the inverted micelles to more intricate supramolecular polymers.

Switchable supramolecular polymers from monomer to dimer, to linear polymer, and to large spherical aggregate, based on the self-assembly of a small ditopic monomer with orthogonal metal–ligand and ion pair interactions, have been disclosed by Schmuck and co-workers.⁴¹ Recently, they further realized reversible switching back and forth between different nanostructures based on the hierarchical assembly of zwitterions **15** upon external stimuli.⁴² Self-complementary zwitterions **15** bearing a sec-amide group at 3-position of the pyrrole could initially and

hierarchically aggregate into planar dimers **16** driven by hydrogen bonding in polar solution, which then further assembled into rigid nanofibers or flat sheets based on the hydrogen bond assisted π – π interactions. In addition, with a pH switch, the zwitterions were converted into typical cationic amphiphiles and the original rodlike aggregates could be completely changed to vesicles, tubes, and flat sheets (Figure 13).

To go further and target more sophisticated dynamic structures, it also appears of importance to implement dynamic reorganization in nanostructured materials. For example, ABA-type triblock copolymers that contained two complementary association motifs could dynamically fold into single-chain polymeric nanoparticles (SCPNS) via orthogonal self-assembly stimulated by thermal- and photo-responsive treatment.⁴³ Such triblock copolymers incorporated two distinct motifs: *o*-nitrobenzyl-protected UPy moieties and benzene-1,3,5-tricarboxamide (BTA) units in a single chain (Figure 14). The use of a photocleavable protecting group on the UPy moiety and a thermal-responsive BTA unit allowed single-chain folding of the polymer based on noninterfering mutual recognition, affording nanometer-sized particles under thermal/photocrosslinking treatment. Such well-defined and stimuli-responsive single-chain nanoparticles not only provide a rational design approach for mimicking the α -helix and β -sheet in proteins, but also show the widespread applicability of orthogonal self-assembly for the development of natural system mimics.

3.3. Dynamic Biological Supramolecular Complexes by Orthogonal Assembly

In recent years, many examples of artificial self-assembling systems have been designed and synthesized to achieve biological supramolecular complexes because of their biocompatibility, biodegradability, defined morphology, and especially excellent dynamic properties. For example, an artificial chemical-responsive self-assembling system composed of single protein building block has been developed by Hayashi et al.⁴⁴ It was formed by a myoglobin-based self-assembly system, where cross-linking of linear fibers of myoglobin was initiated upon addition of H_2O_2 , leading to the formation of a large water-soluble

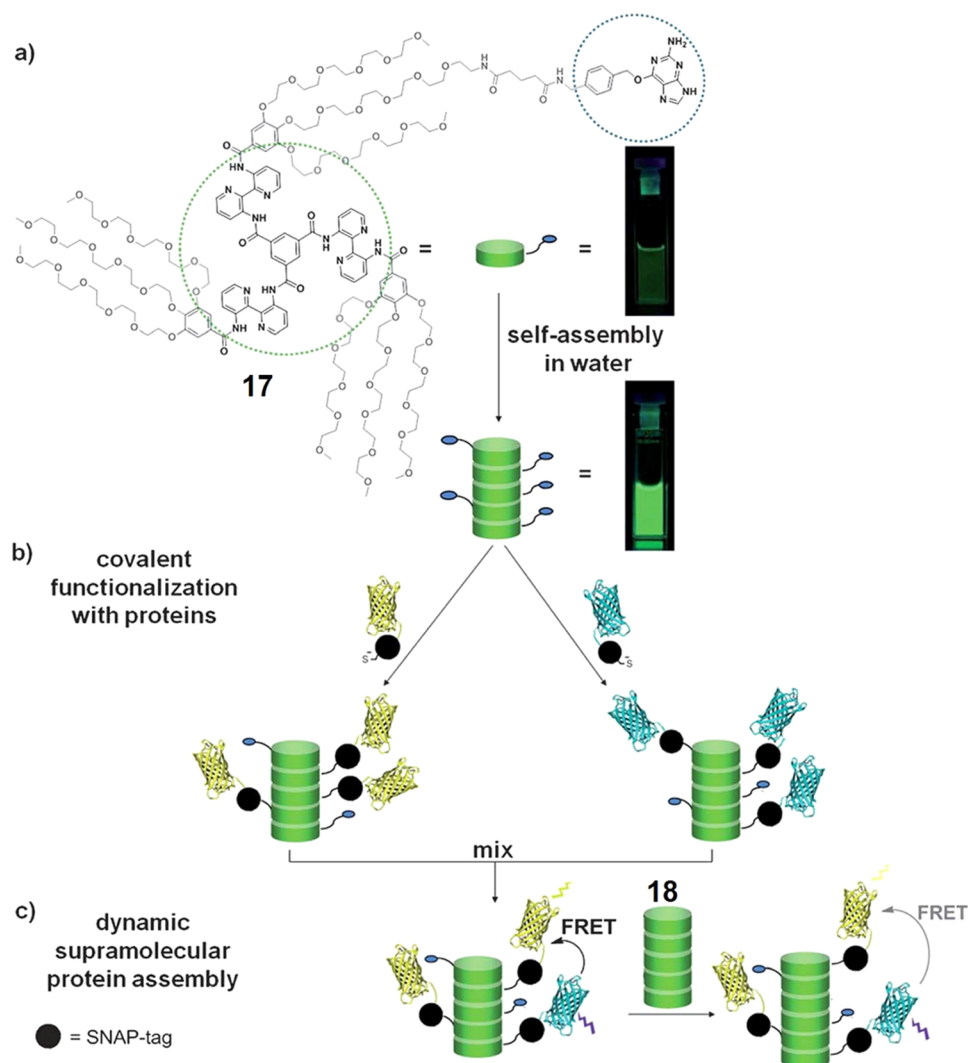


Figure 15. Schematic representation of dynamic and bio-orthogonal protein assembly along a supramolecular polymer. Reproduced with permission from ref 46. Copyright 2013 The Royal Society of Chemistry.

myoglobin cluster. Subsequently, to create dynamic alternating one-dimensional heterotropic protein assembly, they further constructed a size-controllable protein copolymer which could be adjusted by varying the ratio of monomer or by changing the concentration of building blocks. They first synthesized a heme-bis(biotin) conjugate bearing a high-affinity appendage for each of the proteins, and then it could tightly associate with homotetrameric streptavidin (SAv) and myoglobin (Mb), resulting in the formation of alternating alignment through different recognition sites.⁴⁵ It is noteworthy that the physiological function of the heme cofactor was substantially retained in the supramolecular copolymer.

To develop biological supramolecular complexes with dynamic properties that can mimic the natural protein assemblies, Brunsveld and co-workers successfully achieved dynamic protein assembly along with supramolecular columnar polymers through the site-specific covalent attachment of two types of fluorescent proteins to self-assembled benzylguanine-functionalized discotic molecule **17** (Figure 15).⁴⁶ The adaptable nature of this protein-conjugated discotic molecule was confirmed by tuning the protein density or by dynamic intermixing test, which could easily be followed in real time using FRET experiments (Figure 15c), resulting in the formation

of heterofunctionalized supramolecular protein-conjugated polymers. From a biological point of view, this type of system offers an access to mimic the self-regulative natural protein assemblies, since the intrinsic dynamic nature of the supramolecular polymer allows the fluorescent proteins to get together, leading to self-optimization of protein arrangement.

4. CONCLUSION

Self-assembly in supramolecular chemistry has been developed as one of the most important fields in modern research, and particularly, supramolecular complexes constructed by orthogonal self-assembly exhibiting reversible dynamic properties are in the focus, because such supramolecular architectures may find new applications as smart functional materials. Compared with living systems, dynamic chemical self-assembly is still in its infancy; therefore, fabrication of synthetic dynamic supramolecular complexes by orthogonal self-assembly is not only a powerful tool for chemists to understand and mimic the sophisticated and functional natural systems but also a necessary way to create smart materials ranging from environmental sustainability to informational technology. In this Account, we summarized the line of research of dynamic self-assembly of supramolecular complexes of the solution phase with implicit

external responsiveness driven by orthogonal homogeneous to heterogeneous noncovalent interactions, simple supramolecular complexes to complicated ones with multiresponsive dynamic behaviors, and dynamic biological supramolecular complexes.

In decades, many efforts have been made to develop responsive functional supramolecular materials incorporating of more types of noninterfering noncovalent interactions, and we can imagine that the adaptive properties of supramolecular complexes can be advanced to an extraordinary state based on the different noncovalent interactions integrated. Interestingly, the concept of orthogonal self-assembly could also be extended to the interactions between self-assembled macro-level objects, mimicking the complexity and functionality of natural systems.⁴⁷ All of them suggested a very bright future for the field of supramolecular chemistry. Although much has already been achieved, we as yet only begin to understand how to design suitable structures and how to control the assembly process. Therefore, we should not forget that some basic challenges still remain to be understood. One challenge is how to control the orthogonal self-assembling process, which is a spontaneous and fundamental process leading to the formation of well-defined supramolecular architectures but could also be controllable. In this regard, with our increasing understanding of the self-assembly processes, there is still enough room for us to stretch out and finally achieve complete direction and control of the self-assembling process. The second challenge is how to narrow the gap between dynamic supramolecular complexes and real functional materials, which is also the ultimate goal of supramolecular chemistry. Therefore, much more efforts are still necessary to find more connections between interactions in real systems and orthogonal dynamic interactions. The third challenge lies on how to finely mimic the complexity and functionality of natural systems using dynamic artificial self-assembling systems, and then finely tune their biological functions. At this point, theoretical simulation should be closely integrated with experimental studies to establish the functional emulation of living systems. We should also not forget that the field of supramolecular chemistry is still in its infancy period, and we are still far away from the ultimate goal. Further research on orthogonal self-assembly remains a challenging field that is needed to sufficiently unlock our full potential.

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Notes

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