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Molecular Nanoparticles Are Unique Elements for Macromolecular Science: From "Nanoatoms" to Giant Molecules

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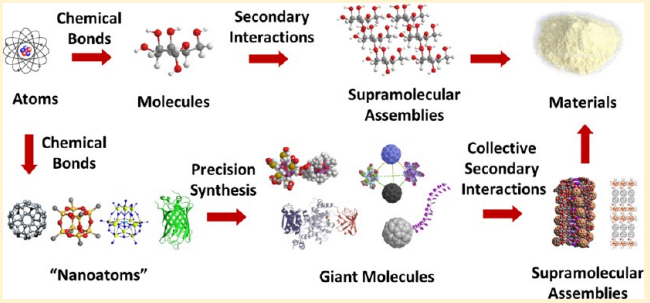
ABSTRACT: In this Perspective, we present a unique approach to the design and synthesis of giant molecules based on "nanoatoms" for engineering structures across multiple length scales and controlling their macroscopic properties. Herein, "nanoatoms" refer to shape-persistent molecular nanoparticles (MNPs) with precisely defined chemical structures and surface functionalities that can serve as elemental building blocks for the precision synthesis of giant molecules by methods such as sequential "click" approach. Typical "nanoatoms" include those MNPs based on fullerenes, polyhedral oligomeric silsesquioxanes, polyoxometalates, and folded globular proteins. The resulting giant molecules are precisely defined macromolecules. They include, but are not limited to, giant surfactants, giant shape amphiphiles, and giant polyhedra. Giant surfactants are polymer tail-tethered "nanoatoms" where the two components have drastic chemical differences to impart amphiphilicity. Giant shape amphiphiles not only are built up by covalently bonded MNPs of distinct shapes where the self-assembly is driven by chemical interactions but also are largely influenced by the packing constraints of each individual shape. Giant polyhedra are either made of a large MNP or by deliberately placing "nanoatoms" at the vertices of a polyhedron. In general, giant molecules capture the essential structural features of their small-molecule counterparts in many ways but possess much larger sizes. They are recognized in certain cases as size-amplified versions of those counterparts, and often, they bridge the gap between small molecules and traditional macromolecules. Highly diverse, thermodynamically stable and metastable hierarchal structures are commonly observed in the bulk, thin film, and solution states of these giant molecules. Controlled structural variations by precision synthesis further reveal a remarkable sensitivity of their self-assembled structures to the primary chemical structures. Unconventional nanostructures can be obtained in confined environments or through directed self-assembly. All the results demonstrate that MNPs are unique elements for macromolecular science, providing a versatile platform for engineering nanostructures that are not only scientifically intriguing but also technologically relevant.



I. INTRODUCTION

"What would the properties of materials be if we could really arrange the atoms the way we want them?"

—Richard Feynman[1]

The past century has witnessed the rapid development of polymer science and engineering ever since Staudinger's macromolecular hypothesis.[2] Polymers have revolutionized many aspects of our society and are now almost ubiquitous in everyday life. Compared to natural polymers such as DNA and proteins, however, the potential of synthetic polymers is far from being fully realized. Feynman has raised a fundamental question in his famous quote: "what ... if we could really arrange the atoms the way we want them?"[1] The importance of hierarchical structure in dictating material properties is best demonstrated in proteins where proper folding precisely arranges the atoms of a linear polypeptide chain in the three-dimensional (3D) space to direct a specific function. Today, synthetic polymers consist mostly of repeating monomer units in linear, branched, or other architectures. Unlike proteins, their properties are more as a function of molecular weight (MW) and topology and less as a result of the controlled supramolecular structures across different length scales. To address Feynman's inquiry in the context of macromolecular science, precise syntheses of primary chemical structures and control over higher level supramolecular structures are prerequisites.

In polymer chemistry, although various living/controlled polymerization techniques are now routinely performed to prepare polymers with a high degree of homogeneity (in terms of polydispersity, tacticity, MW, topology, etc.), it remains a grand challenge to precisely control the sequences of individual monomer units with a definite size[3] and in a specific topology[4] to truly mimic the beautiful complexity of proteins. The development of organic chemistry in the past few decades has afforded powerful tool box containing a myriad of versatile chemical reactions. Its importance has been increasingly recognized by polymer chemists in the hope of building macromolecules with

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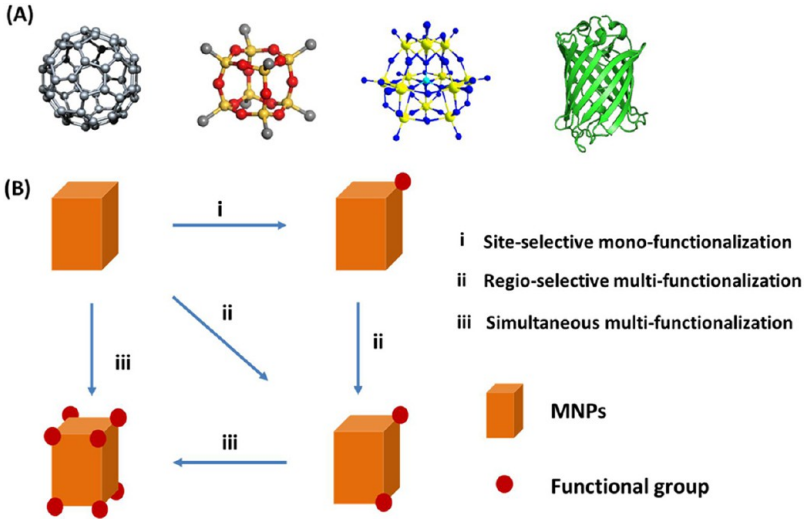

Figure 1. Typical molecular nanoparticles are shown in (A). From left to right, they are [60]fullerenes, T8 POSS, POMs, and a folded globular protein. The functionalization strategies for MNPs are shown in (B), which includes (i) site-selective monofunctionalization, (ii) regioselective multifunctionalization, and (iii) simultaneous multifunctionalization.

the same precision as in small molecules.[5] In polymer physics, although the thermodynamic and kinetic principles of macromolecular self-assembly have been largely understood, it is still nontrivial to design "*a priori*" a series of hierarchical structures and control the resulting morphologies and properties. In other words, simply placing monomers in a desired sequence, like in proteins, is not sufficient for achieving material-specific properties. Therefore, it is important that the principles of chemistry and physics are integrated in the ever-increasing sophistication of molecular design and development of new functional macromolecules. We are obligated to not only learn the design principles and practical techniques from nature but also go *beyond* nature to create new structures and functions.

Synthetically, the unique features of macromolecules (such as large size, a large number of functional groups, difficulty associated with purification, and a high degree of conformational freedom) have made precision macromolecular synthesis a great challenge.[6] One possible solution is to build macromolecules using precise molecular nanobuilding blocks. Among synthetic macromolecules, dendrimers are unique since they can be viewed as precise macromolecules.[7−9] Theoretically, they are regularly branched, monodisperse macromolecules with a cascade topology. Both the exterior functionality and the core composition can be precisely controlled. It has thus been proposed that dendrimers may be used as "quantized nanoelements" to prepare so-called "nanocompounds".[7,10] In fact, dendrons have been widely used as a self-assembling unit in polymers, as evidenced by numerous papers on dendron−polymer conjugates[11,12] and Janus dendrimers[13−15] in the literature. The dendrimers or dendrons in these conjugates usually adopt a flexible conformation as an expanded sphere in solution which collapses into a pancake-like conformation in the solid state upon solvent removal. In other words, most dendrimers/dendrons lack the ability to maintain a well-defined 3D shape, and their conformation and structure are highly dependent upon the environmental parameters. To qualify as "nanoelements", it would be advantageous if these motifs can possess relatively independent, well-defined 3D molecular structure and shape so that their further assembly in "nanocompounds" would be more predictable and robust. The control of primary chemical structures in complex macromolecules can then be realized by linking precisely defined subunits using "click" chemistry and other efficient chemical transformations, while the control of hierarchical structures can be facilitated by tuning the collective physical interactions between these relatively independent nanosized subunits.

Molecular nanoparticles (MNPs) are shape- and volume-persistent nano-objects with well-defined molecular structure and specific symmetry.[16] While MNPs have also been used to describe aggregated nanoparticles assembled from small molecules through noncovalent interactions,[17] the term "MNP" used in this Perspective refers only to those that are well-defined in chemical structure, MW, aggregation number, size, functionality, symmetry, etc. It also shares some similarity to molecular clusters[18−20] but is more general in scope. Because of the lack of precise structure, intramolecularly cross-linked single-chain polymer nanoparticles[21−24] are not discussed. Typical MNPs include folded globular proteins and cage-like compounds (Figure 1A). In folded proteins, the overall molecular shape and 3D conformation are held by the multiple secondary interactions between various residues of the polypeptide chain. Because of the dynamic feature of secondary interactions, folded proteins are only marginally more stable than unfolded proteins.[25] The folded structure may be further stabilized by covalent linkages such as disulfide bonds or isopeptide bonds.[26,27] The overall molecular shape of cage-like compounds can be held either by noncovalent bonds, as demonstrated in the "molecular flasks" reported by Fujita et al.[28,29] and the "tennis ball" reported by Rebek et al.[30] or by covalent bonds such as in polyhedral oligomeric silsesquioxane (POSS),[31] [60]fullerene (C_{60}),[32] and polyoxometalate (POM).[33−35] The collective secondary interactions from the functional groups on the periphery of MNPs constitute the driving force to further assemble MNPs into hierarchal structures. In addition, the overall molecular shape shall impose packing constraints to the self-assembly of MNPs, leading to a variety of unconventional structures and phase behaviors as predicted by computer simulation.[36,37]

Considering the availability of a large variety of MNPs with different sizes, symmetry, surface groups, and functions, they can be used as versatile nanobuilding blocks. In view of their incompressible and impenetrable features, we coin the word "nanoatoms" to describe MNPs. The term is reminiscent of

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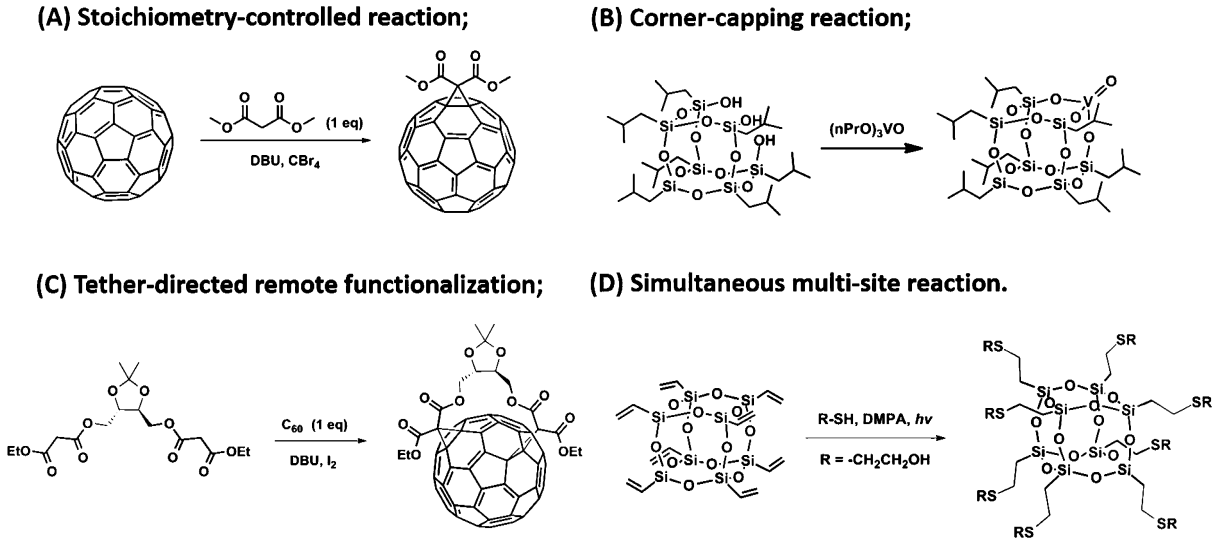

Figure 2. Exemplary MNP functionalization methods: (A) stoichiometry-controlled reaction;[54,55] (B) incomplete condensation followed by corner capping reaction;[65] (C) tether-directed remote functionalization;[70] and (D) simultaneous multisite reaction.[16]

"artificial atoms" that were often used to describe quantum dots[38] or even metal nanoparticles.[39,40] The term is also coincidently similar to the idea of "nanoscale atoms" proposed very recently by Nuckolls et al. in the context of solid-state chemistry, referring to pseudospherical molecular clusters as "atoms" in building up binary crystalline solids with unique electronic and magnetic properties.[41] Correspondingly, we use the words "giant molecules" to describe the *precisely defined* macromolecules made from MNP subunits or its conjugates with other molecular nanobuilding blocks including polymers and dendrimers. In the literature, the words "giant molecules" have been used interchangeably with "macromolecules"[42,43] or to describe structures with a huge number of atoms in general.[44−46] We try to distinguish it from traditional macromolecules in the sense that "giant molecules" can be viewed as large-sized analogues of small molecules with MNPs as the "nanoatom" building blocks. We emphasize that they are prototype monodisperse precise macromolecules. It is also different from "artificial molecules" or "nanocrystal molecules" based on "artificial atoms" that have been developed using methods such as cleaved edge overgrowth[47] or the polyvalent interactions of biological macromolecules.[48−51] In this Perspective, we propose that MNPs are unique and important elements for macromolecular science in building up precise giant molecules. We discuss the concept of "nanoatoms" and giant molecules by reviewing recent research progress in this direction and raising intriguing questions for future investigation.

II. TYPICAL MOLECULAR NANOPARTICLES AS "NANOATOMS"

Important features of MNPs are their well-defined molecular structure and the possibility to perform precise chemical modification. As is typical for molecules with explicit chemical structures, the overall shape and symmetry of MNPs are well-defined and can be maintained during chemical modification. Moreover, the exact number, identity, and position of the surface functional groups on MNPs can often be determined precisely and varied systematically. By contrast, the functional groups introduced onto the surface of most inorganic nanoparticles are usually randomly distributed over the surface area with an average number of functional groups. To prepare functional MNPs as building blocks, or "nanoatoms", for the construction of giant molecules, we need to control, in particular, the surface functional groups. Site-selective monofunctionalization, regioselective multifunctionalization, and simultaneous multisite functionalization are among the most common and important functionalization methods for MNPs (Figure 1B). Highly reactive groups, such as azide and alkyne, may be introduced to facilitate efficient, stoichiometric coupling of MNPs with other building blocks or to enable surface chemistry diversification from a common precursor. Below, we will briefly summarize several typical MNPs (Figure 1) and the ways to functionalize them as "nanoatoms" (Figure 2).

Fullerenes. Fullerenes are fascinating organic "nanoparticles". As a carbon allotrope, they consist solely of carbon atoms arranged in five- and six-member rings. C_{60}, often known as a buckyball, is the smallest stable fullerene and also the most abundant one, with a spherical shape and I_h symmetry. Other higher fullerenes typically have less symmetric shapes, such as C_{70} with a football-like shape. Fullerene chemistry has been thoroughly studied and documented.[52,53] The principles underlying their functionalization strategies shall be equally useful for other MNPs, too, although the detailed chemistry may be different. There are now numerous methods available to functionalize fullerene, such as the Bingel−Hirsch reaction,[54,55] the Prato reaction,[56] and azide addition,[57] just to name a few. Since there are a multitude of double bonds of similar reactivity on fullerene (30 on C_{60}), the reactions often lead to a mixture of unreacted fullerene and products with various degree of functionalization. Controlling reaction stoichiometry is thus a straightforward way to prepare the monoadduct. So far, there are only a few instances where the reaction effectively stops at monoadduct.[58] However, for highly symmetric C_{60}, there are still [5,6]- and [6,6]-isomers for monoadducts. The monoadducts of C_{70} even have regioisomers due to a lower symmetry.[59] The regioselectivity is important because the tethering location could be critical in determining the self-assembly behavior.

The regioselective multiaddition is certainly more complicated but has been well-established in C_{60} chemistry. Strategies like template-mediated multiaddition, topochemically controlled solid-state reaction, and tether-directed remote functionalization are often used to prepare regioselective and/or stereoselective

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multiadducts.[52] T_h-symmetrical hexakis-adducts and mixed hexakis-adducts of various symmetry may be prepared with functional groups on specific 3D locations.[60−62] For example, an alkyne-functionalized fullerene monoadduct (termed "fulleryne") has been used to efficiently couple fullerene with polymers;[63] sugars-coated fullerene derivatives have been reported with a diameter of ∼3 nm,[62] and carboxylic-acid-functionalized C_{60} derivatives have been used to afford amphiphilic MNP−polymer conjugates.[64] Nevertheless, the shortcomings of using fullerene as MNP scaffolds are mainly associated with difficulties to systematically vary the surface functionality. Often, one has to start from the beginning to prepare each individual fullerene derivative with different surface functional groups. In addition, the valuable electronic properties of fullerene are usually compromised to certain degree with increasing degree of functionalization.

Polyhedral Oligomeric Silsesquioxane (POSS). POSS is perhaps the smallest silica nanoparticle. With diameters of ∼1 nm, this family of cage compounds has a variety of sizes and symmetries, among which the cubic T8 cage is the most common one. POSS is usually prepared from the condensation of a silane or silanol precursor. A complete condensation will yield highly symmetric POSS cages, while an incomplete condensation will yield a precursor that can be later converted to heterofunctionalized POSS derivatives.[65] Many POSS derivatives prepared by these methods have been commercialized. However, the side groups on POSS are still limited to simple substituents such as isopropyl, isooctyl, cyclopentyl, phenyl, vinyl, perfluorinated alkyl, and chloropropyl groups. Side chains containing hydrogen-bonding moieties and bulky groups are often not compatible with the condensation method. To achieve selective surface functionalization on POSS, it is more practical to start from a precursor POSS cage with modifiable side groups, such as vinyl and phenyl groups. Selective monofunctionalization in this case is now mainly achieved by controlling stoichiometry followed by chromatography. For example, Feher et al.[66] have demonstrated the monohydroxylation of octavinylPOSS to prepare VPOSS-OH, a versatile intermediate. Recently, we showed that thiol−ene chemistry can be used with controlled stoichiometry to achieve monoaddition.[67] The functional groups that can be installed are not limited to hydroxyls. They also include carboxylic acids, dendrons, ferrocenes, sugar, etc.[67] Regioselective multifunctionalization of POSS presents an immense challenge. Laine and co-workers[68,69] have developed pioneering work in this direction, as shown in the attempts to prepare Janus silsesquioxanes and mixed silsesquioxanes; however, regioadducts are awfully difficult to separate. Future research on POSS may benefit from using strategies similar to those in fullerene chemistry, such as tether-directed remote functionalization,[70,71] to realize selective multifunctionalization.

One distinct advantage of the POSS system is the facile tuning of surface functional groups via simultaneous multisite functionalization. The commercially available octasilane-POSS can be transformed into various functional POSS derivatives in just one step by hydrosilylation.[72,73] Octaiodophenyl-POSS, which was prepared via iodination of octaphenyl-POSS, has been proposed as a "nearly perfect" nanobuilding block due to the high symmetry of the unit and the high reactivity of iodo groups.[74] Octa-azide-POSS, which has been prepared via condensation of chloropropylsilane followed by nucleophilic substitution, was used for further "click" modification.[73,75] Octavinyl-POSS has been used as a simple motif toward functional POSS cages using thiol−ene "click" chemistry,[76] a metal-catalyzed cross-coupling reaction,[74] or olefin metathesis.[77] Examples include sugars-coated POSS,[76] oligofluorene-functionalized POSS,[78] and other POSS-based shape amphiphiles.[79−82] POSS with an even denser number of vinyl groups has been prepared and suggested as a versatile precursor.[72] Efficient chemical transformations, such as the classical "click" chemistry reactions, are critical to both selective monofunctionalizations and simultaneous multifunctionalizations.

Polyoxometalates (POMs). POMs are a unique class of inorganic polyatomic ions with a large, closed 3D framework formed by transition metal oxyanions linked together by sharing oxygen atoms and other possible atoms.[18,33−35] POMs exhibit a remarkable diversity in size, structure, symmetry, and composition.[35] Commonly known ones are Lindqvist $[M_6O_{19}]^{n-}$ (isopolyoxometalate), α-Keggin $[XM_{12}O_{40}]^{n-}$, Dawson $[X_2M_{18}O_{62}]^{n-}$, and Anderson $[H_xXM_6O_{24}]^{n-}$ (heteropolyoxometalates). Covalent linkage with organic species allows the preparation of various hybrid materials based on POMs.[35,83,84] There are usually specific sites for functionalization on POMs, and both monofunctionalization and multifunctionalization have been demonstrated. The regioisomers may or may not be separated, depending on the type of POMs. In addition, the surface chemistry on POMs remains largely ionic. As a result, the counterion also plays an important role in determining the self-assembly behavior, which provides an additional tuning parameters for desired self-assembled structures.

Folded Protein Domains. Once-folded proteins possess well-defined surface chemistry (mostly hydrophilic as described by the oil drop model for globular proteins), overall molecular shape, and symmetry. The stability of folded proteins varies. For example, the superfolder green fluorescent protein (GFP) has rapid folding kinetics in addition to superior stability.[85] CutA, a small trimeric protein from *Pyrococcus horikoshii*, is stable enough to survive boiling water without denaturation.[86] These proteins can be effectively used as MNPs. Installing functional groups at specific locations on the surface may be achieved by site-directed mutagenesis at the genetic level[87] or through the incorporation of noncanonical amino acids via the promiscuous action of enzymes.[88] Hence, both single- and multi-site selective functionalization are possible, assuming the mutation involving a new functional group on the surface does not change the structure and stability of the folded protein too much.

An analogy can be drawn between MNPs and modular protein domains to illustrate the advantages in using MNPs to further build macromolecules. Modular protein domains are relatively conserved protein sequences that have relatively independent folded structures, exhibit certain specific functions, and may evolve independently.[89] A single protein may consist of several protein domains while the same protein domain may be found in several different proteins. There is a remarkable structural and functional diversity among protein domains. Similarly, MNPs also have stable 3D structures that are independent of the rest of the macromolecule. They are certainly not limited to the four classes of compounds discussed above and cover a much broader range of cage compounds and 3D shape-/volume-persistent molecules. The plethora of MNPs makes them suitable as "nanoatoms" or "modular domains" for macromolecules. The giant molecules based on "nanoatoms" are thus of great interest since their self-assembly can be programmed by controlled functionalization of MNPs and new functions may arise from a rational combination of MNPs with different functions.

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III. GIANT MOLECULES BASED ON "NANOATOMS"

Ideally, giant molecules built upon MNP-based "nanoatoms" are monodisperse, have precise primary chemical structure with respect to sequence, composition, and topology, and can form well-defined 3D supramolecular structures. Proteins are a prime example in nature, but it is built mostly from only 20 natural amino acids in a strict linear topology. In contrast, synthetic polymers offer virtually endless possibilities for structural variation. We envision that, by developing precise synthetic polymers, it is promising to achieve properties not found or beyond those found in nature's products. Here, we present three typical giant molecule formulations including "giant surfactants" (composed of MNP−polymer hybrids), "giant shape amphiphiles", and "giant polyhedra" (composed of multiple MNP units). It should be acknowledged that a clear distinction may not be possible and that there is certain overlap between these categories. Nevertheless, such a categorization captures the essential molecular features of the corresponding materials and provides the guideline to molecular design and establishing structure−property relationships. The cartoon shown in Figure 3 provides an illustration of the three categories, and each category will be further elaborated.

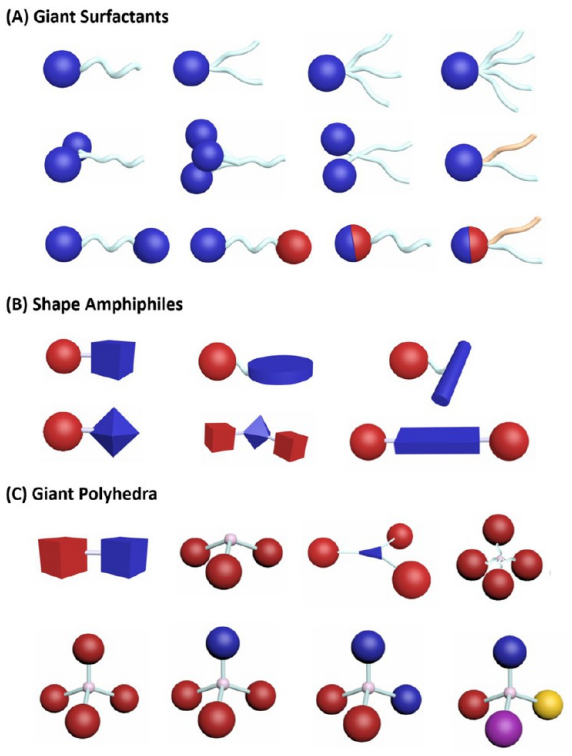

Figure 3. Typical giant molecules include (A) giant surfactants (polymer-tethered MNPs), (B) giant shape amphiphiles (from components of distinct shape and competing interactions), and (C) giant polyhedra, which also include nano-Janus grains (where MNPs possess different surface functionality).

Giant Surfactants. Size amplification of small-molecule self-assembling materials is an intriguing approach to develop new materials.[16] It was first used to describe polymer−biohybrid amphiphiles.[90,91] Since MNPs can be viewed as compact and incompressible heads and polymers as long flexible tails, the combination of these two building blocks gives rise to a new class of giant surfactants (Figure 3A).[80] Giant surfactants capture the essential structural features of small-molecule surfactants but have amplified sizes up to several nanometers, comparable to that of block copolymers. Analogous to small-molecule surfactants, giant bola-form surfactants, giant gemini surfactants, giant multi-headed, and giant multitailed surfactants have been designed and developed.[81,92] Within each subcategory of giant surfactants, further structural variation can be made based on the choice of tails and MNPs. Important molecular parameters include the identity, number, and position of surface functional groups on MNPs, the polydispersity, composition, MW, sequence, and topology of the tethered tails. Strictly speaking, the tethered polymer chains should be monodispersed, but a single-molecular-weight polymer is still a daunting challenge in *state-of-the-art* polymer chemistry. Only limited examples, such as monodisperse long *n*-alkanes,[93] oligo(ε-caprolactones),[94] oligo(L-lactic acids),[95] and a few others[96] have been demonstrated using stepwise, iterative synthetic schemes. Alternatively, narrowly dispersed polymers may be used as a close approximation and can be conveniently synthesized in large quantities by various living/controlled polymerization techniques. It should, however, be kept in mind that while giant surfactants with relatively long tails may tolerate some molecular heterogeneity on chain lengths, the self-assembly of those with relatively short tails would be sensitive to the exact length and the MW distribution even if the difference may be as small as only several repeating units.

Recently, our group has screened the self-assembly behaviors of libraries of giant surfactants.[16] Although those giant surfactants have certain polydispersity in their tails, versatile self-assembly in the bulk, solution, and thin film states was observed. In particular, the phase behaviors of those giant surfactants were found to possess a duality of small-molecule surfactants and block copolymers. This class of materials bridges the gap between the two traditional self-assembling materials and possesses advantages of both at an intermediate length scale of ∼10 nm. Therefore, it has been concluded that they provide a unique and versatile platform to engineer structures with sub-10 nm feature sizes.[16]

Giant Shape Amphiphiles. Shape amphiphiles are built upon molecular segments of distinct shapes and competing interactions.[37,97−99] The term shape amphiphile was first used to describe a discotic−rod liquid crystal mesogen conjugate[97] and later described by Glotzer et al.[98,99] as a broad class of emerging materials. The building blocks that comprise shape amphiphiles have specific 3D shapes with certain geometry, symmetry, and preferred packing scheme, which provide additional parameters for structural engineering. Exemplary shape amphiphiles are shown in the cartoon in Figure 3B. There are numerous ways to combine components of different shape and symmetry, commonly represented by sphere−cube, sphere−disk, sphere−rod, and cube−disk dyads, providing huge potential to engineer diverse self-assembled structures. It should be noted that the components here are not limited to MNPs only, but also include gold nanoparticles, nanorods, single-chain cross-linked nanoparticles, etc.[100,101] In this Perspective, we discuss the shape amphiphiles built up from MNPs and call them "giant shape amphiphiles" in line with the broad class of giant molecules. Giant surfactants may also be viewed as shape amphiphiles because one of the components, the polymer tail, actually possesses no particular shape, while the other component (MNPs) does.[79−81] There have been extensive simulation studies on the self-assembly of shape amphiphiles, and rich phase behavior and unusual hierarchal structures have been predicted.[99,102−105] Computer simulation has been the primary approach to provide a roadmap for the self-assembly of persistent-shape objects.[36] There have

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been relatively few reports on the experimental validation due mainly to the difficulty in synthesizing precisely defined shape amphiphiles from traditional inorganic nanoparticles. With MNPs, however, a series of giant shape amphiphiles have been constructed and studied in detail. These include C_{60}–POSS conjugates (sphere–cube),[106] C_{60}–oligofluorene conjugates (sphere–rod),[107] C_{60}–porphyrin conjugates (sphere–disk),[108−111] POSS–triphenylene conjugates (cube–disk),[112] C_{60}–perylene diimide (PDI) (sphere–plane),[113] POSS–PDI–POSS conjugates (cube–plane–cube),[114] and POSS–terthiophene–POSS[115] shape amphiphiles. In these studies, the distinct enthalpic interaction between building blocks constitutes the major driving force for self-assembly, while the entropic packing constraints of each building block (nanoatom) lead to interesting hierarchical structure formation. Their self-assembly will be discussed in greater detail in the next section.

Giant Polyhedra. There are basically two types of giant polyhedra. The first type is a faceted MNP that by itself is a polyhedron, and the second type is a giant polyhedron built upon multiple smaller MNP units. Examples of the former include higher diamondoid molecules,[116] graphene nanoribbons,[117] and large molecular clusters.[20] The latter are constructed by placing MNPs on the apexes of a polyhedron to form a larger faceted giant nanoparticle, reminiscent of the classic small-molecule VSEPR structures. For example, when four POSS cages are linked to the apex of a tetrahedron, we obtain a giant tetrahedron (Figure 3C). Depending on the linkers, it can be a soft giant polyhedron or a rigid giant polyhedron, and in each case, they might have distinct self-assembly behaviors and form different ordered structures. In these giant polyhedra, the MNPs may possess different surface functionalities to establish the driving force for assembly. Such giant polyhedra may also be regarded as nano-Janus grains (NJGs) and will be discussed later in detail. Interestingly, chirality can be introduced if all four MNPs (POSS in this example) possess different surface functional groups, giving chiral giant tetrahedron (see Figure 3C). These unique chiral giant polyhedra may exhibit additional hierarchical structural diversity with or without the propagation and amplification of chirality. So far, there are very few works reported on this class of materials. It should be noted that even when the amphiphilicity is absent, the unique shape may already be sufficient to cause diverse assembly behavior in many cases.[36]

Geometric and energetic considerations are perhaps the most intuitive factors that direct the self-organization of materials into ordered structures. With increasing sizes, the shape and shape-persistency of these "nanoatoms" in giant molecules become more and more important in determining the final structure formation as long as the interactions among them are strong enough to stabilize the structures. While experiments have shown thermodynamic equilibrium structures for nanoparticle polyhedra,[118] simulation has predicted the formation of even more diverse structures, including liquid crystals, plastic crystals, quasi-crystals, and crystals, from various polyhedra.[36] Directional enthalpic and entropic driving forces are believed to guide the ordering of faceted polyhedra.[119] Therefore, we envision that the molecularly precisely defined giant polyhedra are exciting research targets. Possible polyhedra include the Platonic, Archimedean, Catalan, and Johnson solids and perhaps also zonohedra, prisms, and antiprisms. A 2D nanoplate may also be considered as a special type of "polyhedron".

Amphiphilic giant polyhedra are nano-Janus grains. The term "*Janus grain*" was proposed by Prof. De Gennes in his Nobel lecture and refers largely to colloidal particles with asymmetric surface chemistry.[120] In general, the symmetry breaking occurs in two ways: geometrically and/or chemically. Symmetry breaking in geometry refers to the change of overall molecular symmetry upon functionalization (such as the regioselective mono- and multifunctionalization of MNPs). Symmetry breaking in chemistry refers to the introduction of functional groups that possess different interactions from the rest of the molecule. Nano-Janus grains are nanosized molecules built upon MNPs with rigid 3D conformation and symmetry breaking in both chemistry and geometry.

The first type of nano-Janus grain has asymmetric surface chemistry on the same MNPs and thus may be considered as a "patchy MNP". In fact, there are various examples based on C_{60}. Monofunctionalized C_{60} derivatives may be arguably regarded as the smallest patchy MNPs and have been known to generate various nanoaggregates by self-assembly.[121] Regioselective C_{60} penta-adducts can self-assemble into complex structures such as a double-layered vesicle.[122] [5:1], or [4:2], or [3:3] mixed hexakis-adducts of C_{60} are perhaps much more like "patchy particles".[52] [5:1]Fullerene derivatives with most of the surface covered with alkyl chains and the rest covered by carboxylic acid groups are typical molecular patchy particles and were found to self-assemble into unique shape-persistent micelles.[123] Similar counterparts in POSS are rare. Laine et al.[68,69] have reported preliminary efforts in preparing "Janus silsesquioxanes" by cage exchange. So far, it remains a tough challenge to achieve regioselective multifunctionalization on POSS.

The second type of nano-Janus grains is the ones obtained by closely linking together two or more MNP units with distinct surface functional groups. For example, a POSS–fullerene conjugate (BPOSS–C_{60}) is a nano-Janus grain since the surface chemistries on BPOSS and C_{60} are drastically different.[106] Similarly, a dumbbell-shaped Janus particle can also be prepared by the conjugation of one hydrophobic POSS having isobutyl side groups and the other hydrophilic POSS possessing carboxylic acid side groups (BPOSS–APOSS) (Figure 4A).[82] This BPOSS–APOSS nano-Janus grain formed a unique bilayered structure (Figure 4B) that further packs into crystals with a nanometer-scale superlattice in the bulk. At lower temperatures, the BPOSS within each layer further organized to pull APOSS into the crystalline lattice. Hence, the entire structure is crystal-like, as proved by the computer simulation and transmission electron micrograph (TEM) as shown in Figure 4B. At higher temperatures, only the hydrophilic/hydrophobic bilayered structure was maintained to form a supramolecular liquid crystal phase.[82] It can be envisioned that other nano-Janus grains, such as "snowman" type (e.g., one large hydrophilic/hydrophobic POSS connected with one small hydrophobic/hydrophilic POSS) (Figure 4A) or "Mickey Mouse" type (e.g., one large hydrophilic/hydrophobic POSS connected with two small hydrophobic/hydrophilic POSSs in the given geometry), may be similarly designed and synthesized.[124]

IV. PRECISION SYNTHESIS THROUGH "CLICK" CHEMISTRY

Similar to proteins, the self-assembly of giant molecules is expected to be highly sensitive to the primary chemical structure, just like small molecules where the variation of even one single atom may lead to dramatic difference in final material properties. Thus, precision synthesis is a prerequisite in the study of giant molecules. Because of the large size and the presence of multiple functional groups, it is traditionally difficult to accurately control the chemical structure and functionality at the macromolecular

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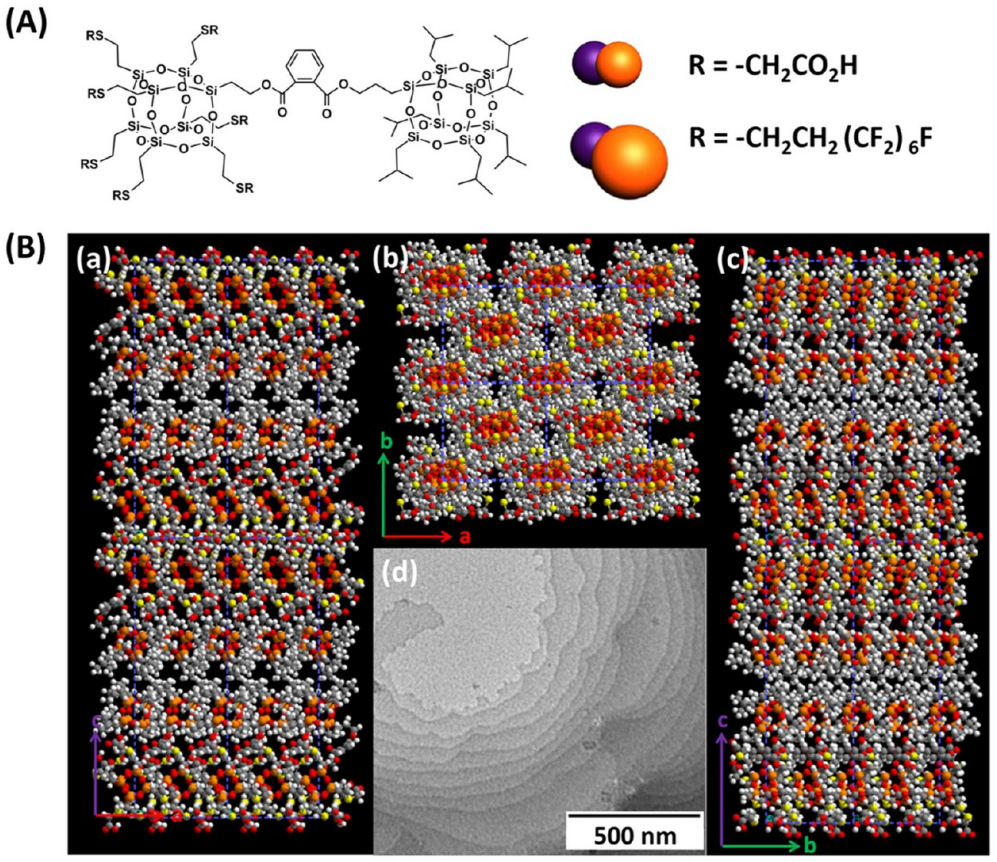

Figure 4. Self-assembled structure of an exemplary nano-Janus grain). (A) The chemical structure of dumbbell-shaped Janus particles, BPOSS−APOSS and BPOSS−FPOSS. (B) Molecular packing of BPOSS−APOSS in the crystal lattice on different planes: (a) *ac*-plane when projected from *b*-axis direction; (b) *ab*-plane when projected from *c*-axis direction; (c) *bc*-plane when projected from *a*-axis direction. (d) Transmission electron microscopic bright-field image of the thermal annealed BPOSS−APOSS film. Adapted with permission from ref 82.

level without defects. To improve the precision of synthesis, we may learn from the "domain" concept in protein science as discussed previously. If each domain (or "nanoatom" in this case) can be precisely synthesized, the synthesis of giant molecules can then be facilitated by simply covalently linking these domains together in a modular fashion. Fortunately, the emergence of "click" chemistry seems to pave the road to giant molecules by offering modular, robust, and efficient ways that would greatly simplify the material synthesis. The concept of "click" chemistry was proposed by Sharpless more than a decade ago and has been embraced by the materials community, especially polymer chemists.[125−128] Following this philosophy, we have developed sequential "click" approaches as a general methodology to synthesize giant molecules.[129−131]

A model sequential "click" route is shown in Figure 5. The method takes advantage of the high efficiency of "click" reactions. When the reactions are not completely orthogonal, it may be carried out in a sequential fashion to achieve selectivity in each step.[128,129] When the reactions are completely orthogonal, it may be further simplified into a "one-pot" process.[131] Although it is named a sequential "click" approach, not every reaction involved has to be a strictly "click" reaction—most highly efficient linking chemistry should also do as long as the purification is not complicated. Typically, "nanoatoms" are first synthesized from various MNPs with well-defined structure and controlled presentation of "click" functionalities on the surface. These "clickable" precursors then may be joined together sequentially in predetermined geometry to construct giant molecules of complex architectures. In Figure 5, the MNP is an alkyne-functionalized heptavinylPOSS (VPOSS-alkyne), and the tail is a well-defined polystyrene (PS) with one azide group at the chain end (PS-N_3). The ligation affords a molecular scaffold for giant surfactants, from which the second thiol−ene "click" reaction can be used to systematically vary the surface chemistry on the MNP. Multiple functional groups, such as hydroxyls, carboxylic acids, perfluorinated chains, etc., have been installed on POSS at the same time, changing the headgroup from hydrophobic (VPOSS) to slightly hydrophilic (HPOSS), hydrophilic (DPOSS or APOSS), and even fluorophilic (FPOSS). Alternatively, MNPs can be modified with protected functional groups to facilitate conjugation at earlier stages. The amphiphilic feature is only revealed by deprotection when necessary. This has been used in the preparation of a series of C_{60}-based giant surfactants.[64] Overall, in just a few steps, a library of giant molecules with similar structures and functions can be modularly constructed from commercially available, simple precursors.[16] This is a general strategy.

For giant surfactants with flexible polymer chains as tails, the "grafting-from" approach[79,132] may also be applied or combined with the "grafting-to" approach.[133−135] However, the control over the molecular parameters of the newly grown polymer chains is usually not as precise as those premade polymers and suffers from issues associated with incomplete initiation[132] and/or side reactions due to the multitude of functional groups present in the molecule.

An important concept in giant molecules is the controlled symmetry breaking in geometry and chemistry. For example,

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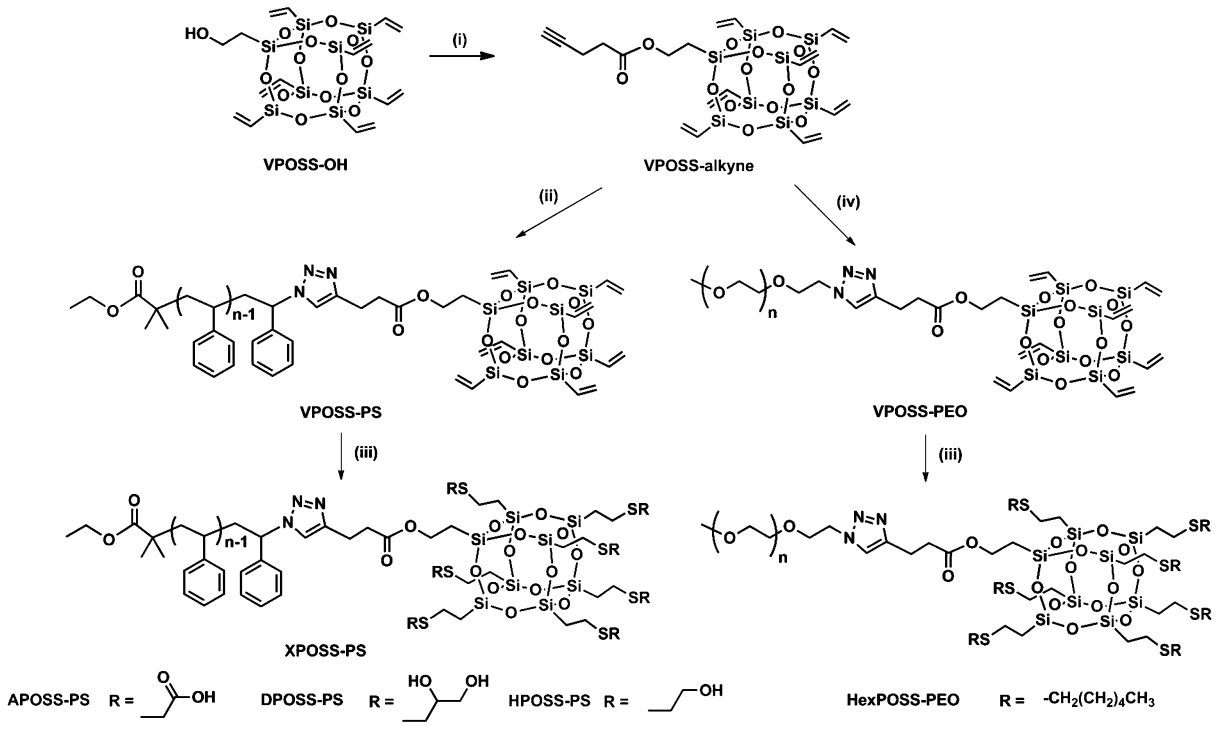

Figure 5. A model sequential "click" route to the synthesis of diverse giant surfactants.[129]

with regards to molecular geometry, monofunctionalization of octavinylPOSS breaks the O_h symmetry to C_{3v} symmetry; concerning chemistry, the "thiol−ene" reaction can be used to systematically change the headgroup from completely hydrophobic to completely hydrophilic in just one step. The sequential "click" approach is thus designed to facilitate the synthesis of giant molecules and make them readily accessible even for nonspecialists. The power of this approach can be further enhanced by changing the following options.

"Click" Reactions. There are limited choices of "click" reactions to use. Cu(I)-catalyzed [3 + 2] azide−alkyne cycloaddition (CuAAC)[136] and thiol−ene chemistry[137,138] are perhaps the most popular prototype "click" reactions. In recent years, copper-free, strain-promoted azide−alkyne cycloaddition (SPAAC) has attracted considerable interest as a highly reactive, bio-orthogonal "click" reaction.[139] We have successfully incorporated SPAAC to develop a sequential triple "click" synthesis based on the drastic difference in reactivity between SPAAC and CuAAC in the absence of Cu(I).[130] There are many other types of "click" chemistry, including the classic Diels−Alder reaction, oxime ligation, and the more recent [4 + 2] tetrazine−alkyne reactions.[140] They can be applied similarly in the sequential click chemistry approach to enable the synthesis of giant molecules with even more complex architectures or to facilitate "one-pot" giant molecule synthesis by orthogonal chemistries.[131] Future challenges would be (i) to develop new "click" chemistries that are orthogonal to current ones and comparably reactive; (ii) to develop new reactions of controllable reactivity that respond to foreign stimuli including light, heat, force, and a small signaling molecule by covalent bond formation, which shall allow the programming of the reactions; and (iii) to develop new reactions that bridge the gap between synthetic macromolecules and biological macromolecules. With these tools, the sequential click chemistry approach could be extremely versatile, going beyond simple preparative purpose to embracing the coding and decoding of information within giant molecular structures and further to tailoring biomacromolecular properties by synthetic motifs.

"Clickable" Precursors. Depending on the chemistry of choice, "clickable" precursors are made from MNPs and other nanosized building blocks with precise arrangement of "click" functionalities. Since the sequential "click" approach is a modular approach, varying the structure of "clickable" precursors is an important way to tune the structure and properties of giant molecules. For example, following exactly the same route shown in Figure 5, other giant surfactants of distinct architecture can be obtained.[81,141] If the azide is located at the middle of the PS chain, it leads to a "giant lipid" with two symmetric tails;[141] if the azide is located at the junction of a PS-*block*-poly(ethylene oxide) (PS-*b*-PEO) chain, a giant lipid with two asymmetric tails can be obtained.[134] The chain topology may also be varied from linear to star, dendritic, hyperbranched, or even cyclic. The structure of the "clickable" precursors strongly affects the properties of the final material.

The introduction of "clickable" functionalities into biological "nanoatoms" is nontrivial. The classical way to introduce nonnatural functionalities, such as alkynes, azides, and alkenes, into proteins and other biomacromolecules has been the use of functionalized substrates, such as noncanonical amino acids, azide-functionalized aliphatic acids, etc., via the promiscuous action enzymes.[142] For example, 3-azidohomoalanine has been used as a methionine surrogate to allow the global incorporation of azide functionality into the recombinant protein.[143] Nevertheless, these methods often suffer from reduced protein expression yield and misfolding. Recently, a fully genetically encodable SpyTag−SpyCatcher protein conjugation chemistry has attracted much attention.[141,1424] It requires only natural amino acids without additives and is fully compatible with the cell environment, which provides an excellent alternative to do "bioorthogonal" chemistry in the biological reactivity space.[144,145]

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The chemistry has been successfully applied to diversify the protein topology to circular, tadpole-like, and branched structures.[4] The relatively small SpyTag (~1.2K), also available through solid-state peptide synthesis, may serve as a bridge between synthetic motifs and biological protein motifs. The size of SpyCatcher has also been successfully reduced to ~84 amino acids.[146] Future challenge would be to develop other orthogonal pairs of genetically encoded protein conjugation chemistry by protein engineering. Hopefully, similar strategies may be applied to develop DNA or RNA sequences that bind and form covalent bonds. The availability of a huge selection of "clickable nanoatoms" with different sizes, various bonding angles, diverse functions, and well-understood interactions is indispensable for rational design and modular development of giant molecules.

"Click" Adaptors. To further broaden the scope of the sequential "click" approach, a small gadget, called the "click adaptor", is especially useful. It consists of a small molecule with one "clickable" functionality and one or more functional groups that are of orthogonal "click" reactivity or are masked "clickable" groups (e.g., halogen groups can be considered a masked "azide" since it is nonreactive in CuAAC or SPAAC but can be readily converted to azide by subsequent nucleophilic substitution).[81] It can be used facilely to convert one "click" functionality to another or to extend the number of "clickable" sites so as to vary the final material topology. We have successfully applied this concept in the preparation of giant multiheaded and multitailed surfactants using the same precursor.[81] Starting from precisely defined "nanoatoms", the above strategies allow the preparation of giant molecules of almost any architecture. We have yet to witness the growing precision and complexity in synthetic macromolecules and its impact in self-assembly and material science. The translation of classical organic chemistry into macromolecular chemistry is, after all, not as straightforward as expected.

V. SELF-ASSEMBLY ACROSS MULTIPLE LENGTH SCALES

Giant molecules can be viewed as size-amplified analogues of small molecules. As a result, their self-assembly is anticipated to exhibit features reminiscent of both small molecules and traditional macromolecules. In general, they form versatile nanostructured morphologies in the bulk, solution, and thin film states. In this section, we will first discuss the general aspects of the thermodynamics and kinetics of giant molecule self-assembly and then present several unique features that are evident from both computational and experimental studies.

Thermodynamics and Kinetics of Giant-Molecule Self-Assembly. Because of large sizes and MWs of these "nanoatoms", it is increasingly important to maintain sufficient interactions among these "nanoatoms" to generate and stabilize self-assembled structures. Collective secondary interactions that act cooperatively and cumulatively are indispensable. Clustering of functional groups provides a convenient way to build collective interactions.[147] In nature, many biological systems interact through polyvalent interactions.[148] Examples include the hybridization of complementary DNA strands, antibody−antigen interactions, bacterium−cell adhesion, etc.[148] Collective interactions are advantageous over monovalent interactions in that they have enhanced overall strength, improved specificity, and versatile tunability. In addition, directional collective interaction is especially favorable in guiding structure formation and might be achieved by selecting MNPs with proper symmetry and rigid linkers. The relatively independent structure of MNPs makes collective interaction from the surface functional groups the primary driving force for a more predictable self-assembly. On the basis of these principles, we have designed, for example, giant surfactants that can form nanostructures with sub-10 nm feature sizes and sharp boundaries, which is difficult for traditional diblock copolymers.[16] To further increase the diversity of assembled structures, it is necessary to use anisotropic MNPs in combination with delicately balanced, directional physical interactions for control over chirality, supramolecular binding, and others. The use of reversible covalent bonding is also an intriguing approach to make these superlattices dynamic and responsive[149] and should enable the development of "smart" materials for various applications.

Because of the lack of chain entanglement, giant molecules usually exhibit fast relaxation and self-assembly dynamics. However, the self-assembly of giant molecules also is prone to different phase formation mechanisms, similar to small molecules. When first-order phase transformations occur via the assembly process, the driving force is of both enthalpic and entropic origin. The classical nucleation and growth model has been well-established when a transition occurs from a metastable state relaxing toward a stable state. On the other hand, if transformations are of higher order, critical phenomena, such as a spinodal decomposition process that describes a transition from an unstable state relaxing toward a stable state, will play a major role. In each of these cases, thermal (density) fluctuation of the system provides the background for these transitions and facilitates the giant molecules' conversion from one phase to another.[150] However, when the size and mass of the building blocks become increasingly larger and heavier, the energy required to generate the thermal (density) fluctuation is raised. In addition to raising the temperature (thermal energy), external force fields, such as mechanical, electrical, and magnetic fields, have been commonly adopted to stimulate the transformations of those giant molecules. The major features of giant molecule self-assembly are presented with examples as follows.

1. Hierarchical Structures Are Common in Giant Molecules. Macroscopic properties of materials are not only highly related to chemical structures at the molecular level, but also critically associated with formation of hierarchical structures across multiple length scales. Again, proteins are a prime example. Even if the primary chemical structures are exactly identical, unfolded proteins and folded proteins show dramatic differences in property and function. Giant molecules provide a system uniquely suitable for engineering hierarchical structures. Their self-organization is influenced by both incommensurate interactions and shape disparities. Considering the nanometer size of typical MNPs (such as functionalized POSS, C_{60}, and POM derivatives), nanophase separation between the different components of giant molecules provide a versatile system to engineer structures with sub-10 nm feature sizes and provide a suitable template to extend the rational design into synthetic macromolecules. Within the segregated region, the MNPs may further self-organize via the collective secondary interactions between functional groups on their surfaces. Hierarchical structures are thus commonly formed in giant molecules.

For example, the BPOSS−C_{60} dyad, a typical nano-Janus grain (Figure 6A), self-assembles into a double-layered lamellar structure due to the comparable sizes of BPOSS and C_{60}.[106] More intriguingly, polymorphism was observed due to the different packing symmetry of these two units at the initial stage: a tetragonal lattice is induced when the packing of BPOSS cages dominate the phase structure, while a hexagonal lattice is adopted

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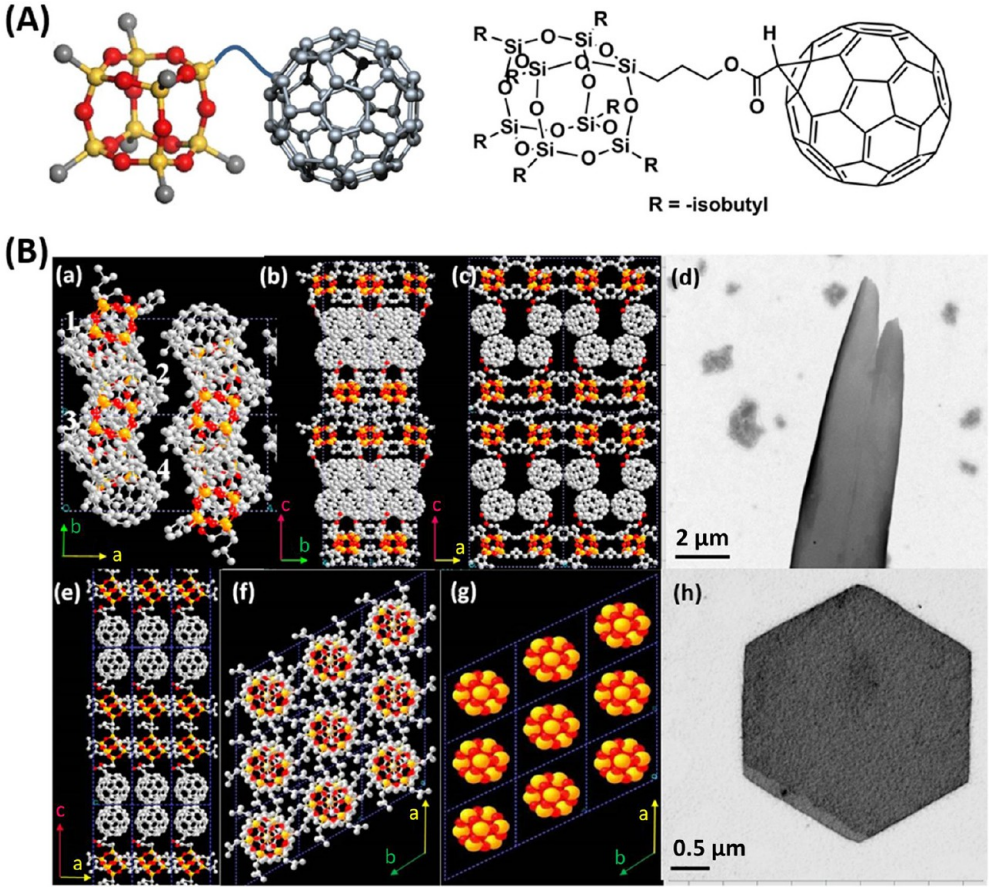

Figure 6. Self-assembled structures of BPOSS−C_{60}. (A) The cartoon and chemical structure of BPOSS−C_{60} (R = isobutyl). (B) Molecular packing in the tetragonal crystal (a−c) and the corresponding morphology (d) and in the hexagonal crystal (e−g) and morphological difference between these two crystals (h). Adapted with permission from ref 106. Copyright 2011 The Royal Society of Chemistry.

when C_{60}s initiate the crystallization (Figure 6B).[106] There is practical significance of this structure since C_{60}s are semiconductive/conductive upon doping and BPOSS cages are insulators. Such an alternating structure of conductor/semiconductor and insulator in nanometer scale is a potential nanocapacitor.[100] It has also been shown to improve the performance of bulk heterojunction (BHJ) polymer solar cells (PSCs) with an inverted device configuration. Compared to the reference PSC using poly[(4,4′-bis(2-ethylhexyl)dithieno[3,2-*b*:2′,3′-*d*]silole)-2,6-diyl-*alt*-(4,7-bis(2-thienyl)-2,1,3-benzothiadiazole)-5,5′-diyl] (SiPCPDTBT) as the donor and [6,6]-phenyl C_{61}-butyric acid methyl ester (PCBM) as the acceptor, the PSC using the same donor and BPOSS−C_{60} as the acceptor revealed a higher J_{sc} and a higher power conversion efficiency (by a factor of 1.63).[151]

When the two components are highly incommensurate in terms of size, shape, composition, and interaction, even more complex structures may form. This is the case for a series of shape amphiphiles based on porphyrin−C_{60} conjugates (see Figure 7A).[108−110] The structural disparity is apparent since porphyrin moieties prefer to pack into liquid crystalline columns in the bulk due to their flat-like disk structure, while pristine spherical C_{60} tends to crystallize into face-centered-cubic (FCC) structure. When these two components are linked together by a covalent bond, the porphyrin was found to possess the columnar LC phase with the C_{60} wrapped around the column to form 1D channels. Proved by X-ray and electron diffraction (Figure 7B), the structure was identified as a unique 129_{44} helical "supramolecular double-cable structure" (Figure 7C) with individual channels for both hole and electron transportation.[109] By removing the long alkyl groups on the porphyrin, the C_{60} particles preferred to interact intercolumnly and form separate continuous domains parallel to the column direction, resulting in another double-cable structure.[110] Interestingly, a *trans*-di-C_{60}-tethered porphyrin also formed a supramolecular structure with segregated domains of donors and acceptors.[108] These giant molecules not only fulfill the structure design as desired but also exhibit property enhancement in PSC devices. Indeed, ultrafast charge transfer and charge separation were observed with long lifetimes in blends of SiPCPDTBT and these dyads.[109,110] BHJ PSCs fabricated using such blends as the active layer show higher J_{sc} and larger V_{oc} than that of reference PSCs using PCBM as the acceptor.[109,110]

More complicated molecular designs, such as giant tetrahedrons, can also be envisioned. Since different functional groups can be introduced at the peripheries of each MNPs at the apexes of the tetrahedron, directional interactions may be introduced to induce the formation of various superlattices. The most attractive one is perhaps the chiral giant tetrahedron where each of the MNPs on the apex is different (see Figure 3C). We are currently pursuing the superlattice of such a chiral giant tetrahedron and its formation mechanism.

2. Confined/Directed Self-Assembly of Giant Molecules Hold Great Promise for Generating Unconventional Nanostructures. Block copolymers are known as "designer soft materials" to form various microphase-separated structures dictated by the Flory−Huggins interaction parameter, χ, and

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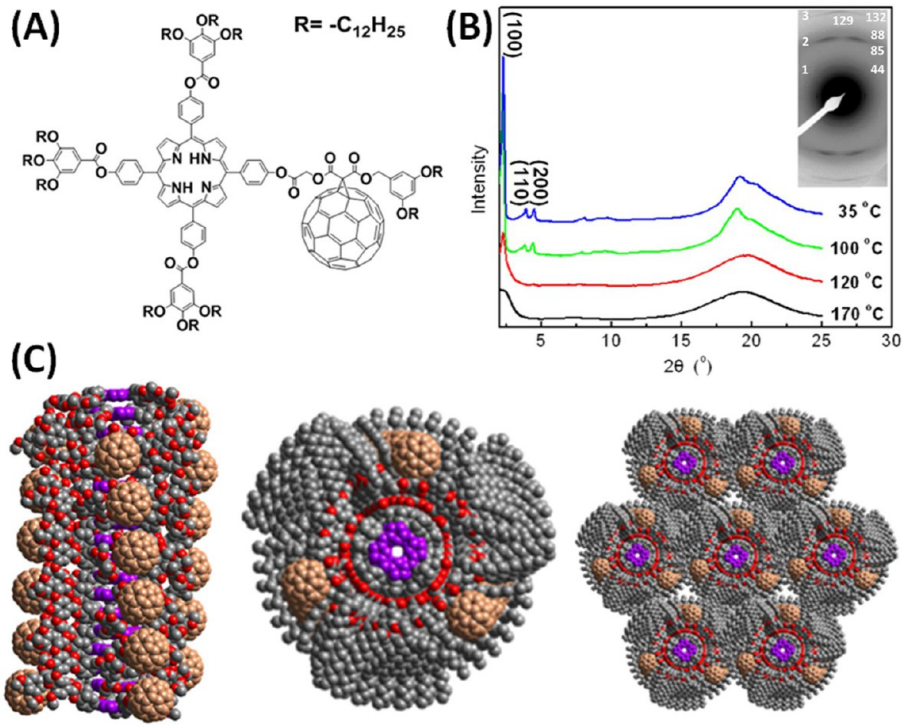

Figure 7. Self-assembled structure of a shape amphiphile, porphyrin−C_{60}. (A) The chemical structure. (B) Wide-angle X-ray diffraction pattern and electron diffraction pattern (inset) of porphyrin−C_{60} to determine its 129_{44} helical structure. (C) Molecular packing of the 129_{44} helix of the column and their packing into a columnar phase, the discotic liquid crystals viewed along the column, and the hexagonal packing of columns. Adapted with permission from ref 109. Copyright 2012 Wiley-VCH.

the degree of polymerization, N.[152] It may be used as an analogy in understanding the interactions between MNPs although the theoretical approach would be very different due to the rigidity of the MNP. The clustering of functional groups at the periphery of MNPs in giant molecules leads to a strong interaction parameter and thus a strong nanophase separation. Giant surfactants, for example, possess a duality of both small-molecule surfactants and block copolymers. They readily form thermodynamic-equilibrium phase-separated structures in the bulk simply upon thermal annealing and/or solvent annealing. Similar to diblock copolymers, typical morphologies such as sphere, cylinder, double gyroid, and lamellar phases have been observed with feature sizes of 10 nm or less.[16] This is practically important in developing advanced nanopatterning techniques for applications in microelectronics. In solution, giant surfactants form common micellar structures, such as spheres, worm-like cylinders, and vesicles.[64,80,92,130] Furthermore, these nanophase-separated morphologies can also be modified by intervening with other phase transitions such as crystallization and liquid crystal phase formation to form a variety of hierarchical structures.[150]

The packing constraints from the rigid conformation and specific molecular shape of MNPs are expected to generate intriguing unconventional morphologies.[153] Although most of the structures should possess thermodynamic equilibrium states, the shape effects (or packing constraints) would be profound under confined environments or during directed self-assembly. In this case, the altered Gibbs free energy minimization pathway may lead to the formation of unconventional nanostructures with different metastabilities. For example, in the lamellar crystals of POSS−PEO and C_{60}−PEO, chain-folded PEO tails must generate a surface area that is at least comparable to the cross-sectional area of the MNP tethered on the PEO lamellar surface due to the incompressibility of the C_{60}. This leads to highly unconventional situations where the polymer chain ends remain trapped below the crystal surface and are located in the middle of the lamellar crystal core as defects (Figure 8A).[153] Metastable PEO crystal structures with 1.5, 2, and 2.5 stem numbers (Figure 8B) were observed via small-angle X-ray scattering (SAXS) and atomic force microscopy, and their different thermodynamic stabilities have been investigated by ultrafast chip calorimetry (Figures 8C,D).

In the bulk, giant surfactants, such as DPOSS−PS, formed different phase structures ranging from lamellae to body-centered-cubic (BCC) spheres with increasing tail length (Figure 9), as confirmed by both SAXS and TEM. This represents a general phase behavior for most giant surfactants. Figure 9B represents a "half" phase diagram. This is because one of the components has a fixed size, and it becomes impractical experimentally to decrease the N of PS while maintaining a narrow polydispersity with current techniques for decreasing the volume fraction of PS further. Nevertheless, the other half of the phase diagram may be explored by increasing the size of the head or the number of the MNPs at the head, even though the phase diagram may change due to the difference in head interactions. Indeed, an inverse hexagonal cylinder phase was observed in a conjugate 3POSS−PS, where the head is consisted of three POSS units.[16]

When this family of giant surfactants is spin-coated into a thin film, 2D nanopatterns are formed upon solvent treatment or thermal annealing. Figure 10A shows a TEM bright-field image that represents the line pattern obtained from a thin film of DPOSS−PS_{35} in the cylindrical phase, and Figure 10B shows the formation of the metastable rectangular lattice of APOSS−PS_{80}.[16] The structure identifications were obtained by grazing-incidence small-angle X-ray scattering (GISAXS) experiments as shown in the insets of the figures. For example, the diffraction in

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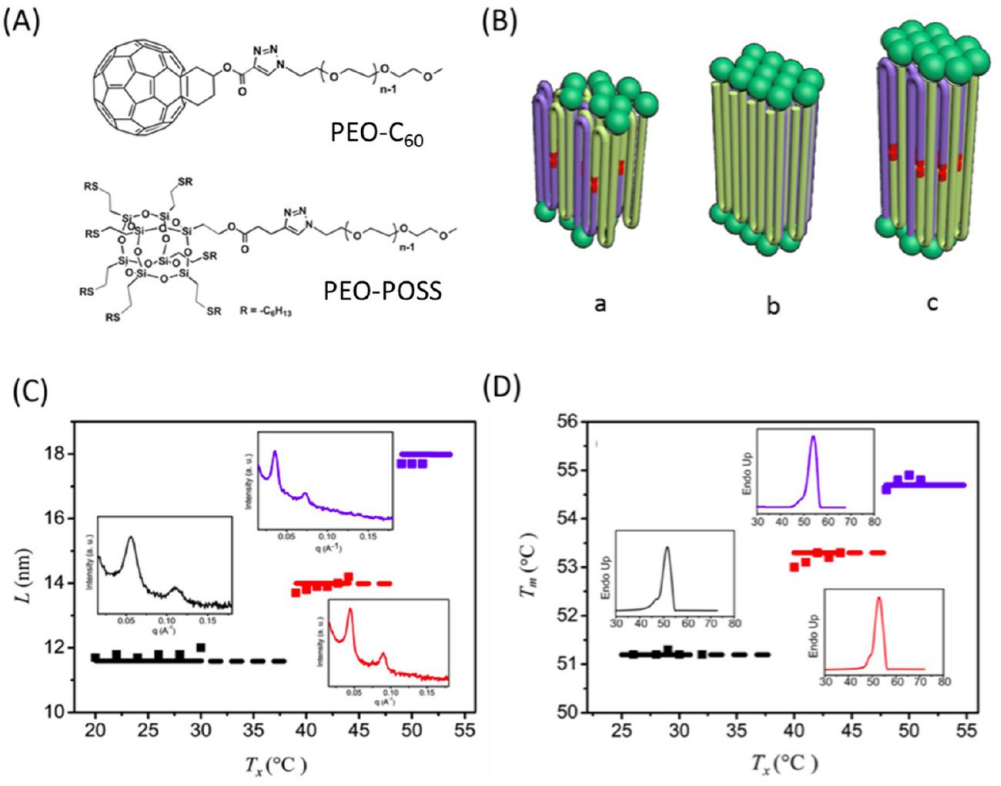

Figure 8. (A) Chemical structures of PEO−C_{60} and PEO−POSS. (B) Cartoons of the MNP with a PEO tail with the IF and half-stemmed crystals: the stem number of 2.5 (a), the stem number of 2 (b), and the stem number of 1.5 (c). (C) Relationships between the long period, L, and crystallization temperature, T_x. (D) Relationship between the crystal melting temperature T_m and T_x for hexyl-POSS with a PEO tail having $N = 86$ repeating units. Solid squares represent experimental data of the PEO crystal with the stem number of 2.5 (black), PEO crystal with the stem number of 2 (red), and PEO crystal with the stem number of 1.5 (blue). Solid and dashed lines are the calculated values. Small-angle X-ray scattering in (C) and ultrafast heating chip DSC thermograms in (D) of PEO($s = 2.5$) (black), PEO($s = 2.0$) (red), and PEO($s = 1.5$) (blue) crystals are also inserted. Adapted with permission from ref 153.

the inset of Figure 10A shows that the cylinders lie parallel with the substrate surface in a hexagonal arrangement in which the cylinders are oriented along the {10} plane, parallel to the film substrate. The spacing between cylinders can be calculated based on this result of the inset is ca. 11.0 nm, and this value matches with the TEM observations. Therefore, the line spacing is ca. 6.0 nm since the superposition of several layers of the cylinders.[16] These as-assembled patterns are compatible with the current device configurations in microelectronics and may be easily integrated to industrial processes. Morphological evolution under confined environments is also of interest. In addition, directed assembly techniques, such as grapho-epitaxy or self-assembly under external fields, have been widely used to guide structure formation in soft matter science. They may be adopted here to manipulate the self-assembly of giant molecules, providing additional processing parameters for structural control. We expect that more unconventional nanostructured morphologies, whether predicted by theoretical calculations or not, may appear in these giant molecules.

3. Self-Assembly of Giant Molecules Is Sensitive to Primary Chemical Structures. A remarkable feature that we anticipate from giant molecules is the unusual sensitivity of self-assembly to primary chemical structures at a level comparable to that of small molecules. In small-molecule surfactants, the self-assembly behavior varies significantly when the chemical structure, such as tail number and head identity, is changed. However, the sensitivity is significantly decreased in block copolymers due to their compressibility and elasticity. While the dependence of block copolymer self-assembly on MW may be described by the scaling law in most cases, the change in small molecules with respect to chemical structure is less predictable. The odd−even effect is one of the empirical laws that describe the dependence. In protein science, the structure and function exhibit different dependence on primary sequence. Even after random mutation, the folded structure can be maintained in most cases, while the function (or performance) may vary by several orders of magnitude. Giant molecules are perhaps somewhere in between. For example, two amphiphilic fullerenes with a difference of only two amide bonds in chemical structure exhibit significantly different self-assembly behavior: one forming "buckysomes",[154] while the other giving "shape-persistent micelles".[155] Giant surfactants show similar sensitivity to molecular structure, which is discussed below in detail.

Owing to a duality of small-molecule surfactants and block copolymers, giant surfactants self-assemble into nanostructures in the bulk (Figure 9) and form micelles in solution (Figure 11A). Changing head functionality, head number, tail composition, and tail number all have profound effects on their phase behavior. Specifically, two families of giant surfactants based on APOSS−PS[80] and AC_{60}−PS[64] have been investigated. The head groups in this case were functionalized with carboxylic acid groups to impart amphiphilicity (hydrophilic heads with hydrophobic PS tails). With an increase in the degree of ionization, the micellar morphology changes from vesicle to cylinder to sphere likely due to increased head repulsion (Figure 11A). Similar observations were made in gemini-type giant surfactants $(APOSS−PS)_2$.[92]

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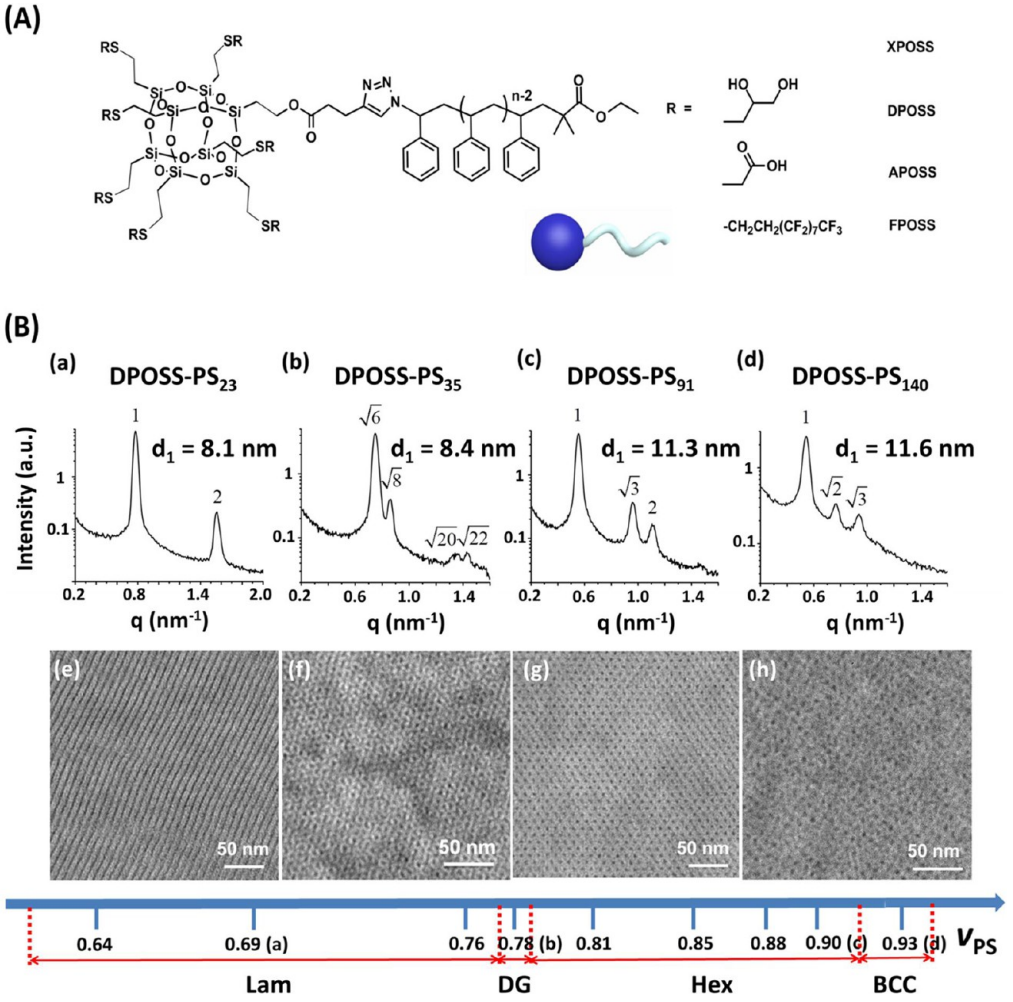

Figure 9. Self-assembled structures of giant surfactants. (A) The chemical structure of giant surfactants DPOSS−PS, APOSS−PS, and FPOSS−PS. (B) Half phase diagram of DPOSS−PS observed via SAXS and TEM experiments.[16]

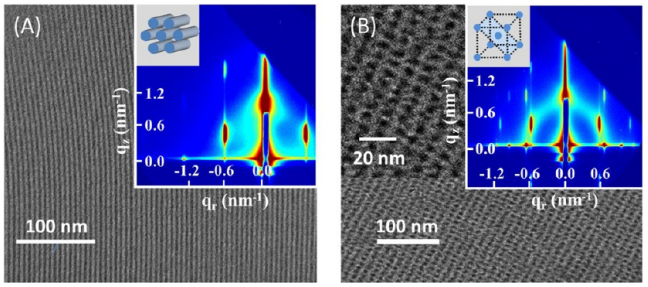

Figure 10. (A) Bright image and GISAXS pattern in the reciprocal space of hexagonal packing parallel cylinder of DPOSS-PS_{35} (N = 35) in thin film. (B) TEM bright image and GISAXS pattern in the reciprocal space of FCO packing spherical structure of APOSS-PS_{80} (N = 80) in thin film. The inset shows a zoomed-in view of the TEM image and an illustrated structure in real space. The dots are packed in a rectangular lattice with the sphere diameter of ca. 4.0 nm.[16]

Furthermore, it was found that the polymer tails are stretched in the assemblies, a feature reminiscent of small-molecule surfactants, instead of a random coil conformation common for polymers. The tail stretching in spheres was found to be the highest and decreased in cylinders and vesicles, as revealed by a stretching ratio parameter defined as the ratio between the radius of the PS core and its corresponding random coil radius.[64]

The sensitivity is perhaps best illustrated in pairs of topological isomers that have basically the same composition but distinct molecular architecture. For example, a carboxylic acid functionalized C_{60} (AC_{60}) tethered with one or two PS tails of identical *overall* MW are a pair of topological isomers. When micelles were prepared in the 1,4-dioxane/DMF mixture as the common solvent and water as the selective solvent, AC_{60}−PS_{44} formed spheres, while AC_{60}−$2PS_{23}$ formed vesicles.[64] The different morphologies and size distributions are clearly supported by TEM (Figure 11B) and dynamic light scattering experiments. In the mixture of 1,4-dioxane/water, both giant surfactants formed large colloidal particles. AC_{60}−PS_{44} self-assembled into spherical colloidal particles with an onion-like inner structure (Figure 11C), while AC_{60}−$2PS_{23}$ formed faceted, double-truncated, conical colloidal particles with hexagonal superlattice inner structures (Figure 11D).[16] These studies highlight the unusual topological effect in giant surfactants, which is much less prominent in traditional amphiphilic polymers.

In the bulk, the AC_{60} with a single PS tail (N = 44) formed a lamellar phase structure, while the AC_{60} with two PS tails (N = 23, N_{total} = 46) exhibited a hexagonal cylinder phase structure, as illustrated by SAXS patterns shown in Figure 12A. Similar topological effects were observed in other topological isomers based on different MNPs.[16] For example, DPOSS−PS with one PS tail (N = 35) showed a double gyroid phase structure, whereas

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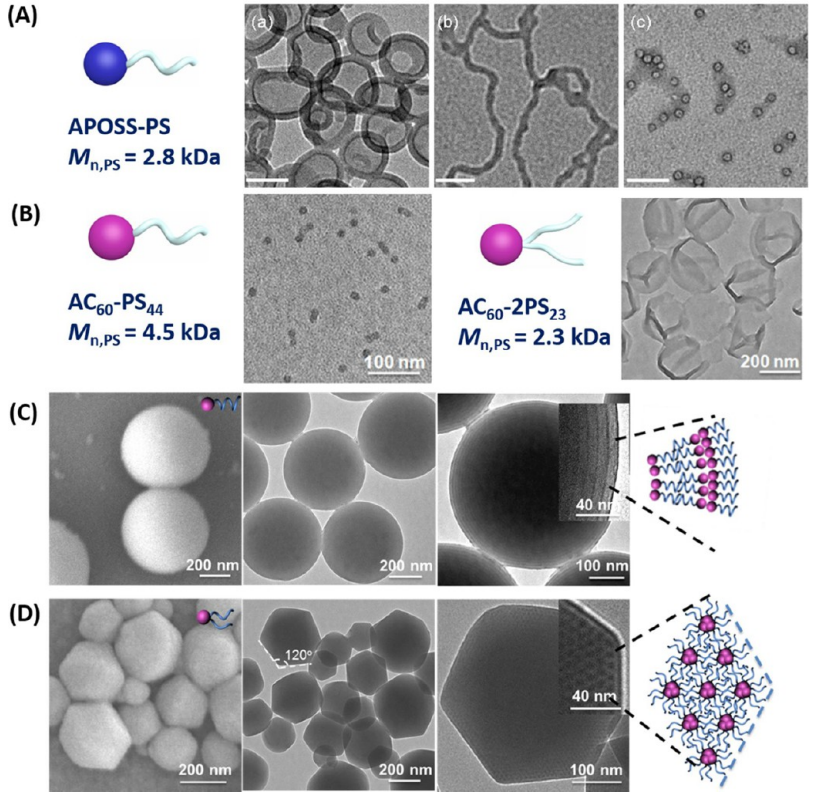

Figure 11. Self-assembled morphologies of different giant surfactants in solution. (A) TEM images of APOSS−PS micelles in solution with an initial concentration of 0.8% and a final water content >50% using (a) 1,4-dioxane, (b) DMF, and (c) DMF/NaOH. (B) TEM images of a pair of topological isomers, AC_{60}−PS_{44} and AC_{60}−$2PS_{23}$, in solution with a mixture of 1,4-dioxane and DMF (w/w = 1/1) as the common solvent and water as the selective solvent. (C) Scanning electron microscopy (left) and TEM bright images (right two) of self-assembled morphologies of AC_{60}−$2PS_{23}$ under similar conditions. The dark regions are the AC_{60} head domains and the gray regions are the PS tail domains. Part A is adapted with permission from ref 80, part B is adapted with permission from ref 64, and parts C and D are adapted from ref 16.

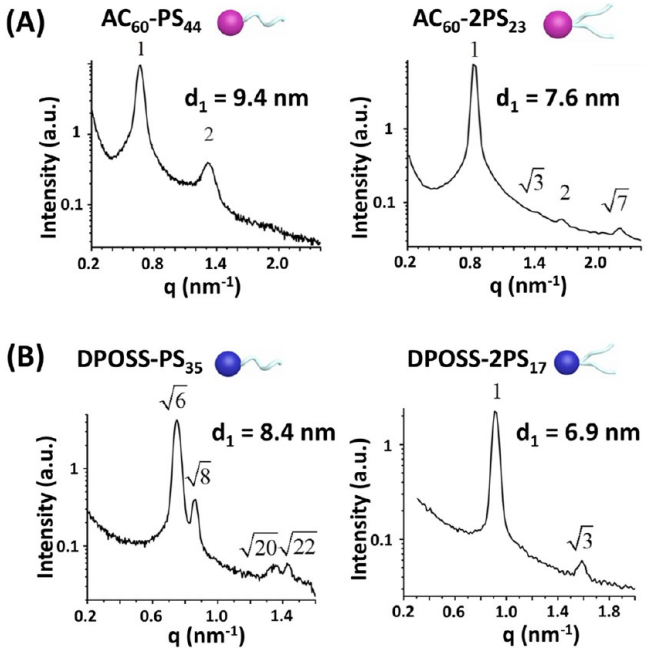

Figure 12. (A) 1D SAXS profiles obtained from a pair of topological isomers AC_{60}−PS_{44} and AC_{60}−$2PS_{23}$. (B) 1D SAXS profiles obtained from another pair of topological isomers DPOSS−PS_{35} and DPOSS−$2PS_{17}$.[16]

DPOSS−2PS with two PS tails (N = 17, N_{total} = 34) exhibited a hexagonal cylinder phase in the bulk (Figure 12B). Therefore, it is not sufficient to use a single order parameter (f_{PS}, volume fraction) to describe the phase separation and structure formation of giant surfactants. Additional order parameters associated with the geometrical shapes and molecular architecture should be introduced. We speculate that the ratio between the cross-sectional area of the head and tails is likely an important parameter.

VI. SUMMARY

In this Perspective, we have shown that molecular nanoparticles are indeed a versatile class of nanobuilding blocks for macromolecular science. With precisely defined structures (including core composition and peripheral functional groups) and shape-/volume-persistency, they can be viewed as unique modular macromolecular domains, or so-called "nanoatoms". They may be used to design and prepare precisely defined "giant molecules", including giant surfactants, shape amphiphiles, and giant polyhedra. Their precision synthesis can be facilitated by clicking "nanoatoms" together sequentially. Within the giant molecules, the "nanoatoms" interact with the rest of the macromolecule via collective secondary interactions and self-assembly into superlattices with phase separated regions where they further organize into hierarchical structures. The self-assembly of giant molecules exhibits an unusual sensitivity to their primary chemical structure and holds great promise in creating unconventional, technologically relevant nanostructures using relatively simple processes. Proteins can be regarded as natural giant molecules, and their unique structural diversity and

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functional plasticity are a direct consequence of the well-defined structure. Inspired by nature, polymer scientists are adopting both the design principles and assembling motifs to create hybrid materials. More specifically, we try to address Feynman's inquiry by answering the following questions: "How can we organize molecules into ordered complex structures? What kind of structures do we need to transfer and amplify microscopic functionalities to macroscopic properties? Can we combine different functionalities to achieve new properties beyond the conventional approaches?" It is anticipated that eventually libraries (or even new "periodic tables") of "nanoatoms" could be developed and categorized by their structure-forming characteristics and unique functions and equipped with "clickable" groups in a specific geometry as a mimicry to valence and bonding. Then, giant molecules of complex structure can be prepared with molecular precision through a series of "click" reactions from "nanoatoms". We envision that the development of materials would begin with the function in mind and be aided by computer design in selection of proper building blocks and designed hierarchical structures. This is essentially a materials genome approach[156] where the first principles of chemistry and physics are integrated in the design and programming of hierarchical structures responsible for a specific function. In this way, advanced materials could be achieved in a rational and modular fashion with performances that are not only mimics of those in nature but also beyond those in nature.

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Notes

The authors declare no competing financial interest.

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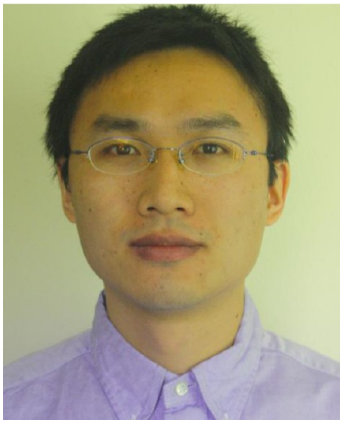
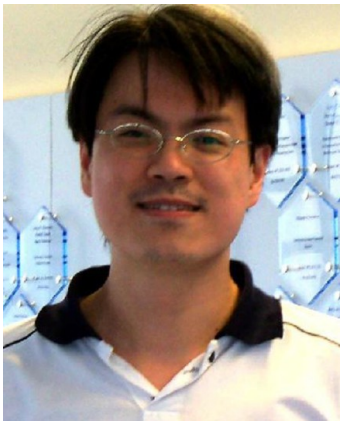


Xinfei Yu received his B.S. degree in Polymer Chemistry at Fudan University in 2005 and a Ph.D. degree in Polymer Science at the University of Akron in 2012. His research topic was synthesis and self-assembly of molecular shape amphiphiles: polystyrene-tethered hydrophilic polyhedral oligomeric silsesquioxanes and fullerene. He is currently a postdoctoral research associate in the Materials Science and Engineering Division at the National Institute of Standards and Technology under the supervision of Dr. Wen-li Wu and Dr. Dean M. DeLongchamp. His research interests focus on design, synthesis, and self-assembly of functional polymers and understanding their structure–property relationships with advanced measurement methods such as X-ray scattering and electron transmission microscopy.



Chien-Lung Wang received his Ph.D. degree in Polymer Science at the University of Akron in 2011. His research topic was synthesis and characterization of C_{60}–porphyrin derivatives for enhanced photovoltaic performance through efficient charge generation and transport. After spending six months as a postdoctoral assistant in Prof. Xiong Gong's research group at the Department of Polymer Engineering, the University of Akron, he joined the Department of Applied Chemistry, National Chiao Tung University, in Taiwan as an Assistant Professor. His current research focuses are on the phase transitions and supramolecular structures of conjugated molecules and self-assembled functional materials for organic optoelectronics.

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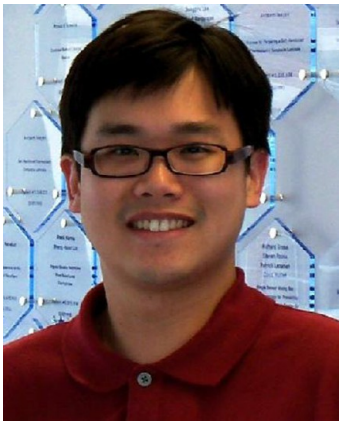
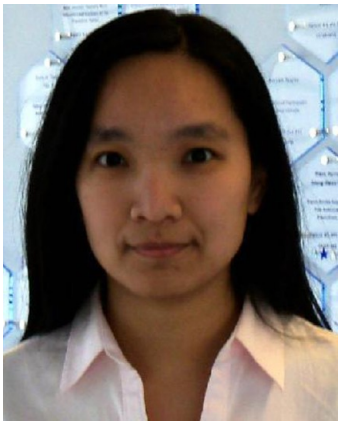
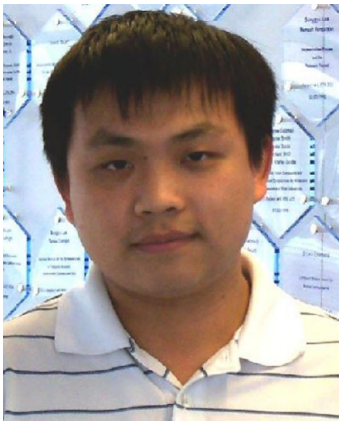


Hao-Jan Sun received his B. S. degree in Chemical Engineering at National Tsing-Hua University, Taiwan, in 2005 and his Ph.D. degree in polymer science at the University of Akron in 2012. His research topic was phase behaviors and Janus hierarchical supramolecular structures based on geometrically and chemically asymmetric building blocks. Hao-Jan then joined Prof. Virgil Percec's group as a postdoctoral fellow at the University of Pennsylvania. His research interests are natural and synthesized chiral supramolecular structures, sugar-containing Janus dendrimers, reversible complex/decomplex supramolecular structures, and dendronized π-conjugated molecules as building blocks for organic solar cell and photovoltaic applications.



I-Fan Hsieh received her B.S. and M.S. degrees in Chemical Engineering at National Tsing-Hua University and a Ph.D. degree in Polymer Science at the University of Akron in May 2013. Her research topics were pattern formation and phase behaviors of thin films of polystyrene-*block*-polydimethlysiloxane block copolymer and giant surfactants. After graduation, she joined Bridgestone Americans Center for Research and Technology as a scientist, working on the applications of microscopy in rubber systems.



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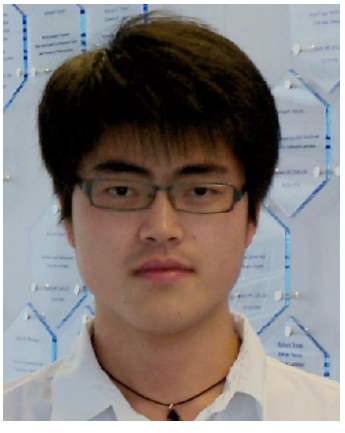

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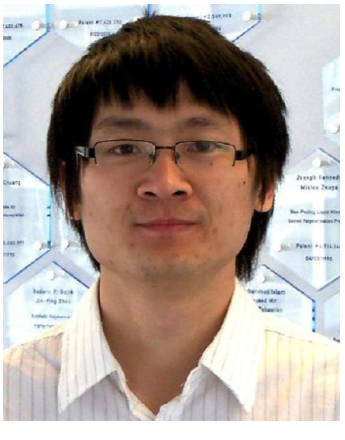

Kan Yue received his B.S. degree in Chemistry at Peking University in 2008. He jointed Department of Polymer Science at The University of Akron as a Ph.D. graduate student and received his Ph.D. degree in Polymer Science in December 2013. His research topic was design, synthesis, and self-assembly of giant surfactants based on polyhedral oligomeric silsesquioxane–polymer conjugates.

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Stephen Z. D. Cheng received his Ph.D. degree at Rensselaer Polytechnic Institute at Troy, New York, in 1985. His research interests are in the area of chemistry, physics, and engineering of polymers and advanced functional materials including ordered structure, morphology, phase transition thermodynamics, kinetics, and molecular motions. His recent interests in particular are focusing on nanohybrid materials with different molecular chemical structures and physical topologies, architectures, and interactions and their assemblies in the bulk, solution, and thin films. He is also active in developing researches of conducting polymers, photovoltaics, polymer optics, and photonics. Stephen Z. D. Cheng currently holds the R. C. Musson & Trustees Professor and serves as the Dean of the College of Polymer Science and Polymer Engineering at the University of Akron. He is the recipient of Presidential Young Investigator Award (1991), John H. Dillon Medal (APS, 1995), Mettler-Toledo Award (NATAS, 1999), TA-Instrument Award (ICTAC, 2004), PMSE Cooperative Research Award (ACS, 2005), Polymer Physics Prize (APS, 2013), and other awards and recognitions. Cheng has been a Fellow of AAAS and APS and an Honorable Fellow of Chinese Chemical Society. He has been elected as a member of the National Academic of Engineering of US (2008).

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