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COMMUNICATION

Sequence Mandated, Distinct Assembly of Giant Molecules

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Abstract: Although controlling primary structures is by itself an enormous challenge for synthetic polymers, the potential of sequence control for tailoring hierarchical structures remains to be exploited, especially in the creation of new and unconventional phases. Herein, we design and synthesize a series of model amphiphilic chain-like giant molecules by interconnecting both hydrophobic and hydrophilic molecular nanoparticles in precisely defined sequence and composition to investigate their intriguing sequence-dependent phase structures. Not only has compositional variation changed the self-assembled supramolecular phases, but also specific sequences are found to induce unconventional phase formation, including Frank-Kasper phases. The formation mechanism has been attributed to the conformational change driven by the collective hydrogen bonding and the sequence-mandated topology of the molecules. These results support that sequence-control in synthetic polymers can have dramatic impacts on the polymer properties and self-assembly.

Natural polymers, such as deoxyribonucleic acids, ribonucleic acid, and proteins, accomplish highly sophisticated functions to sustain life with a small set of simple building blocks arranged in precisely defined composition, length, sequence and stereochemistry. Their properties and performances are in fact mandated by the information encoded in polymer sequences. The importance of sequence has also been demonstrated in some bio-resembling polymers, such as peptides, peptoids and nucleic acids,[1] which inspired the next generation sequence-controlled synthetic polymers. Recently, with contributions from Lutz, Du Prez, Haddleton, Liu and others, tremendous progress has been made on the synthetic methodologies.[2] Although the synthesis of sequence-controlled polymers at a similar level of precision to natural polymers is an enormous endeavor by itself,[3] it remains to be demonstrated how sequence could dictate molecular topology and assembly toward different structures and functions in synthetic polymer.[2c, 4] While assembly of most synthetic macromolecules is driven by interaction of monomers,[5] the minute differences between individual monomers are often insufficient to discriminate assembly pathways. Thus, precisely controlled collective and cooperative interactions have been increasingly recognized as the key process to form hierarchical structures with feature sizes of only a few nanometers.[6] In this case, oligomers/polymers with nano-sized "macro-monomers"[7] is an effective approach to build phase-separated nanostructures with the most significant impact of sequence. The imposing challenge that we are facing is not only to achieve a macromolecule with precisely defined sequences and sizes, but also to design and control their self-assembled structures and develop desired properties. Recent advances of "click" chemistries and other efficient transformations allow scientists to achieve macromolecules with high structural precision and controlled heterogeneity. On the other hand, the supramolecular structures are modularly assembled from a set of building blocks and thus, the topology and interaction of each building block are critically important to the final assembled structures. They, in turn, must be accurately determined by the composition and sequence of the macromolecule. Aiming at such an enormous task, we begin by rationally designing a series of model amphiphilic giant molecules (so-called "giant" relative to their small-molecule counterparts)[8] as for the study of sequence-phase relationships and the role of sequences in the formation unconventional phases in soft matters.[9] More specifically, these giant molecules here refer to precise macromolecules build-up by molecular nanoparticle building blocks. We have previously investigated the effects of composition and topology on the self-assembly of giant molecules.[4b, 6c, 9d, 10] However, the importance of sequence has not been systematically explored in terms of their impact on phase formation.

Herein, the rational design of model compounds was based on linearly-like configured, monodisperse giant molecules with consecutively connected polyhedral oligomeric silsesquioxane (POSS) molecular nanoparticles (NP). For simplicity, only two types of repeating units were employed: the hydrophobic BPOSS (~1 kDa with 7 *sec*-butyl groups) and the hydrophilic DPOSS (~1.5 kDa with 14 hydroxyl groups). Each POSS NP is a building block, which can be viewed as a "macromonomer" or a "precise block of polymer". The detailed molecular structures are illustrated in Figure 1. We believe that the collective interaction between different macromonomers could enable efficient construction of novel nanostructures, thus the attachment of large-sized NPs will make the sequence effect even more pronounced. This series of amphiphilic giant molecules could thus serve as a good platform to understand the sequence effect in synthetic macromolecules. From chemistry point of view, tuning exact number of nanoparticles with precise chemical structures to build the giant molecules eliminates the batch to batch variations in conventional polymers due to polydispersity.[11] We could also precisely manipulate their connecting sequence to achieve different "sequence isomers" in a way similar to playing with "*Lego*" blocks. From physics point of view, they have large enough immiscibility to induce nanophase separation between different NPs. The thermodynamic driving force is the strong collective hydrogen bonding formed via dense hydroxyl groups on the peripheries of DPOSS cages among giant molecules. The hydrophobic BPOSS NPs are nanophase separated from DPOSS NPs (χ > 0.3, see SI for calculation[12]). Due to the incompatibility of these two kinds of nanoparticles, BPOSS NPs tend to stay away from DPOSS NPs.[10a]

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Notably, their selective interactions dominate the formation of building blocks via macromolecular packing arrangements, and become the most important factor in determining their assembled structures. The building blocks are thus constructed by a core of DPOSS NPs aggregated together and covered with a thick shell formed by BPOSS NPs. It should be noted that stereochemistry refers another important parameter in natural polymers. However, this factor is not the focus of the current study and thus are not further discussed in this paper.

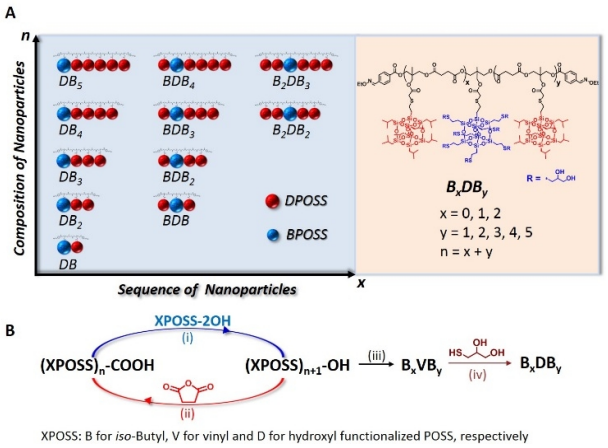

Figure 1. A. Illustration of chain-like giant molecules with precisely controlled sequences and compositions built up by both hydrophilic and hydrophobic (D and B) POSS NPs. (*x* and *y* are the number of BPOSS nanoparticles on the left and right side of the DPOSS in the linear-like giant molecules. *n* is the total number of the BPOSS NPs.) B. illustration of general synthetic strategy for these molecules.

Therefore, there are two dimensions to tune their structures and properties–composition and sequence. In detail, the local conformation of individual giant molecules would be relatively extended in the tails when $x = 0$ in Figure 1. We speculate that as the number of hydrophobic BPOSS (n) increases, it becomes increasingly difficult to force the BPOSS NPs to line up within the cross-section area of one DPOSS NP due to the progressively elevated entropic penalty. This would possibly lead to phase structures evolving from LAM → HEX → BCC, like many asymmetric block copolymers. When $x \neq 0$ in Figure 1, the local conformation of individual molecules would be in distinct folded states with respect to the DPOSS NP in the tails by specific design of DPOSS position in the chain sequence. From left to right along the horizontal lines (as x increases) in Figure 1, the tail conformation changes from non-folded to asymmetric, and finally to symmetric/close-to-symmetric folded conformations with changing the NP sequence at designated composition. We hypothesize that the sequence effect in the molecules could induce folded conformation driven by the collective hydrogen bonding among the hydrophilic molecular NPs and influenced by the sequence-mandated topology of the hydrophobic NPs, finally determining the interfacial areas of the two phases at designate composition. This would result in different "fan-angles", "cone-angles" of the whole molecules, which could affect the aggregation numbers or even possibly induce phase transformations.

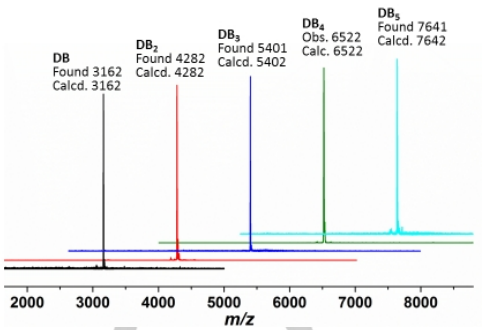

Figure 2. MALDI-TOF spectra of DB_n (n = 1-5). All the samples show peaks of $[M{\cdot}Ag]^+$ corresponding to the calculated molecular weights.

These monodisperse giant molecules (with molecular weight as high as >7k) exhibit single lines which are accurate to the atomic level based on matrix assisted laser desorption/ionization-time of flight (MALDI-TOF) mass spectra as shown in Figure 2. The general synthetic illustration is shown in Figure 1B and the detailed routes and characterizations (^{1}H, ^{13}C NMR and other MS spectra) are outlined in supporting information (SI).

These amphiphilic giant molecules exhibit versatile ordered supramolecular phases with sub-10 nm feature sizes typically after thermal annealing for 2 hours at about 150 °C. When BPOSS cage does not crystallize, multiple hydrophilic DPOSS cages start aggregating together via the collective hydrogen bonding which forms one nanophase, and push out the rest hydrophobic BPOSS cages to organize into the other phase.

For DB ($n = 1$, $x = 0$ in Figure 1), it has no sequence isomer. With more or less commensurate size of the two NPs, an alternating layered structure is expected from this molecule. A small angle X-ray scattering (SAXS) pattern shows multiple peaks of equal q interval, indicating a lamellar (LAM) lattice with layer spacing of 6.81 nm (Figure 3A(i)). The lamellar structure is also confirmed by the bright field (BF) TEM image in real space (Figure 3A(ii)).

For DB_2 ($n = 2$, $x = 0$), a double gyroid (DG) lattice (with a space group of $Ia\bar{3}d$) can be observed based on characteristic q ratio of diffractions of $\sqrt{6}{:}\sqrt{8}$ in the SAXS pattern (Figure 3B(i)). In this DG lattice, two BPOSS cages are sequentially and linearly-like tethered on the DPOSS cage, and the aggregated DPOSS cages via collective hydrogen bonding are imbedded in the BPOSS matrix (Figure 3B(ii)). However, by moving the DPOSS cage to the second position ($x = 1$), the sequence isomer BDB adopts a symmetric folded conformation with unbalanced interface between DPOSS and two BPOSS cages. The SAXS pattern of BDB exhibits scattering vector q ratio of $1{:}\sqrt{3}{:}\sqrt{4}$ in Figure 3C(i), indicating the formation of a hexagonal packed cylindrical (HEX) structure. The real space image observed via BF TEM is shown in Figure 3C(iv). The average fan angles (α) for each molecule can be estimated in BDB to be about 30° (Table 1, for detailed calculation, see SI).

DB_3 ($n = 3$, $x = 0$) and its isomer BDB_2 ($n = 3$, $x = 1$) both exhibit HEX structures (Figure 3C), yet with different lattice sizes (6.79 and 6.58 nm). Among them, each BDB_2 molecule possesses an asymmetric folded conformation in the assembly, while DB_3 does not. Therefore, BDB_2 sample contains a larger fan angle, less number of molecules per unit length of the cylinder (10 molecules per DPOSS cage thickness, α ~36°, Table 1, see SI for calculation) compared to the DB_3 (12 molecules per

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DPOSS cage thickness, α ~30°), which leads to a smaller lattice size of BDB_2 (6.58 nm) than that of DB_3 (6.79 nm, Table 1).

When BPOSS cage number exceeds three, the incommensurate volumes between DPOSS and BPOSS cages become increasingly large. This may cause the molecules to form a cone-like shape to accommodate this volume difference, the shape of building blocks must be spherical, leading to further assemble into spherical phases. For example, in traditional diblock copolymer systems, BCC structures are usually observed in cases with spherical building blocks. Interestingly enough, however, DB_4 (n = 4, x = 0) shows an unanticipated Frank-Kasper (F-K) A15 phase (space group $Pm\bar{3}n$ (O_h^3)) with characteristic q ratio of $\sqrt{2}:\sqrt{4}:\sqrt{5}:\sqrt{6}$ in the SAXS patterns as shown in Figure 3D(i) and a representative tiling number of 4^4 in the BF TEM images along the [001] zone in Figure 3D(iv).[10a] Note that F-K phases were originally found in many metal alloys which possess topological close packing combining the Frank lattice (distorted icosahedral with coordination number, CN, of 12) and the Kasper polyhedra (with CN of 14, 15, or 16).[13] Some F-K phases were also recently found in soft materials, such as dendrimers, block copolymers etc.[9a, 9b, 9d, 14] The A15 is one of three basic phases in the series of F-K phases with two types of slightly different sizes of the spherical building blocks in a ratio of 1:3.[15] Its crystal structure (space group $Pm\bar{3}n$ (O_h^3)) involves both the Frank lattice (CN: 12) and the Kasper polyhedra (CN: 14). Although the F-K phase formation mechanism remains elusive in soft matters, the formation of F-K A15 phase is probably due to the deformable and squishable nature and volume exchange of the spherical building blocks. Thermodynamically, the A15 phase possesses a better sphericity of building blocks,[16] and a lower interfacial tension with higher stretching energy compared with those in BCC.[17] When we move the DPOSS cage from the chain end to the second position, BDB_3 (n = 4, x = 1) starts to adopt the folded conformation. However, with the asymmetric number of BPOSS cages on both side of the DPOSS cage, this might generate "surface defects" at the spherical building blocks of BDB_3. In this case, the supramolecular structure of BDB_3 is identified to be a dodecagonal quasicrystal (DQC), as illustrated by the characteristic SAXS pattern (the 00002, 12100, 10102, and 12101 diffractions in Figure 3D(ii)). More than one representative tiling patterns of $3^2.4.3.4$, $3^3.4^2$, 4^4 and 3^6 could be observed in the BF TEM image in Figure 3D(v), illustrating that the structure losses the translational symmetry along the a^*b^*-plane.[9d, 14a] For B_2DB_2 (n = 4, x = 2), the sequence change resulted in a shorter but symmetric BPOSS tails, it forms an A15 phase again. In this A15 structure, each molecule adopts the folded conformation in the assembly and possesses a larger cone angle (~38°, Table 1, see SI for calculation), a smaller average number of molecules in one spherical building block (μ = 36, Table 1, see SI for calculation) and thus, a smaller lattice spacing (a = 13.5 nm) compared to the DB_4 case (with a cone angle 33°, μ = 47, a = 14.8 nm).

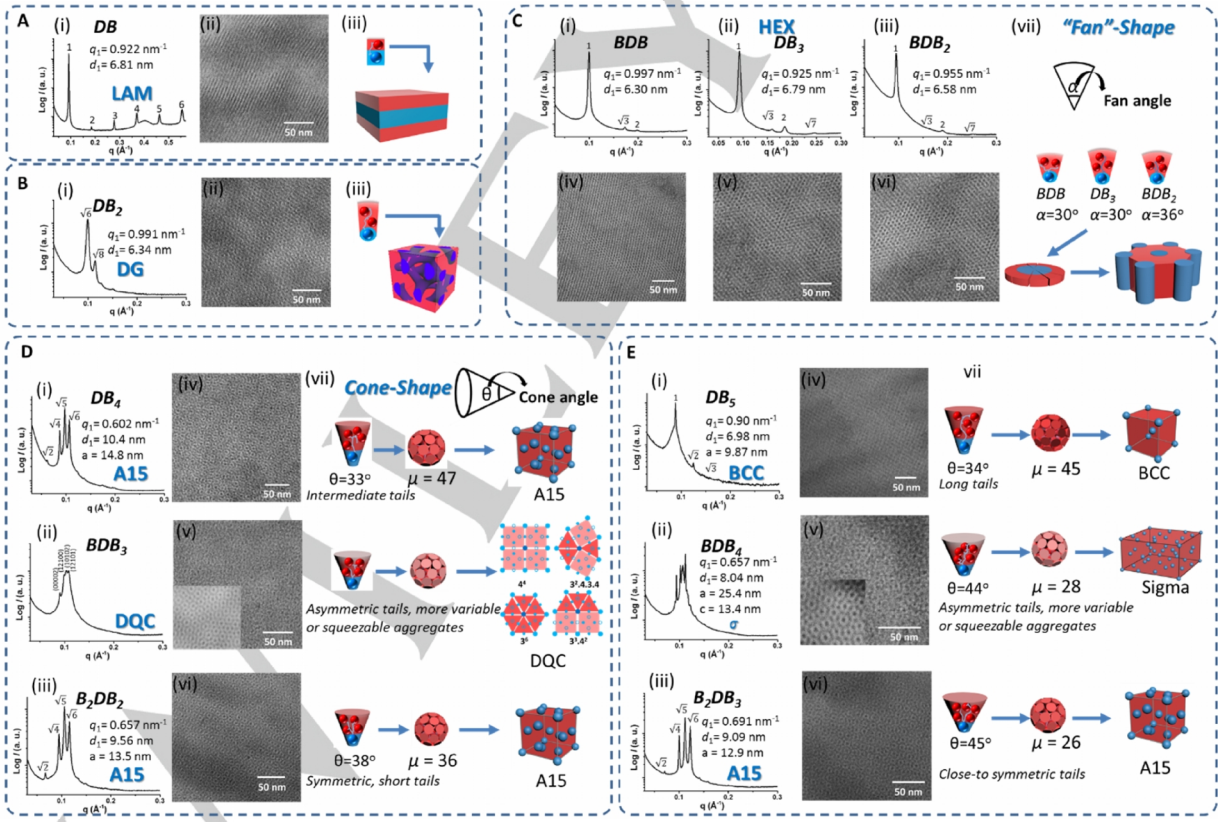

Figure 3. SAXS patterns, TEM images and packing models of giant molecules. (A). DB forms a LAM phase. (B) DB_2 forms a DG phase. (C). BDB, DB_3, and BDB_2 adopt fan-shapes and form HEX phases. (D). DB_4, BDB_3, and B_2DB_2 adopt cone-shapes and form A15, DQC and A15 phases, respectively. The inset in (v) is the Fourier filtered image. (E). DB_5, BDB_4, and B_2DB_3 adopt cone-shape and form BCC, σ and A15 phases, respectively. The inset in (v) is the Fourier filtered image.

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By further increasing the number of BPOSS cages to five, the long BPOSS tail length in DB_5 (n = 5, x = 0) would impose higher entropy penalty if it remains in an extended chain conformation. It is found to form a BCC structures (space group of *Im3m*) with a = 9.86 nm as shown in Figure 3E(i) and (iv). While for BDB_4 (n = 5, x =1) with asymmetric folded conformation, the resulting SAXS pattern shows a set of peaks that can be assigned as a σ lattice (space group of $P4_2/mnm$) with tetragonal unit cell parameter a = b = 25.4 nm, c = 13.4 nm as shown in Figure 3E(ii) and (v). In σ phase, there are two spherical building blocks with different sizes in equal number ratio, which are packed in a way combining the Frank Lattice (CN: 12) and two types of Kasper polyhedra (CN: 14 and 15).[9a, 14b] For B_2DB_3 (n = 5, x = 2) with close to symmetric conformation and shortened BPOSS chain length (only 3), it possesses an A15 lattice with a = 12.9 nm (Figure 3E). Detailed supramolecular lattice parameters for all these self-assembled structures are listed in Table 1.

Table 1. Supramolecular structure analysis of giant molecules.

Molecules	Phase	a (nm)[a]	r (nm)[b]	μ[c]	α or θ [d]
DB	LAM	6.81	-	-	-
DB_2	DG	6.34	-	-	-
BDB	HEX	6.30	3.64	12	30°
DB_3	HEX	6.79	3.92	12	30°
BDB_2	HEX	6.58	3.80	10	36°
DB_4	A15	14.8	4.59	47	33°
BDB_3	DQC	-	-	-	-
B_2DB_2	A15	13.5	4.19	36	38°
DB_5	BCC	9.87	4.86	45	34°
BDB_4	σ	25.4^2×13.4	4.09	28	43.6°
B_2DB_3	A15	12.9	4.00	26	45.2°

[a] Dimensions of the phase: lamellar periodicities, inter-column distances of HEX lattice, lattice dimensions of A15, BCC and σ lattices. [b] dimensions of the motif: radiuses plates in HEX, radiuses of spheres in A15, BCC and σ lattices. [c] number of molecules per spherical building block. [d] fan-angle (α) or cone angle (θ).

How to understand these experimental observations and what are the general implications? If we exam the first left column in Figure 1, it is evident that this series of samples only represent the compositional variation without alternating the sequences. With increasing the volume fraction of the BPOSS cages from ~1/2 to 5/6, the supramolecular structure evolves from LAM to DG to HEX to A15 and finally, to BCC phases. This phase sequence with the volume fraction has been reported experimentally,[9d] and predicted theoretically.[18] It is very interesting that phase structures also change with identical volume fraction but distinct sequences. For example, in the first line of DB_5 series in Figure 1, with moving the DPOSS cage from x = 0 to x = 3, the phase structure changes from BCC to σ and to A15 phases (also see the second row of DB_4 series). The rationale for the phase structure changes in this series of chain-like giant molecules is probably due to the effect of overall macromolecular topologies dominated by the folded conformation. Namely, the sequence variation first transcripts into the disparity in macromolecular topology, which, in turn, translates into the distinct molecular packing, leading to different ordered supramolecular lattices. The incommensurate cross-section areas between hydrophilic and hydrophobic components lead to curved interfaces to stabilize the supramolecular lattices. In addition, the deformability and squeezability of the spherical building blocks are also mainly attributed to the rearrangement and relocation of the BPOSS cages after the folded conformation and the confined packing of each giant molecule in the assembly. Note that no matter how these BPOSS cages pack in the thick shell of the spherical aggregates, their density must remain constant (measured to be ~1.2 g/cm^3). In comparison to previous cases with F-K phases formed by block copolymers, our results highlight the ability to tune phase structures with precise composition and sequence.

In summary, we have specifically designed this library of chain-like giant molecules with precisely defined sequences and compositions. This system contains a pair of interactions: collective hydrogen bonding and nanophase separation, namely, the hydrogen bonding and hydrophilic/hydrophobic interactions. Starting from DPOSS nanoparticle located at one end of the chain and increasing the number of hydrophobic BPOSS, these chain-like giant molecules create lattices from LAM, DG, to HEX, F-K A15 and BCC structures. By moving the DPOSS nanoparticle toward the center of the chain, a series of sequence isomers with identical composition was prepared. The distinct locations of DPOSS mandate the folded conformation of giant molecules into different conformations, which further results in different supramolecular lattices including F-K A15, σ as well as DQC structures. As designed, the molecules with symmetric/asymmetric folded conformation significantly affect the ordered lattice structure formations within this window of unconventional phases. This work has demonstrated the importance of primary structure, especially molecular sequence, in mandating molecular topologies to affect their self-assembly behaviors in these linear-like POSS-based giant molecules. We envision that the building blocks are not limited as POSS nanoparticles and could also include other functional motifs (e.g. optical, electric, magnetic). Tremendous interesting materials could be constructed by incorporating more complicated precise sequence with multiple cooperative/competing interactions or functionalities. Inspired by this work and general rule in giant molecules, to systematically develop macromolecules with precision at molecular weight scale as well as at the sequence scale, a new field of synthetic polymeric materials would be opening.

Experimental Section

The detailed synthetic routes, characterization methods, samples preparation and other data are described in the Supporting Information.

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Keywords: sequence • polymer • supramolecular structure • POSS • Frank-Kasper phase

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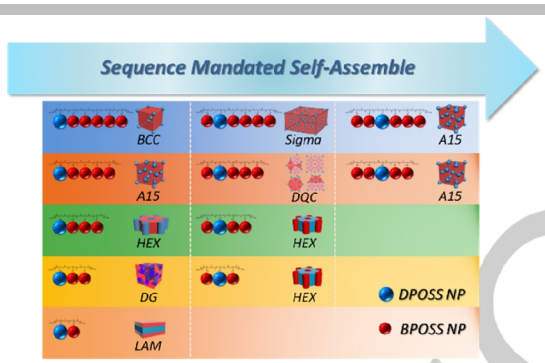
Molecular nanoparticles can be precisely connected into chain-like macromolecules as sequence controlled polymers.

The sequence, in addition to the composition of the synthetic polymers can be specifically designed to mandate their supramolecular phase structures.



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Sequence Mandated, Distinct Assembly of Giant Molecules