

Self-Assembly of Repetitive Segment and Random Segment Polymer Architectures

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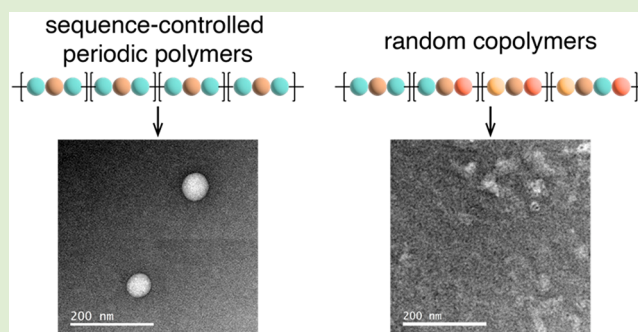
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ABSTRACT: Recent advances in chemical synthesis have created new methodologies for synthesizing sequence-controlled synthetic polymers, but rational design of monomer sequence for desired properties remains challenging. In this work, we synthesize periodic polymers with repetitive segments using a sequence-controlled ring-opening metathesis polymerization (ROMP) method, which draws inspiration from proteins containing repetitive sequence motifs. The repetitive segment architecture is shown to dramatically affect the self-assembly behavior of these materials. Our results show that polymers with identical repetitive sequences assemble into uniform spherical nanoparticles after thermal annealing, whereas copolymers with random placement of segments with different sequences exhibit disordered assemblies without a well-defined morphology. Overall, these results bring a new understanding to the role of periodic repetitive sequences in polymer assembly.



The synthetic toolbox for controlling monomer sequences in non-natural polymers has recently expanded, enabling new opportunities to prepare synthetic materials with a high level of structural and functional diversity.^{1–6} Unlike small molecules, the primary monomer sequence in synthetic macromolecules leads to complex chemical assembly landscapes that are dictated by multiple inter- and intrachain interactions.⁷ Despite recent advances, the ability to rationally design monomer sequences to control macromolecular assembly remains a key challenge in the field due to limited knowledge on sequence–structure–property relationships in synthetic polymers.^{2,8}

The link between sequence, structure, and function in proteins over evolutionary history provides a strategy to identify predictable sequence–property relationships in synthetic polymers.^{9–11} A budding theory in the field of molecular evolution posits that nature took advantage of ancestral proto-peptides and evolved them into various protein domains with structural complexity and desired functionality.^{12–14} Protein tandem repeats are a ubiquitous class of proto-peptide structural motifs in proteomes and occur in at least 14% of all proteins.¹⁵ Moreover, tandem repeats with short repetitive units are more frequently observed than other repeat motifs. For example, crystalline aggregates are formed by regions with 1 or 2 residue long repeats, and fibrous structures are stabilized by interchain interactions with 3 to 7 residue repeats.^{16,17} In addition, utilizing and incorporating repetitive amino acid sequences form the basis of the consensus protein design strategy,^{18,19} which leverages monomer-level engineering of the tandem peptide repeats to

produce structurally defined scaffolds and to mediate protein–protein interactions.²⁰

Motivated by the success of using tandem peptide repeats in rational protein design, we hypothesized that, by engineering repetitive segments of peptide sequences into the polymer backbone and leveraging the polymer's conformational flexibility, the resulting sequence-controlled periodic polymers (SCPPs) will exhibit unique self-assembled morphologies that can be tuned by adjusting the monomer sequence of the repetitive segments. In this work, we demonstrate the synthesis of SCPPs containing different repetitive peptide sequences and the role of repetitive segment versus random segment polymer architecture in solution self-assembly. We find that the synthesized SCPPs predominantly assemble into spherical particles in aqueous solution, whereas copolymers with random placement of different sequence segments generate disordered aggregates under the same conditions. Analysis using transmission electron microscopy (TEM) further indicates that the average particle size and assembly type are tuned through the peptide sequence of the repetitive segment. Broadly, the strategy used in this work is highly customizable and can be expanded to design and engineer new synthetic

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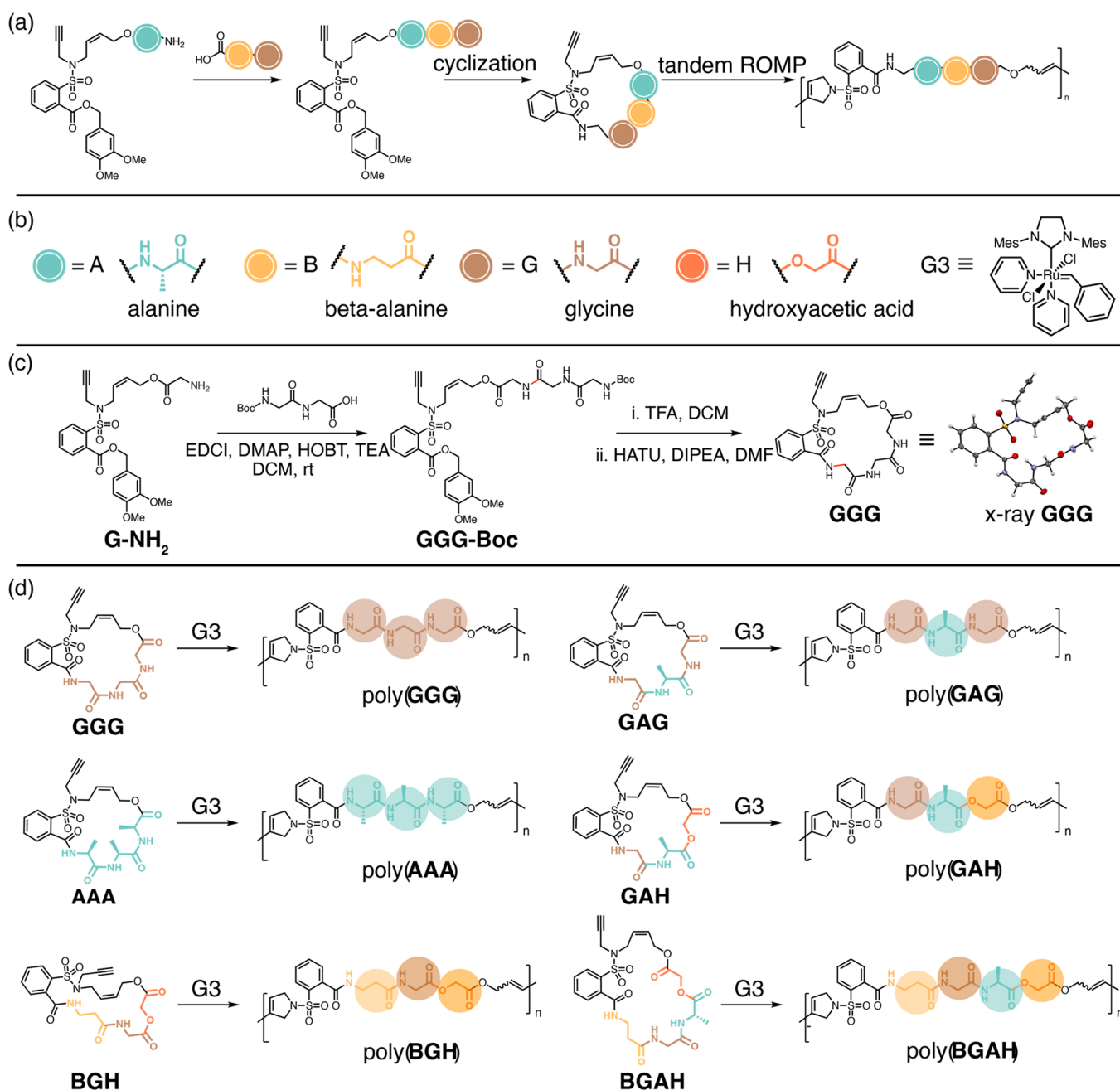


Figure 1. (a) Overall synthetic approach involving cyclization to prepare macrocycles embedded with tri- and tetrapeptide sequences and polymer synthesis using a tandem ROMP reaction. (b) Monomer building blocks for sequence construction: A (alanine), B (β -alanine), G (glycine), and H (hydroxyacetic acid). Pyridine-modified Grubbs third-generation catalyst (G3) was used for tandem ROMP. (c) Synthesis and crystal structure of macrocyclic monomer GGG. (d) Set of sequence-controlled periodic copolymers prepared by tandem ROMP.

polymeric materials by leveraging the diverse scope of available monomers.

To prepare polymers containing the desired repetitive sequence motifs, we used a tandem ring-opening metathesis polymerization (ROMP) method reported by Gutekunst and Hawker (Figure 1a).²¹ In this polymerization process, the Grubbs catalyst is highly reactive toward terminal alkynes and generates an initial carbene complex, which is subsequently transferred to open the adjacent cyclic olefin and form a propagating species.^{22,23} Due to this replay-type metathesis polymerization, a well-defined head-to-tail directionality and connectivity is achieved, thereby enabling incorporation of segments with sequence directionality. Overall, this synthetic

approach involves two steps: (1) preparation of the cyclic olefin monomer embedded with sequence-defined segments and (2) polymerization of the cyclic monomer using tandem ROMP.

In this work, we chose alanine (A), β -alanine (B), glycine (G), and hydroxyacetic acid (H) for sequence construction (Figure 1b). The alternating Gly-Ala motif is a well-known complementary sequence for the formation of antiparallel β -sheets in silk proteins and is widely used to control hierarchical structures in synthetic materials.^{24–26} We hypothesized that incorporating this motif into the polymer backbone in a periodic manner would lead to the formation of compact assemblies in aqueous solution. Moreover, glycine (G) and β -

alanine (B) are the conformationally flexible α - and β -amino acids. Prior work has shown that sequence variation of these two amino acids can alter the solution folding behavior of tetrapeptides.²⁷ Finally, hydroxyacetic acid (H) was inserted into the repetitive sequence due to its structural character and solubility. Hydroxyacetic acid is a structural analogue of glycine (G) and β -alanine (B) but does not form complementary H-bonding with an amide bond. In this way, hydroxyacetic acid is used to tune the assembled structure while circumventing potential poor solubility of the peptide-containing polymers. Here, we specifically chose non-charged building blocks to avoid electrostatic interactions which bring additional interactions to the energetic landscape for self-assembly. We therefore anticipate that the hydrophobic interactions and the complementary H-bonding interactions are the main driving forces for self-assembly in our designed SCPPs.

A series of macrocyclic monomers were first prepared using an amide coupling reaction and intramolecular cyclization (Figure 1c). Our initial attempts to directly couple oligopeptides to the sulfonamide precursor **4** revealed a low yield (<10%) (Supporting Information, Scheme S1). We therefore first coupled a single amino acid to the precursor **4** to yield an intermediate (for example, **G-NH₂** in Figure 1c), followed by subsequently coupling desired oligopeptides to the intermediate. Using this approach, we built the desired sequence and synthesized six different macrocyclic monomers with defined segment sequences (synthetic details in the Supporting Information, Figures S1–S64).

Using the tandem ROMP method,²¹ we prepared a series of SCPPs with the desired segment sequence motifs (Figure 1d). In all cases, polymerization was performed with a monomer to initiator ratio (M/I) of 50:1 in the presence of an additional ligand, 3,5-dichloropyridine. Following polymerization, the ruthenium catalyst (G3) was removed using a thiol-functionalized resin (Quadrasil MP) before further characterization.²⁸ The purified polymers were characterized by NMR, GPC, MALDI-TOF, DSC, TGA, and FT-IR (additional discussions in the Supporting Information under section S5). The characterization data are summarized in Table 1. The prepared polymers show moderate solubility in DMF and a mixture of DCM/MeOH (9:1), except for poly(GGG). Attempts at characterizing the polymers using circular dichroism (CD) spectroscopy were unsuccessful because the targeted wave-

length range (200–220 nm) was obscured by the strong solvent background of DMF or DCM. In general, the polymers exhibit control of polydispersity and olefin stereoselectivity, which is consistent with prior reports.²¹ The polymers' NMR spectra are well-resolved due to the good regioselectivity using the tandem ROMP method (Figure 2a and Supporting Information, Figures S65–S76). MALDI-TOF mass spectrometry further confirmed a mass difference corresponding to the mass of the repeat unit (Figure 2b and Supporting Information, Figures S77–S80).

The structures of synthesized SCPPs were analyzed using 2D ¹H–¹H COSY and NOESY NMR (Figure 2c and Supporting Information, Figures S81–S90). We identified the proton signals in the *E/Z* isomers of the acyclic alkene (**H_a**) and determined the *E/Z* ratio accordingly. Protons in each peptide segment were also identified using COSY NMR, confirming the polymer's primary structure. In addition, we used 2D ¹H–¹H NOESY NMR experiments to study the polymer conformation in solution. Interestingly, our results show that the *s-trans* conformation is dominant between the cyclic and acyclic alkenes (Figure 3). As implied by the crystal structure (Figure 1c), we conjecture that it is sterically favorable that the addition of active Ru carbene to the terminal alkyne occurs on the lateral side that faces away from the macrocycle, which favors an *s-trans* diene conformation during chain propagation and subsequently leads to a dominant *s-trans* conformation in the polymer backbone.

To investigate the role of repetitive segment versus random segment architecture, we further prepared the copolymer (poly[(GAG)-*ran*-(GAH)-*ran*-(BGH)-*ran*-(BGAH)]). This random segment copolymer was synthesized by copolymerizing four cyclic monomers (BGAH, GAG, BGH, and GAH) in a 1:1:1:1 molar ratio using the same conditions as for SCPPs synthesis (Figure 4a). We hypothesized that the heterogeneity induced by randomly linked sequence segments would interrupt the complementary hydrogen-bonding between tandem repeats and consequently lead to a disordered self-assembled morphology. By comparing the self-assembly behaviors between the random segment copolymer and SCPPs, we aimed to understand how sequence precision affects self-assembly.

To investigate the self-assembly behavior of the synthesized SCPPs in solution, we began by screening for a suitable solvent system using dynamic light scattering (DLS). Mixtures of DMF and water in DMF/water volumetric ratios of 4:6, 3:7, 2:8, and 1:9 were chosen, with water acting as a poor solvent to drive the assembly (Supporting Information, Figures S95–S96). The prepared polymer solutions (0.1 mg/mL) were heated to 70 °C for 30 min and slowly cooled to room temperature to facilitate self-assembly.²⁹ DLS results indicate that the 20% DMF/water solvent system leads to the formation of the most compact nanostructures, with the hydrodynamic diameter of SCPPs ranging from 50 to 75 nm.

We next used TEM to study the details of the self-assembled morphologies (Figure 4b and Supporting Information, Figures S97–S102). Interestingly, we found that SCPPs predominantly assemble into spherical nanoparticles, whereas the copolymer with random segments shows disordered aggregates under the same conditions. This key observation supports our hypothesis that polymers with controlled monomer sequences exhibit more ordered self-assembled morphologies relative to its random analogues, which can be attributed to the uniformity of sequence segments along the polymer backbone. Prior work

Table 1. Summary of Material Characterization for the Prepared SCPPs

entry ^a	M_n GPC ^b (kDa)	\mathcal{D}	M_n NMR ^c (kDa)	<i>E/Z</i> ratio ^d	T_g (°C)	T_d (°C)
poly(GAG)	22.3	1.23	16.7	3.2:1	–	260
poly(GAH)	18.2	1.13	22.8	3.0:1	73	260
poly(BGH)	18.0	1.08	14.3	5.0:1	–	250
poly(BGAH)	11.6	1.27	16.4	4.5:1	95	270
poly(AAA)	21.2	1.29	15.6	3.8:1	–	290
poly[(GAG)- <i>ran</i> -(GAH)- <i>ran</i> -(BGH)- <i>ran</i> -(BGAH)]	15.0	1.13	14.8	3.5:1	90	252

^aPrepared with monomer/initiator ratio = 50:1. Polymer poly(GGG) exhibits poor solubility and precipitated from solution during polymerization. ^bDetermined using DMF GPC equipped with a light scattering detector. ^cDetermined by end group analysis using ¹H NMR. ^d*Cis/trans* isomers were identified by 2D COSY NMR, and the ratio was calculated using ¹H NMR.

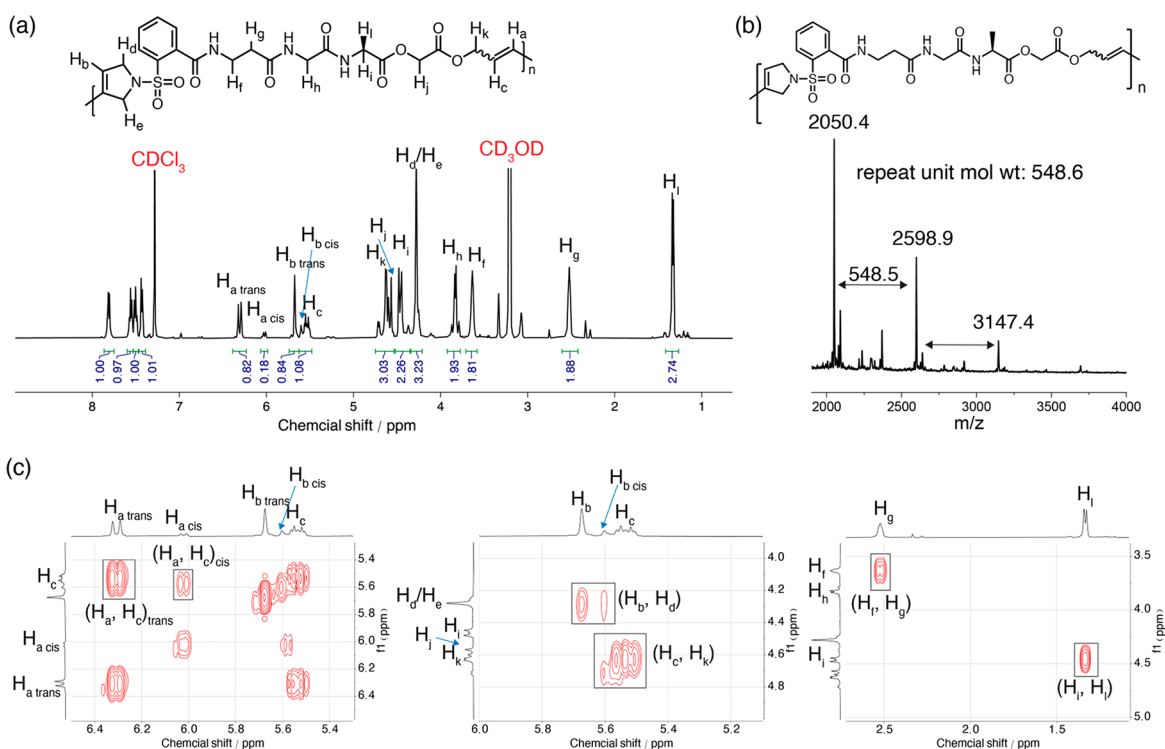


Figure 2. NMR spectroscopy (500 MHz, 25 °C, and $\text{CDCl}_3/\text{CD}_3\text{OD}$ 9:1) and MALDI-TOF mass spectrometry characterization of sequence fidelity. (a) ^1H NMR spectra of poly(BGAH) and proton assignments. (b) MALDI-TOF spectrum of low-molecular-weight poly(BGAH). (c) Partial 2D ^1H - ^1H COSY spectra of poly(BGAH) revealing the olefin stereoselectivity and backbone structure.

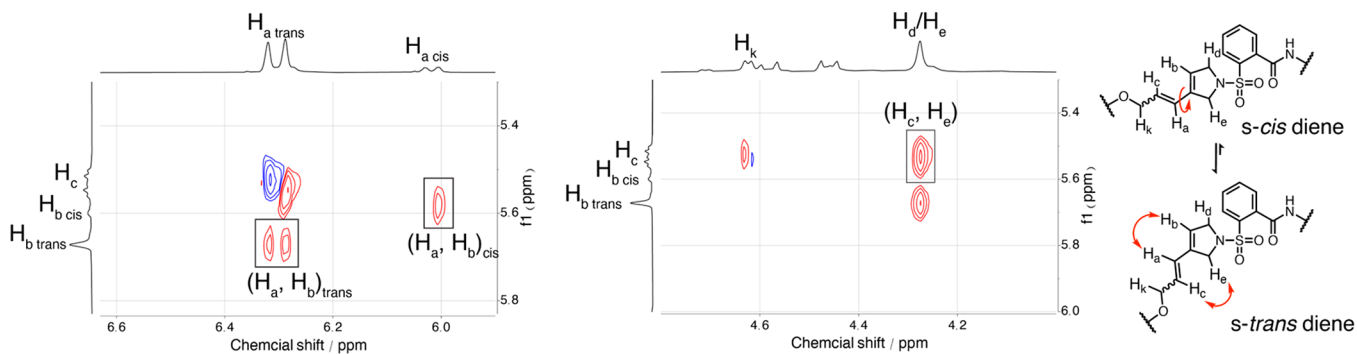


Figure 3. Partial NOESY NMR spectra containing major NOEs (500 MHz, 25 °C, mixing time: 500 ms, and $\text{CDCl}_3/\text{CD}_3\text{OD}$ 9:1). NOEs are indicated with red arrows, revealing that the *s-trans* conformation is dominant in the diene moiety. Because of the through-bond couplings between H_a and H_c and between H_c and H_k , anti-phase COSY-type signals (shown in blue) were also observed in the NOESY NMR spectra.

on AB-type copolymers has shown that polymers with segmented monomer distributions tend to fold into globular protein-like structures compared to analogues with random sequences.³⁰ The findings presented in this work further show that the homogeneity of peptide segments favors a uniform self-assembly profile.

To further study the self-assembly profile of SCPPs, a custom MATLAB program using a circular Hough transform was written to analyze the particle size distributions measured by TEM (Supporting Information, Figures S103–S106). Our results show that the diameter of the observed particles is generally larger than 10 nm, suggesting multi-chain assemblies. Spherical particles formed by poly(BGH), poly(GAH), and poly(GAH) exhibit a narrow size distribution in the range of 10–20 nm, whereas poly(BGAH) accesses a broad range of particle sizes from 10 to 70 nm. Compared to our DLS results, the statistically averaged particle size measured by TEM is

generally smaller. We attribute this difference to the facts that (1) the number-averaged hydrodynamic diameter (H_d) from DLS was calculated over all particle assemblies, including both single particles and particle clusters, consequently leading to a larger average particle size,³¹ and (2) the samples in TEM, although preserved in the presence of staining agents, are measured in a vacuum. In contrast, the image analysis program enables us to identify individual particles in particle clusters and to calculate particle diameters accordingly, subsequently giving the statistical distribution of particle sizes.

Detailed self-assembled structure types observed in our TEM experiments were further sorted into four categories: single particle, dimer particle, satellite assembly (small particles distributed around one large particle), or particle chain aggregate (multiple nanoparticles linked into strings) (Supporting Information, Figure S107). For the synthesized SCPPs, we only observed the formation of isotropic sphere particles,

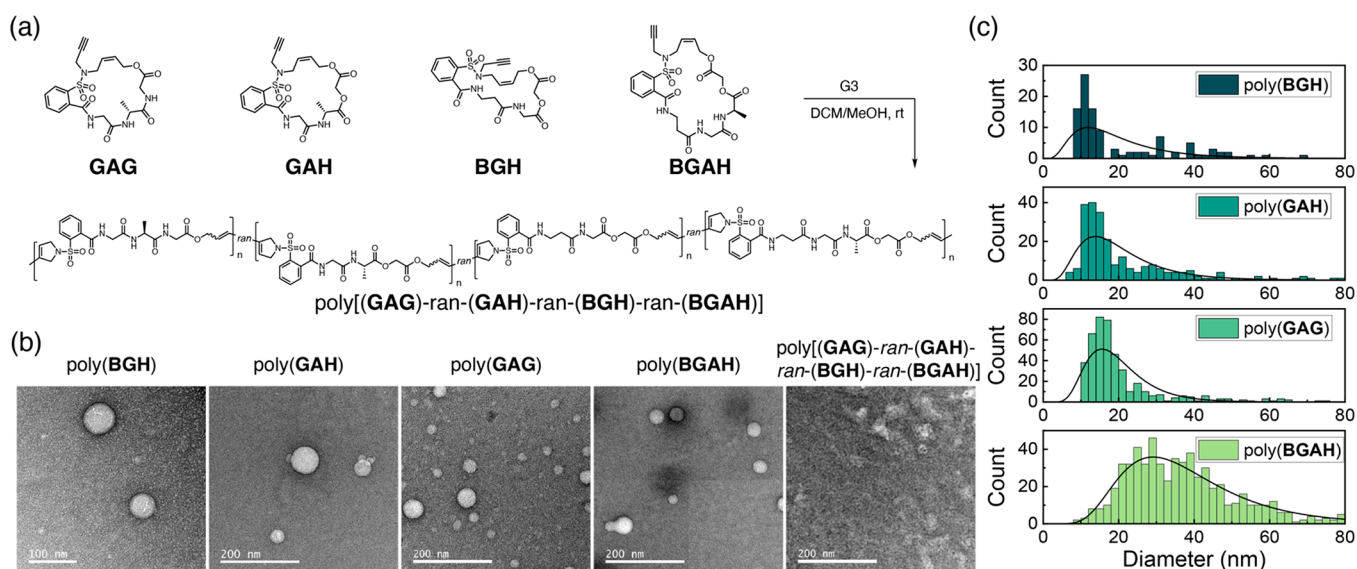


Figure 4. Assembled structures of sequence-controlled periodic copolymers. (a) Synthesis of random copolymers prepared by copolymerizing four cyclic monomers (BGAH, GAG, BGH, and GAH) in a 1:1:1:1 molar ratio. $M_n = 15.0$; PDI = 1.13; E/Z ratio = 3.5:1. (b) Representative stained TEM images of sequence-controlled periodic copolymers and the random copolymer. Scale bar represents 200 nm. (c) Particle size distributions of spherical particles measured from TEM images.

while anisotropic assembled structures such as worm and cylinder were not observed. To gain a better understanding of the role of sequence precision, additional control experiments using samples containing mixed sequence-controlled polymers (poly(GAG), poly(GAH), poly(BGH), and poly(BGAH) in 1:1:1:1 weight ratio) were performed. Interestingly, our results show that the samples containing four mixed SCPPs also assemble into spherical nanoparticles (Supporting Information, Figures S108 and S109), further supporting our findings that sequence precision at the monomer level contributes to ordered polymer assembly.

The model SCPPs presented in this work are constructed with nonpolar, uncharged amino acids, and the sulfonamide linker between the repetitive sequences further increases the overall hydrophobicity compared with natural proteins. We therefore select a water/DMF binary solvent to promote the assembly of our model SCPPs and reason that the solvophobic interactions are the predominant driving forces. We conjecture that the solvophobic interactions also contribute to similar spherical assemblies across the sequence variations presented in this work. Nevertheless, it is important to note that cosolvents can also affect the polymer assembly. Prior work on polymers containing amphiphilic peptides has shown that the polarity of the cosolvent affects polymer chain assembly.^{32–34} The effect of solvent on polymer assembly, however, remains largely underexplored in the field of sequence-controlled polymers. We envision that future investigation on how solvent affects the assembly of amphiphilic SCPPs will enhance our understanding of sequence–structure–property relationships in synthetic polymers.

In this work, the synthesis of SCPPs containing peptide repeats is described together with investigations on their self-assembly properties. A series of SCPPs was found to self-assemble into uniform spherical nanoparticles. The results for sequence-controlled repetitive polymers are in stark contrast with those for their random analog, which forms only disordered aggregates without defined morphologies under the same conditions. These observations demonstrate the

important role of sequence precision in self-assembly of synthetic polymers. The design strategy used in this work combines a sequence-controlled polymerization method with the inspiration of repeat sequences commonly observed in protein structures. We anticipate that this strategy will provide a model system to elucidate the sequence–structure–property relationships in synthetic polymers. The methodology described here can be further expanded to incorporate amphiphilic repetitive sequences into synthetic polymers, which will provide opportunities for designing new biomimetic materials. Future work will focus on studying the self-assembly mechanism and leveraging computational modeling to gain a deeper understanding of the SCPPs' chain alignments during the assembly process.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at <https://pubs.acs.org/doi/10.1021/acsmacrolett.2c00495>.

General methods, synthetic details, NMR spectra and MALDI-TOF results, single-crystal X-ray crystallographic analysis, polymer characterizations, and TEM analysis (PDF)

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Notes

The authors declare no competing financial interest.

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REFERENCES

- (1) Meier, M. A. R.; Barner-Kowollik, C. A New Class of Materials: Sequence-Defined Macromolecules and Their Emerging Applications. *Adv. Mater.* **2019**, *31* (26), 1806027.
- (2) Lutz, J.-F.; Ouchi, M.; Sawamoto, M.; Meyer, T. Y. *Sequence-Controlled Polymers: Synthesis, Self-Assembly, and Properties*; ACS Symposium Series 1170; American Chemical Society, 2014.
- (3) Li, J.; Stayshich, R. M.; Meyer, T. Y. Exploiting Sequence To Control the Hydrolysis Behavior of Biodegradable PLGA Copolymers. *J. Am. Chem. Soc.* **2011**, *133* (18), 6910–6913.
- (4) Roy, R. K.; Lutz, J.-F. Compartmentalization of Single Polymer Chains by Stepwise Intramolecular Cross-Linking of Sequence-Controlled Macromolecules. *J. Am. Chem. Soc.* **2014**, *136* (37), 12888–12891.
- (5) Patterson, A. L.; Danielsen, S. P. O.; Yu, B.; Davidson, E. C.; Fredrickson, G. H.; Segalman, R. A. Sequence Effects on Block Copolymer Self-Assembly through Tuning Chain Conformation and Segregation Strength Utilizing Sequence-Defined Polypeptides. *Macromolecules* **2019**, *52* (3), 1277–1286.
- (6) Sun, J.; Liao, X.; Minor, A. M.; Balsara, N. P.; Zuckermann, R. N. Morphology-Conductivity Relationship in Crystalline and Amorphous Sequence-Defined Peptoid Block Copolymer Electrolytes. *J. Am. Chem. Soc.* **2014**, *136* (42), 14990–14997.
- (7) Allen, B. P.; Wright, Z. M.; Taylor, H. F.; Oweida, T. J.; Kader-Pinky, S.; Patteson, E. F.; Bucci, K. M.; Cox, C. A.; Senthilvel, A. S.; Yingling, Y. G.; Knight, A. S. Mapping the Morphological Landscape of Oligomeric Di-Block Peptide–Polymer Amphiphiles. *Angew. Chem., Int. Ed.* **2022**, *61* (14), e202115547.
- (8) Lutz, J.-F. Defining the Field of Sequence-Controlled Polymers. *Macromol. Rapid Commun.* **2017**, *38* (24), 1700582.
- (9) Lutz, J.-F.; Ouchi, M.; Liu, D. R.; Sawamoto, M. Sequence-Controlled Polymers. *Science* **2013**, *341* (6146), 1238149.
- (10) Panganiban, B.; Qiao, B.; Jiang, T.; DelRe, C.; Obadia, M. M.; Nguyen, T. D.; Smith, A. A. A.; Hall, A.; Sit, I.; Crosby, M. G.; Dennis, P. B.; Drockenmuller, E.; Olvera de la Cruz, M.; Xu, T. Random heteropolymers preserve protein function in foreign environments. *Science* **2018**, *359* (6381), 1239–1243.
- (11) Jiang, T.; Hall, A.; Eres, M.; Hemmatian, Z.; Qiao, B.; Zhou, Y.; Ruan, Z.; Couse, A. D.; Heller, W. T.; Huang, H.; de la Cruz, M. O.; Rolandi, M.; Xu, T. Single-Chain Heteropolymers Transport Protons Selectively and Rapidly. *Nature* **2020**, *577* (7789), 216–220.
- (12) Berezovsky, I. N.; Grosberg, A. Y.; Trifonov, E. N. Closed Loops of Nearly Standard Size: Common Basic Element of Protein Structure. *FEBS Lett.* **2000**, *466* (2–3), 283–286.
- (13) Alva, V.; Söding, J.; Lupas, A. N. A Vocabulary of Ancient Peptides at the Origin of Folded Proteins. *Elife* **2015**, *4*, No. e09410.
- (14) Kovacs, N. A.; Petrov, A. S.; Lanier, K. A.; Williams, L. D. Frozen in Time: The History of Proteins. *Mol. Biol. Evol.* **2017**, *34* (5), 1252–1260.
- (15) Vetting, M. W.; Hegde, S. S.; Fajardo, J. E.; Fiser, A.; Roderick, S. L.; Takiff, H. E.; Blanchard, J. S. Pentapeptide Repeat Proteins. *Biochemistry* **2006**, *45* (1), 1–10.
- (16) Kajava, A. V. Tandem Repeats in Proteins: From Sequence to Structure. *J. Struct. Biol.* **2012**, *179* (3), 279–288.
- (17) Paladin, L.; Hirsh, L.; Piovesan, D.; Andrade-Navarro, M. A.; Kajava, A. V.; Tosatto, S. C. E. RepeatsDB 2.0: Improved Annotation, Classification, Search and Visualization of Repeat Protein Structures. *Nucleic Acids Res.* **2017**, *45* (D1), D308–D312.
- (18) Porebski, B. T.; Buckle, A. M. Consensus Protein Design. *Protein Eng. Des. Sel.* **2016**, *29* (7), 245–251.
- (19) Sternke, M.; Tripp, K. W.; Barrick, D. Consensus Sequence Design as a General Strategy to Create Hyperstable, Biologically Active Proteins. *Proc. Natl. Acad. Sci. U. S. A.* **2019**, *116* (23), 11275–11284.
- (20) Chang, M. P.; Huang, W.; Mai, D. J. Monomer-scale Design of Functional Protein Polymers Using Consensus Repeat Sequences. *J. Polym. Sci.* **2021**, *59*, 2644–2664.
- (21) Gutekunst, W. R.; Hawker, C. J. A General Approach to Sequence-Controlled Polymers Using Macrocyclic Ring Opening Metathesis Polymerization. *J. Am. Chem. Soc.* **2015**, *137* (25), 8038–8041.
- (22) Park, H.; Kang, E.-H.; Müller, L.; Choi, T.-L. Versatile Tandem Ring-Opening/Ring-Closing Metathesis Polymerization: Strategies for Successful Polymerization of Challenging Monomers and Their Mechanistic Studies. *J. Am. Chem. Soc.* **2016**, *138* (7), 2244–2251.
- (23) Park, H.; Lee, H. K.; Choi, T. L. Tandem Ring-Opening/Ring-Closing Metathesis Polymerization: Relationship between Monomer Structure and Reactivity. *J. Am. Chem. Soc.* **2013**, *135* (29), 10769–10775.
- (24) Krejchi, M. T.; Atkins, E. D.; Waddon, A. J.; Fournier, M. J.; Mason, T. L.; Tirrell, D. A. Chemical Sequence Control of Beta-Sheet Assembly in Macromolecular Crystals of Periodic Polypeptides. *Science* **1994**, *265* (5177), 1427–1432.
- (25) Yu, T.-B.; Bai, J. Z.; Guan, Z. Cycloaddition-Promoted Self-Assembly of a Polymer into Well-Defined β Sheets and Hierarchical Nanofibrils. *Angew. Chem.* **2009**, *121* (6), 1117–1121.
- (26) Fink, T. D.; Zha, R. H. Silk and Silk-Like Supramolecular Materials. *Macromol. Rapid Commun.* **2018**, *39* (17), 1700834.
- (27) Zhang, Y.; Zhong, Y.; Connor, A. L.; Miller, D. P.; Cao, R.; Shen, J.; Song, B.; Baker, E. S.; Tang, Q.; Pulavarti, S. V. S. R. K.; Liu, R.; Wang, Q.; Lu, Z. L.; Szyperski, T.; Zeng, H.; Li, X.; Smith, R. D.; Zurek, E.; Zhu, J.; Gong, B. Folding and Assembly of Short α , β , \bar{I} -Hybrid Peptides: Minor Variations in Sequence and Drastic Differences in Higher-Level Structures. *J. Am. Chem. Soc.* **2019**, *141* (36), 14239–14248.

(28) Nowalk, J. A.; Fang, C.; Short, A. L.; Weiss, R. M.; Swisher, J. H.; Liu, P.; Meyer, T. Y. Sequence-Controlled Polymers Through Entropy-Driven Ring-Opening Metathesis Polymerization: Theory, Molecular Weight Control, and Monomer Design. *J. Am. Chem. Soc.* **2019**, *141* (14), 5741–5752.

(29) Warren, J. L.; Dykeman-Birmingham, P. A.; Knight, A. S. Controlling Amphiphilic Polymer Folding beyond the Primary Structure with Protein-Mimetic Di(Phenylalanine). *J. Am. Chem. Soc.* **2021**, *143* (33), 13228–13234.

(30) Siu, M. H.; Zhang, G.; Wu, C. Effect of Comonomer Distribution on the Coil-to-Globule Transition of a Single AB Copolymer Chain in Dilute Solution. *Macromolecules* **2002**, *35* (7), 2723–2727.

(31) Pencer, J.; Hallett, F. R. Effects of Vesicle Size and Shape on Static and Dynamic Light Scattering Measurements. *Langmuir* **2003**, *19* (18), 7488–7497.

(32) Barnhill, S. A.; Bell, N. C.; Patterson, J. P.; Olds, D. P.; Gianneschi, N. C. Phase Diagrams of Polynorbornene Amphiphilic Block Copolymers in Solution. *Macromolecules* **2015**, *48* (4), 1152–1161.

(33) Aggeli, A.; Bell, M.; Boden, N.; Keen, J. N.; McLeish, T. C. B.; Nyrkova, I.; Radford, S. E.; Semenov, A. Engineering of Peptide β -Sheet Nanotapes. *J. Mater. Chem.* **1997**, *7* (7), 1135–1145.

(34) Hentschel, J.; Börner, H. G. Peptide-Directed Microstructure Formation of Polymers in Organic Media. *J. Am. Chem. Soc.* **2006**, *128* (43), 14142–14149.

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