

Solvent Remodeling in Single-Chain Amphiphilic Heteropolymer Systems

Shayna L. Hilburg[†], Alfredo Alexander-Katz^{†,}*

[†]Department of Materials Science and Engineering, Massachusetts Institute of Technology,
Cambridge, Massachusetts 02139, USA

ABSTRACT

Through molecular dynamics simulations, we demonstrate how single-chain nanoparticles (SCNPs) assembled via transient linkages in water can remodel in organic solvent. Methacrylate-based random heteropolymers (RHPs) have shown promise in an assortment of applications that harness their bio-inspired properties. While their molecular behavior has been broadly characterized in water, many newer applications include the use of organic solvent rather than biomimetic conditions in which the polymer assemblies, typically driven by the hydrophobic effect, are less well understood. Here, we examine a specific RHP system which forms compact globular morphologies in highly polar and non-polar environments while adopting extended conformations in solvents of intermediate polarity. We also demonstrate the pivotal role of electrostatic interactions between charge groups in low dielectric mediums. Finally, we compare high temperature anneal cycles to room temperature equilibrations to illuminate activation barriers to remodeling upon environmental changes.

LETTER

Single-chain nanoparticles (SCNPs) harness synthetic macromolecules as promising drug delivery systems, nanomedicines, catalysts, and more.¹ While many SCNPs rely on covalent or other strongly associating linkages to assemble, a promising subset of materials use reversible, dynamic associations in their assembly.² One of the simplest and most cost effective SCNP designs is the combination of moieties with varying interaction energies which use solvophobic effects as a driving force to assembly. Methacrylate-based random heteropolymers (RHPs) are one such system, which self-assembles into nano-scale particles containing single or few chains in water, and offers an exciting avenue for protein stabilization and mimicry, nanofiltration, and other promising applications.³⁻⁷ Behavior of methacrylate-based designs in water have been studied most in depth, as many of their applications occur in aqueous environments.^{8,9}

We previously studied a specific RHP design-space through molecular dynamics (MD) simulations and elucidated the resulting SCNP structure and dynamics.¹⁰ The work demonstrated that while theories are helpful in understanding these polymer systems, the inclusion of specific chemistries is necessary for a full picture of the molecular behavior. While the work has been pivotal in gaining a mechanistic picture of how the RHPs behave in water, several potential applications occur in, or require processing steps performed in, other solvents. The compactness and mobility of chains in solvents with different affinities for the varied chemical substituents has been leveraged to control structures of resulting membranes, gels, and other nanomaterials.^{7,11,12} Characterizing the relationship between polymer behavior and its solvent environment allows such methods to be applied predictably for a variety of polymer-solvent systems.

While covalently cross-linked SCNPs would not be considerably altered by the presence of organic solvent, we expect drastic changes in systems, including ours, driven by transient

linkages reliant upon solvent interactions to drive assembly. Amphiphilic synthetic polymer systems which form compact assemblies in water can adopt extended conformations in solvents of intermediate polarity, within which both hydrophobic and hydrophilic components energetically prefer the enthalpic contributions to solvation over the entropic restriction of compactification, or reverse micelles in solvents which invert typical aqueous behavior, leading hydrophilic components to invert together while hydrophobic moieties preferentially orient to an assembly's surface. This behavior has been experimentally observed for amphiphilic homopolymers with amphiphilic monomers,^{13,14} as well as for heteropolymers with both hydrophobic and hydrophilic monomers, most well characterized for 2-component copolymer systems.¹⁵⁻¹⁹ The specific intramolecular interactions dictate how each polymer will adapt, with some systems maintaining monomer contacts in organic media compared to aqueous solvent due to strong intrachain associations which persist in the new environment.^{19,20}

Our particular polymer of interest has been used to stabilize enzymes for the creation of sustainably degradable polyesters through solution-casting in toluene or dichloromethane.²¹ In the current work, we leverage our previously demonstrated simulation methods and broaden them to a variety of organic solvents, namely tetrahydrofuran (THF), dimethyl sulfoxide (DMSO), and hexane. We use atomistic molecular dynamics (MD) simulations, having seen the importance of incorporating this level of chemical resolution through our prior work, as well as within the literature. While coarse-grained simulations have been useful for RHP systems, such as in demonstrating the correlation between stronger monomer interactions and smaller, denser nanoparticle formation in copolymers,²² the methods require a fixed polarity and lack the atomic solvent structures, making inherently amphiphilic molecular substituents such as poly(ethylene glycol) difficult to model as they interact. Including chemical detail is vital to capturing the

65 configurational entropy for side chain reorientation when transferring solvents and maintaining
66 separate assessment of backbone and side chain segments, which depending on their affinities to
67 the solvent will greatly alter resulting morphologies.^{23,24} In addition to our atomistic simulations of
68 the four-component RHPs in water, atomistic resolution has been leveraged in simulating two-
69 component amphiphilic copolymers in both water and chloroform.²⁵ We use similar techniques on
70 our more complex system with more in-depth analysis and demonstrate the impact of added
71 compositional complexity in a broader variety of solvents. The results we present show substantial
72 differences in monomer accessibility and conformational flexibility which depend on solvent
73 polarity and structure, as well as RHP chemistry. These behaviors affect how the molecules would
74 interface during post-synthetic processing steps or at end application in non-aqueous solvents and,
75 therefore, greatly impact their use. Beyond applications in organic solvent, our results also offer
76 significant insight to potential interactions with other organic substances such as small molecules
77 or hydrophobic biomacromolecules.

78 Herein, we explore RHP behavior using unbiased atomistic molecular dynamic methods
79 with the Amber MD package, similar to our prior work.^{10,26} Through a series of successive anneal
80 cycles to 500 K in implicit water, ten conformations each of two distinct polymer sequences were
81 created and then annealed to 650 K in explicit solvent: water, DMSO, THF, or hexane. The
82 resulting single chain conformations at 300 K from these simulations were used for analysis.
83 Equilibrated structures from explicit water were then transferred to DMSO, THF, or hexane for
84 further study at room temperature as they adjust to the new solvent environments. Parameterization
85 and simulation details are provided in the Supplementary Information.

86 The two random heteropolymer sequences investigated, Sequence 1 and Sequence 2 as shown
87 in Figure 1, are composed of the methacrylate-based building blocks studied previously.¹⁰

Sequence 1 contains all four monomer species—methyl methacrylate (MMA), oligo(ethylene glycol)methacrylate (OEGMA), 2-ethylhexyl methacrylate (EHMA), and 3-sulfopropyl methacrylate (SPMA)—used in the prior work, while Sequence 2 is similar but lacks the anionic SPMA monomer.

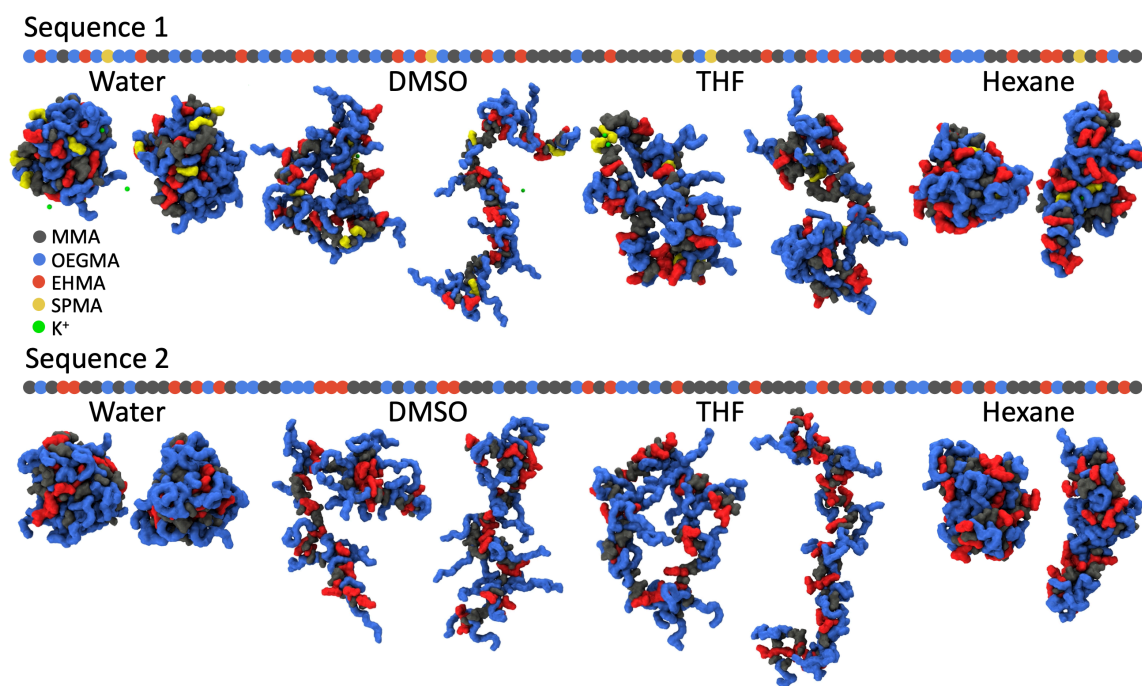


Figure 1. Sequences and renderings of the conformations with the minimum (left) and maximum (right) mean radius of gyration for each system. Solvent is omitted for clarity.

Both sequences formed compact globular structures in water and hexane, with distinct surface compositions in each solvent apparent by visual inspection in Figure 1. DMSO and THF led to contrastingly extended conformations. Quantitatively, the mean radius of gyration (R_g) and solvent accessible surface area (SASA) for each equilibrated conformation is presented in Figure 2. The R_g , from which a minimum and maximum were selected for rendering in Figure 1, has a narrow distribution for compact structures in water and broader distributions for the organic solvents of interest. SASA, calculated in each solvent using Amber's default radius size to allow

cross-comparison, shows similar distributions within each dataset, indicating that the configurations as adopted for the interaction energies between solvent and polymer have similar amounts of contact despite entropically unique topologies indicated by unique R_g values. Sequence 1 and 2 have similar ranges for both properties in each examined environment, with the exception of THF solvated structures which shows lower extension and solvation of sequence 1.

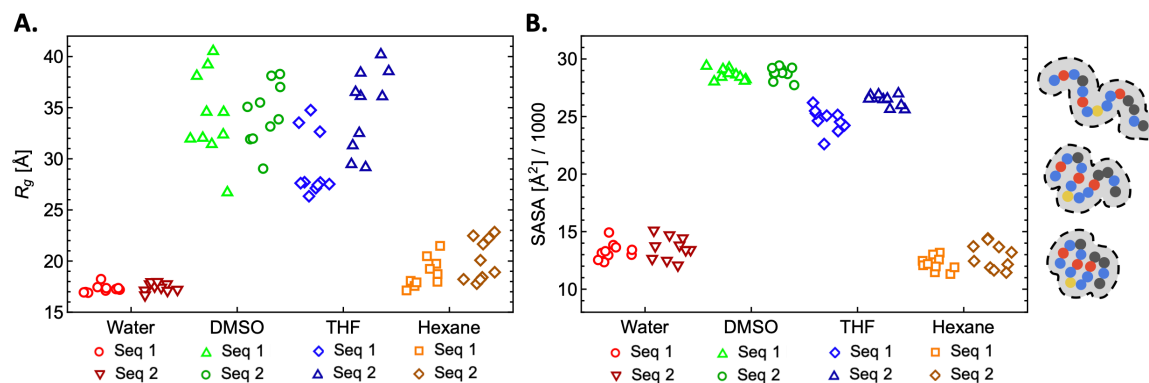


Figure 2. (A) Radius of gyration (R_g) and (B) total solvent accessible surface area (SASA) with schematic representation (right) of how conformation and accessible surface area relate. Results represent the mean value from equilibrated structures after annealing in solvent of interest for each conformation.

Mobility of the polymer backbone and side-chains generally scales with chain extension, albeit with several notable trends by monomer type (Supplementary Figures 1-2). While mobility in THF is high and mobility in hexane is low, corresponding to the compactness, low backbone mobility in SPMA monomer residues lead to lower values for Sequence 1 as compared to Sequence 2. Mobility of the side-chains themselves are impacted by moiety sizes, with OEGMA consistently having high fluctuations in all solvents due to its long side-chain length, as well as being soluble in water, THF, and DMSO. As EHMA and SPMA have similar side chain lengths, their relative side-chain mobilities are indicative, instead, of freedom of motion in the polymer configuration.

In water, SPMA fluctuates more than EHMA, while the trend is flipped in all three organic solvents. In hexane, SPMA is practically immobilized and EHMA has significantly higher fluctuations.

Polymer compactification and monomer mobilities all indicate that SPMA greatly impacts chain behavior. An assessment of the radial distribution function (RDF) between sulfur atoms in the SPMA's anionic sulfonate group, shown in Figure 3, shows that while some liquid-like features can be seen between SPMA moieties in water, increasingly pronounced features and short distances appear for the RHPs in DMSO, THF, and hexane. A similar analysis between sulfur and potassium counterions (Supplementary Figure 3) indicates that salt bridging leads to these effects. Intrachain associations have been observed in literature to restrict heteropolymer assembly through salt bridging in water amongst anionic and cationic monomers and in organic solvent via strong fluorocarbon associations.^{4,19} The extremely high correlations between sulfur positions in THF and hexane in our conformations naturally explain the mobility and configurational differences between sequence 1 and 2, locking sequence 1 into place due to electrostatic interactions in the low dielectric mediums.

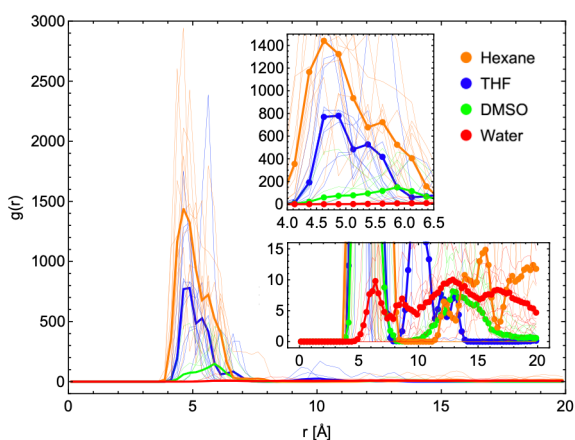


Figure 3. Radial distribution function of anionic moieties as measured between sulfur atoms within the sulfonate groups of SPMA monomers. Bold lines show mean values over ten conformations (each shown as thin lines) for the equilibrated sequence as annealed in each solvent of interest.

With equilibrated structures characterized, we turn to the transformation from water to organic solvent. Data presented thus far annealed polymer chains in the explicit solvent of interest before equilibrating for 60ns at 300 K, of which the final 40ns was used for the above analyses. While some adjustment to the R_g occurred at the beginning of equilibration following the anneal (Supplementary Figure 4), the relative solvent accessibility (RSA) of each monomer type—the partial SASA normalized by maximum monomer solvation (calculation details in Supplementary Information)—stabilized quickly (Supplementary Figure 5). It should be noted that the resulting trends between monomer species follow the aforementioned mobility data, with higher RSA for monomers which showed greater fluctuations. Unexpectedly, however, monomer RSA is not strictly correlated to overall chain extension and SASA, with SPMA residues showing significantly lower accessibility in THF than in water despite adopting a conformation with nearly double the R_g . If rather than being annealed in organic solvent, the polymers are instead annealed in explicit water and then transferred to the solvent of interest for equilibration at room temperature, we find that the same 60 ns is grossly insufficient for full remodeling. After 200 ns, conformations in THF and DMSO show increased R_g , though the majority remain far from corresponding equilibrium values (Supplementary Figure 4). Figure 4 shows more rapid adaptation of RSA at room temperature, with values trending towards equilibrium for THF and DMSO. Trends towards equilibrium values indicate that kinetic barriers to rearrangement in THF and DMSO exist but can be overcome through temperature—as in the annealed simulations—or time, as could be expected if current trends continued in the room temperature simulations. Contrastingly, in hexane, RSA

plateaus before reaching the equilibrium values. While behavior in hexane at room temperature is observed to deviate from behavior in water, the assembly remains compact as R_g maintains values below those of the configurations in DMSO and THF. The activation barrier to backbone reconfiguration appears to trend with the driving force to compactification, and therefore the changes observed in RSA seemingly approach a meta-stable kinetically-trapped state in which side-chains have reoriented but the conformation is not entirely reconfigured. The property which deviates from the water behavior most quickly at 300 K is the accessibility of SPMA in hexane. This rapid change in RSA highlights the high energetic cost of sulfonate exposure to hexane and the strong driving force for it to bury within the SCNP core, even if a full remodel is not energetically favorable.

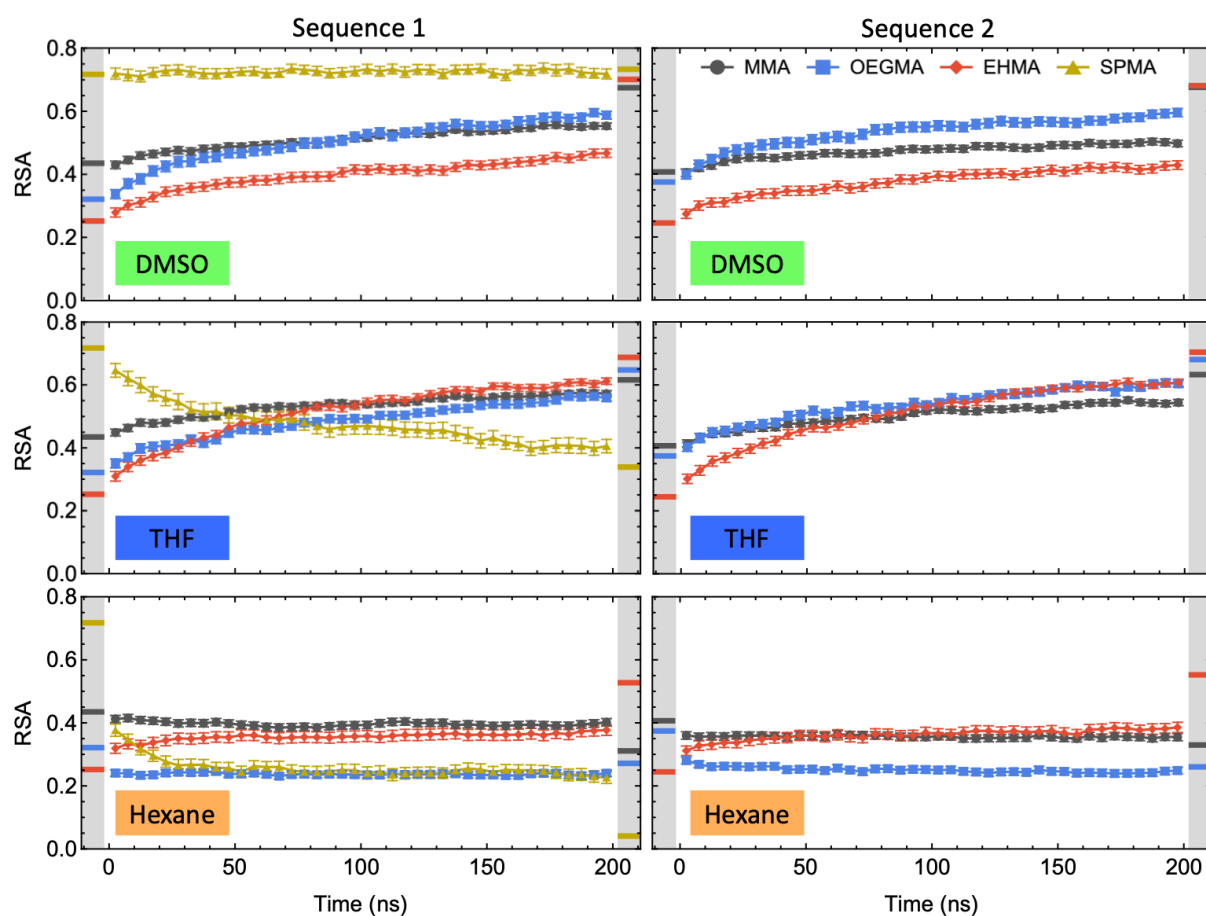


Figure 4. Change in relative solvent accessibility (RSA) of monomers over time after transfer to solvent of interest at 300 K. Each datapoint shows mean and standard error of the 5 ns average RSA for each monomer of a given species within the sequence over all conformations. Shaded regions on the left of each plot show mean RSA from conformations equilibrated in water while shaded regions on the right of each plot show mean RSA from conformations equilibrated in the solvent of interest (Supplementary Figure 5).

The results presented demonstrate that the covalently bound heterogenous monomers in our RHP system will lead to compact globules with heterogeneous surfaces in both highly polar (water) and highly nonpolar (hexane) solvents, though the driving forces differ greatly. The hydrophobic effect, which drives assembly in water, leads to well solvated polar monomers with more shielded hydrophobic moieties. In contrast, in hexane, the oleophobic polar and charged groups avoid exposure and instead bury into the globule core, with hydrocarbon chemistries prevailing at the assembly's surface. Therefore, the SCNP can exist in drastically different configurations while still maintaining a compact geometry if the surface energy between the solvent and monomers is high enough. Contrastingly, if entropic driving forces to polymer motion outweigh the enthalpic costs to solvent exposure, the chain extends. In DMSO and THF, the majority of monomers interact favorably with both solvents such that the RHP is generally open and exposed. SPMA associations can limit extension and motion, but the small quantity of them in the chain still affords enough freedom for other segments to maintain significant solvation. This association nonetheless impacts accessibility to SPMA and its neighboring residues to solvent, which has implications to post-synthetic modification strategies that could be employed. The equilibrated structures illuminate the potential for interactions between RHPs or amongst RHPs

and their environment in various settings, such as during processing in organic solvent to create self-degrading polyesters or within the hydrophobic interior of cell membranes.^{21,27}

Beyond equilibrium behavior, our simulations also provide insight into how the polymer chains get to those unique conformations and could behave upon transfer to distinct environments. A change in solvent-monomer interaction energies can prompt either unfolding or remodeling, with some reconfiguration possible without need for expansion to take place. Full reconfiguration is best achieved using heat to overcome kinetic barriers on simulation timescales, though we also demonstrated a near immediate adjustment to the new environment without thermal initiation.

In summary, the specific chemistry of the monomers selected for a heteropolymer as well as their interactions with surrounding media prove to be of utmost importance to determining polymer behavior. The structure which results from a given chemistry can lead to more traditional SCNPs driven by hydrophobic interactions or other attractive and repulsive forces in certain conditions while behaving as fully solvated, extended chains in others. The ratios of monomer chemistries and the solvent polarities can be tailored to make specific moieties—and/or their neighboring species—accessible or inaccessible. We have shown that reconfiguration can occur significantly and rapidly with full remodeling possible at room temperature on timescales beyond those typically accessible in simulation. This observed behavior has profound implications to how the polymers may fold and assemble as they interface with proteins, surfaces, and other molecules which impact intramolecular interactions.

ASSOCIATED CONTENT

Supporting Information. The Supporting Information is available on the **XX** website.

Simulation methods, backbone and side-chain mobility, sulfur-potassium RDF, and R_g over time (PDF)

215 **AUTHOR INFORMATION**

216 **Corresponding Author**

217 * aalexand@mit.edu

218 **Funding Sources**

219 This work was supported by the Defense Threat Reduction Agency contract HDTRA11910011.

220 **ACKNOWLEDGEMENTS**

221 We are thankful to Ting Xu and Marco Eres for insightful discussion in the preparation of this
222 work.

223 **REFERENCES**

224 (1) Alqarni, M. A. M.; Waldron, C.; Yilmaz, G.; Becer, C. R. Synthetic Routes to Single Chain
225 Polymer Nanoparticles (SCNPs): Current Status and Perspectives. *Macromol. Rapid Commun.*
226 **2021**, *154* (15), 2100035.

227 (2) Blazquez-martín, A.; Verde-sesto, E.; Moreno, A. J.; Arbe, A.; Colmenero, J. Advances in
228 the Multi-Orthogonal Folding of Single Polymer Chains into Single-Chain Nanoparticles. **2021**,
229 1–17.

230 (3) Gao, J.; Le, S.; Thayumanavan, S. Enzyme Catalysis in Non-native Environment with
231 Unnatural Selectivity Using Polymeric Nanoreactors. *Angew. Chemie Int. Ed.* **2021**.

232 (4) Bhat, R.; Foster, L. L.; Rani, G.; Vemparala, S.; Kuroda, K. The function of peptide-
233 mimetic anionic groups and salt bridges in the antimicrobial activity and conformation of cationic
234 amphiphilic copolymers. *RSC Adv.* **2021**, *11* (36), 22044–22056.

- 235 (5) Lamm, R. J.; Pichon, T. J.; Huyan, F.; Wang, X.; Prossnitz, A. N.; Manner, K. T.; White,
236 N. J.; Pun, S. H. Optimizing the Polymer Chemistry and Synthesis Method of PolySTAT, an
237 Injectable Hemostat. *ACS Biomater. Sci. Eng.* **2020**, 6 (12), 7011–7020.
- 238 (6) Panganiban, B.; Qiao, B.; Jiang, T.; DelRe, C.; Obadia, M. M.; Nguyen, T. D.; Smith, A.
239 A. A.; Hall, A.; Sit, I.; Crosby, M. G.; Dennis, P. B.; Drockenmuller, E.; Olvera de la Cruz, M.;
240 Xu, T. Random heteropolymers preserve protein function in foreign environments. *Science* (80-
241). **2018**, 359 (6381), 1239–1243.
- 242 (7) Yu, W.-H.; Qiu, Z.-L.; Wang, J.-R.; Shen, Y.-J.; Han, J.; Fang, L.-F.; Zhu, B.-K. Novel
243 nanofiltration membrane prepared by amphiphilic random copolymer nanoparticles packing for
244 high-efficiency biomolecules separation. *Chem. Eng. J.* **2022**, 430, 132914.
- 245 (8) Verde-Sesto, E.; Arbe, A.; Moreno, A. J.; Cangialosi, D.; Alegría, A.; Colmenero, J.;
246 Pomposo, J. A. Single-chain nanoparticles: Opportunities provided by internal and external
247 confinement. *Mater. Horizons* **2020**, 7 (9), 2292–2313.
- 248 (9) Frisch, H.; Tuten, B. T.; Barner-Kowollik, C. Macromolecular Superstructures: A Future
249 Beyond Single Chain Nanoparticles. *Isr. J. Chem.* **2020**, 60 (1–2), 86–99.
- 250 (10) Hilburg, S. L.; Ruan, Z.; Xu, T.; Alexander-Katz, A. Behavior of Protein-Inspired
251 Synthetic Random Heteropolymers. *Macromolecules* **2020**, 53 (21), 9187–9199.
- 252 (11) Scheutz, G. M.; Elgoyhen, J.; Bentz, K. C.; Xia, Y.; Sun, H.; Zhao, J.; Savin, D. A.;
253 Sumerlin, B. S. Mediating covalent crosslinking of single-chain nanoparticles through
254 solvophobicity in organic solvents. *Polym. Chem.* **2021**, 12 (31), 4462–4466.

- 255 (12) Zhang, Y. Y.; Jia, X. M.; Shi, R.; Li, S. J.; Zhao, H.; Qian, H. J.; Lu, Z. Y. Synthesis of
256 Polymer Single-Chain Nanoparticle with High Compactness in Cosolvent Condition: A Computer
257 Simulation Study. *Macromol. Rapid Commun.* **2020**, *41* (24), 1–7.
- 258 (13) Guazzelli, E.; Masotti, E.; Calosi, M.; Kriechbaum, M.; Uhlig, F.; Galli, G.; Martinelli, E.
259 Single-chain folding and self-assembling of amphiphilic polyethyleneglycol-modified fluorinated
260 styrene homopolymers in water solution. *Polymer (Guildf)*. **2021**, *231*, 124107.
- 261 (14) Li, Q.; Constantinou, A. P.; Georgiou, T. K. A library of thermoresponsive PEG-based
262 methacrylate homopolymers: How do the molar mass and number of ethylene glycol groups affect
263 the cloud point? *J. Polym. Sci.* **2021**, *59* (3), 230–239.
- 264 (15) Goswami, K. G.; Mete, S.; Chaudhury, S. S.; Sar, P.; Ksendzov, E.; Mukhopadhyay, C.
265 Das; Kostjuk, S. V.; De, P. Self-Assembly of Amphiphilic Copolymers with Sequence-Controlled
266 Alternating Hydrophilic-Hydrophobic Pendant Side Chains. *ACS Appl. Polym. Mater.* **2020**, *2* (5),
267 2035–2045.
- 268 (16) Sadeghi, I.; Asatekin, A. Spontaneous Self-Assembly and Micellization of Random
269 Copolymers in Organic Solvents. *Macromol. Chem. Phys.* **2017**, *218* (20), 1–9.
- 270 (17) Uddin, M. A.; Yu, H.; Wang, L.; Naveed, K.-R.; Amin, B. U.; Mehmood, S.; Haq, F.;
271 Nazir, A.; Lin, T.; Chen, X.; Ni, Z. Multiple-stimuli-responsiveness and conformational inversion
272 of smart supramolecular nanoparticles assembled from spin labeled amphiphilic random
273 copolymers. *J. Colloid Interface Sci.* **2021**, *585*, 237–249.

274 (18) Hattori, G.; Takenaka, M.; Sawamoto, M.; Terashima, T. Nanostructured Materials via the
 275 Pendant Self-Assembly of Amphiphilic Crystalline Random Copolymers. *J. Am. Chem. Soc.* **2018**,
 276 *140* (27), 8376–8379.

277 (19) Koda, Y.; Terashima, T.; Sawamoto, M. Multimode Self-Folding Polymers via Reversible
 278 and Thermoresponsive Self-Assembly of Amphiphilic/Fluorous Random Copolymers.
 279 *Macromolecules* **2016**, *49* (12), 4534–4543.

280 (20) Matsumoto, K.; Terashima, T.; Sugita, T.; Takenaka, M.; Sawamoto, M. Amphiphilic
 281 Random Copolymers with Hydrophobic/Hydrogen-Bonding Urea Pendants: Self-Folding
 282 Polymers in Aqueous and Organic Media. *Macromolecules* **2016**, *49* (20), 7917–7927.

283 (21) DelRe, C.; Jiang, Y.; Kang, P.; Kwon, J.; Hall, A.; Jayapurna, I.; Ruan, Z.; Ma, L.; Zolkin,
 284 K.; Li, T.; Scown, C. D.; Ritchie, R. O.; Russell, T. P.; Xu, T. Near-complete depolymerization of
 285 polyesters with nano-dispersed enzymes. *Nature* **2021**, *592* (7855), 558–563.

286 (22) Vao-soongnern, V. Molecular simulation of molecular and surface properties of random
 287 copolymer nanoparticle. *J. Mol. Liq.* **2021**, *342*, 117556.

288 (23) Chawathe, M.; Patel, A.; Jonnalagadda, S.; Sidorenko, A. Design of hybrid molecular
 289 brushes with reversible surface adaptability on exposure to specific solvents. *Biointerphases* **2018**,
 290 *13* (4), 041006.

291 (24) Buglakov, A. I.; Larin, D. E.; Vasilevskaya, V. V. Orientation- and cosolvent-induced self-
 292 assembly of amphiphilic homopolymers in selective solvents. *Polymer (Guildf)*. **2021**, *232*,
 293 124160.

294 (25) Guazzelli, E.; Martinelli, E.; Galli, G.; Cupellini, L.; Jurinovich, S.; Mennucci, B. Single-
 295 chain self-folding in an amphiphilic copolymer: An integrated experimental and computational
 296 study. *Polymer (Guildf)*. **2019**, *161* (November 2018), 33–40.

297 (26) D.A. Case, I.Y. Ben-Shalom, S.R. Brozell, D.S. Cerutti, T.E. Cheatham, III, V.W.D.
 298 Cruzeiro, T.A. Darden, R.E. Duke, D. Ghoreishi, G. Giambasu, T. Giese, M.K. Gilson, H. Gohlke,
 299 A.W. Goetz, D. Greene, R Harris, N. Homeyer, Y. Huang, S. Izadi, A. Kovalenko, R. Krasny, T.
 300 Kurtzman, T.S. Lee, S. LeGrand, P. Li, C. Lin, J. Liu, T. Luchko, R. Luo, V. Man, D.J.
 301 Mermelstein, K.M. Merz, Y. Miao, G. Monard, C. Nguyen, H. Nguyen, A. Onufriev, F. Pan, R.
 302 Qi, D.R. Roe, A. Roitberg, C. Sagui, S. Schott-Verdugo, J. Shen, C.L. Simmerling, J. Smith, J.
 303 Swails, R.C. Walker, J. Wang, H. Wei, L. Wilson, R.M. Wolf, X. Wu, L. Xiao, Y. Xiong, D.M.
 304 York and P.A. Kollman (2019), AMBER 2019, University of California, San Francisco.

305 (27) Jiang, T.; Hall, A.; Eres, M.; Hemmatian, Z.; Qiao, B.; Zhou, Y.; Ruan, Z.; Couse, A. D.;
 306 Heller, W. T.; Huang, H.; de la Cruz, M. O.; Rolandi, M.; Xu, T. Single-chain heteropolymers
 307 transport protons selectively and rapidly. *Nature* **2020**, *577* (7789), 216–220.

308