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Pathway Complexity in Supramolecular Polymerization of Peptide Amphiphiles

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In supramolecular systems, pathway complexity provides access to metastable and kinetically trapped states, offering control over material properties. Through adjustment of experimental conditions, supramolecular polymerization can yield tailored structures and diverse morphologies from identical precursors. By combining experimental and computational efforts, this study focuses on the pathway complexity in the supramolecular polymerization of peptidic, water-soluble Zn(II) porphyrins. Two peptide designs, consisting of glycine (G) and phenylalanine (F), were examined: a rigid GF_3 sequence and a more flexible G_2F_3 sequence. Both are equipped with a PEG domain for water solubility and thermoresponsive behavior. The GF_3 sequence shows rapid, spontaneous polymerization over a wide range of temperatures, while in the case of G_2F_3 an activation barrier restricts the polymerization to temperatures above 40 °C. To further characterize the supramolecular polymerization mechanisms, we developed a model with planar monomers and key parameters such as intermolecular interactions, bead size, and linker flexibility. Consistent with experimental observations, simulations demonstrated that stronger interactions promote polymerization, while increased flexibility inhibits it due to sterics. While the model indicates a power-law relationship between polymerization half-times and initial monomer concentrations, experimental results showed no concentration dependence, suggesting that more complex on- and off-pathway mechanisms exist. A minimum free energy model revealed a linear relationship between the binding free energy and the number of bonds between monomers, with stiffer monomers exhibiting higher binding energies, which implies the formation of more stable supramolecular polymers. With hybrid MD-MC simulations, we intend to map the free energy of polymers of different sizes and to generate a phase diagram to deepen our understanding of structure formation.