

Molecular Conformation as a Determinant of Self-Assembly in Sequence-Isomeric Tripeptides

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In this work, we evaluate whether computed conformational ensembles of seven tripeptides—the six C-terminal amidated D/Y/F sequence isomers and the closely related sequence FFD—are informative of their self-assembly propensity. Using all-atom molecular dynamics (AA-MD) simulations and intra-molecular side-chain dihedral angles as a collective variable, we calculate conformational free-energy landscapes (FELs) for these sequences. We then introduce a novel method to numerically characterize the computed FELs and find a correlation between thermal conformational accessibility and a sequence's tendency to self-assemble or remain in solution. In addition, we evaluate and rationalize the impact of water model selection on conformational ensembles in terms of peptide-water interaction strengths, and also investigate the influence of ionization state on conformation. The presented methodology implicitly accounts for amino acid sequence context, which is a major determinant of divergent properties for sequence isomers. It also has a low associated computational cost, making use of single-molecule simulations to predict supramolecular assembly outcomes. These features are an important advancement toward a general scheme for the theory-informed design of peptide materials.

Keywords: *peptides, free energy landscape, conformational flexibility*

