Molecular dynamics simulation for structure-lipophilicity relationships of cyclic peptides

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In the development of peptide therapeutics for various targets, cyclization has emerged as one possible strategy to improve the binding affinity, membrane permeability, or proteolytic stability by pre-selecting certain poses. At the same time, cyclic peptides still exhibit a significant amount of conformational flexibility, allowing them to adapt to environments of different polarity, a property that has been termed chameleonicity. Thus, understanding polarity is a prerequisite for computational modeling of chameleonicity and related biophysical quantities. Molecular dynamics (MD) simulation is a physics-based method to compute conformational ensembles, and provides a powerful tool for detailed analysis of chameleonicity. Here, we combine MD simulations with simple physical models of polarity to study the lipophilicity and chameleonicity of cyclic peptides. Our results provide insights into the mechanisms underlying membrane permeability and chameleonicity, and demonstrate that MD-based ensembles can improve in-silico predictions of lipophilicity.