Energetics of π - π Stacking Interactions: Implications in the Phase Separation of Intrinsically Disordered Proteins

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π-π stacking interactions are found throughout the proteome and have been shown to play a role in the liquid-liquid phase separation of intrinsically disordered proteins; however, the structural and energetic properties of π-π interactions that drive intra- and intermolecular protein interactions are poorly understood. In this study, we investigate the pairwise interactions of sp^2-hybridized groups within proteins through an analysis of the Protein Data Bank. Along with these statistical data, small-molecule representations of these groups are simulated using molecular dynamics, while quantum mechanical and molecular mechanical calculations are used to characterize the energies of π-π interactions across their conformational distributions. Ultimately, this study provides a thorough quantification of the energetics of π-stacking contacts in proteins and evaluates the strengths and limitations of different computational methods in accurately modelling these types of interactions.