β-Peptide Foldamer Stabilized by Cation-π Interaction

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The cation-π interaction has been recognized as an important noncovalent interaction to provide significant stability in the structure of proteins, particularly at the solvent-exposed surface. Recent studies have shown that the cation-π interaction in various natural peptide model systems can stabilize the folded structure of a peptide just as in proteins. However, the strength of cation-π interactions and their role in protein/peptide folding is still in debate. The question of the relative strength of cation-π versus salt-bridge interactions led us to design an experimental study with an unnatural peptide model system, from which we could observe unseen aspect of the interactions. We have chosen a helical β^3-peptide scaffold composed of acyclic residues for this purpose because the stabilization effect by salt-bridge interactions in aqueous solution has been well studied in the system.

β-Peptides (unnatural peptides composed of β-amino acids) have recruited enormous attention due to their ability to form diverse secondary structures found in proteins and their potential biological activities[1,2]. β^3-Peptides have proteinogenic side-chains and are known to adopt stable 14-helical conformation via intramolecular hydrogen bonding between backbone amides in organic solvent, but it requires additional stabilization strategy to enhance the helical propensity in aqueous solution. Several groups have reported that β^3-peptides could be stabilized by charge-charge interaction (called "salt-bridge") between residues at i and i+3 positions. One can expect that the cation-π interaction could be an alternative strategy to stabilize the 14-helical β^3-peptides in aqueous solution because both theoretical and experimental studies suggested that the stabilization energy of cation-π interactions would be comparable to salt-bridge interactions. Despite of this prominence of evaluations, utilization of the interaction for β-peptide design has not been attempted yet. If the observed degree of stabilization effect in the α-peptide model systems can be simply extrapolated to β-peptide oligomers, the β^3-peptides stabilized by cation-π interaction should have comparable helical stability with those stabilized by salt-bridge interaction. In this presentation, I will discuss about the degree of stabilization effect of cation-π interaction in β^3-peptide model system[3].

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