Amyloid-β(25-35) oligomers in solution: structure and thermodynamics

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Amyloidoses such as Alzheimer's disease are associated with the conversion of proteins from a soluble and functional form into β-sheet rich structures that often tend to precipitate in the form of fibrils. The development of specific agents against amyloidoses requires an understanding of the early stages of fibril nucleation at the microscopic level.

We have used all atom replica exchange molecular dynamics simulations to study the fibrillogenic Alzheimer amyloid-β(25-35) peptide in dimeric and trimeric form in explicit water. As known from previous studies on monomers, this fragment forms β-hairpin structures in water [1]. The dimers predominantly form compact structures in which peptides adopt β-hairpin-like or unstructured U-shaped conformations with a broad distribution of relative orientations. In addition, we observe dimer structures in which peptides form extended, marginally stable, anti-parallel in- or out-of-register intermolecular β-sheets. We find that compact conformations are entropically favored while extended conformations are stabilized due favorable covalent and coulombic peptide-peptide interactions.

The trimer system also shows a variety of different, poorly populated conformations. Although, we find compact as well as partly extended structures a simple two state model is not appropriate for this system. Here, we focus on the formation of trimers by analyzing the equilibrium between trimer *versus* dimer and monomer. The thermodynamic forces driving the aggregation are dissected.

[1] G. Wei, J. Shea, *Biophys. J.*, **2006**, *91*, 1638-1647.