Microscopic factors that control β-sheet registry in Amyloid fibrils formed by 11-25 fragment of Amyloid β peptide: Insights from computer simulations

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Short fragments of amyloidogenic proteins are widely used in studies of amyloid formation as convenient model systems. A recent solid-state NMR study of Tycko et al. [*J. Mol. Biol. 335 (2004) 247*] demonstrated that the fragment consisting of residues 11 to 25 of the amyloid β peptide involved in Alzheimers disease (Aβ11-25) can form fibrils composed of anti-parallel β-sheets. Interestingly, fibrils grown under neutral and acidic conditions were seen to possess different registries of their inter-β-strand hydrogen bonds. In an effort to explain the microscopic origin of this pH dependence, we study Aβ11-25 fibrils using methods of theoretical modeling. Several structural models are built for fibrils at low and neutral pH levels and examined in short molecular dynamics simulations in explicit water. The models that display lowest free energy, as estimated using an implicit solvent model, are selected as representative of the true fibrillar structure. It is shown that the registry of these models agrees well with the experimental results. At the neutral pH, the main contribution to the free energy difference between the two registries comes from the electrostatic interactions. The charge group of the carboxy terminal makes a large contribution to these interactions and thus appears to play a critical role in determining the registry.