Possible Methyl-Donated Hydrogen Bonding in the Glycine-29 to Isoleucine-32 Bend Region of Amyloid-β(1-42) Fibrils

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The formation of neuritic plaques by the aggregation of soluble amyloid-beta (Aβ) peptides into insoluble fibrils is strongly implicated in Alzheimer's disease pathology. The key suspect is a 42-mer, Aβ(1-42), which aggregates more aggressively and with higher neurotoxicity than other Aβ n-mers. In recent solid-state NMR structures for Aβ(1-42), the β-strand-turn-β-strand motif is stabilized by an intermolecular salt-bridge between residues D23 and K28 and numerous hydrophobic contacts. We suggest that the stability of Aβ(1-42) fibrils may in large part be due to a network of weak methyl CH/π and CH--O interactions. Our hypothesis is that these interactions in the turn region that is spanned by residues G29-I32 enhance the strength of the D23-K28 salt bridge by subtle geometric shifts in a network of weak hydrogen bonds sharing a common energy pool. We call this effect molecular commensalism. We report *ab initio* energies of 4- and 5-peptide fragment models in evidence of our hypothesis.