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Chaotic (“Non-Pathway”) Aggregation of β -Amyloid Congener Peptides

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We compared $A\beta_{21-30}$ and $A\beta_{16-34}$, with or without N-terminal Cys or cyclization. All $A\beta_{21-30}$ variants were monomeric and unstructured. In contrast, $A\beta_{16-34}$ and Cys- $A\beta_{16-34}$ formed fibrils – the latter more rapidly, due to disulfide bond formation. NMR showed no long-range nOes. In serial NOESYs, after changing pH (3 to 7.4) to initiate aggregation, some chemical shifts did not change, while others changed dramatically. In addition, although signals diminished globally with aggregation, the decay rates for individual peaks varied over ~ 4 -fold range. We attribute selective signal loss to conformational constraints restricting local tumbling and/or static structural heterogeneity. Signal decays for $A\beta_{16-34}$ and Cys- $A\beta_{16-34}$ differed in three ways: 1) Decay rates for Cys- $A\beta_{16-34} > A\beta_{16-34}$; 2) variances for rate constants of Cys- $A\beta_{16-34} < A\beta_{16-34}$ across replicate experiments; 3) smaller variances of rate constants within single experiments for Cys- $A\beta_{16-34}$ than $A\beta_{16-34}$. These results indicate both acceleration and ordering of aggregation by the disulfide bond in Cys- $A\beta_{16-34}$ compared to which aggregation of $A\beta_{16-34}$ was chaotic and disordered. Our results highlight several essential differences between protein folding and unfolded protein aggregation.

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