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Dynamically stable beta-sheets in Cu-initiated misfolding of α-synuclein FRANCIS ROSE, MIROSLAV HODAK, JERRY BERNHOLC, NC State University — The human protein α-synuclein has been implicated as a central constituent in multiple neurodegenerative diseases. In Parkinson disease it is even thought to be the causative link. α-synuclein can be stimulated to aggregate into deleterious fibrillar structures by mutation, metal binding, and agitation. In particular, Cu^{2+} has been found in high concentrations in neural tissues of Parkinson sufferers. We propose a scenario involving the metal ion Cu^{2+} as the misfolding β-sheet initiator of fibrillogenesis. A model fragment of the metal-bound protein was investigated using DFT to obtain conformational details of the energetically favorable geometries. Feasible β-sheet structures incorporating the DFT geometries were explored using heuristic β-sheet guidelines and inverse kinematics. The resulting structures were tested for dynamic stability by simulating the fully solvated protein by classical MD constrained by the DFT geometries. Our results indicate that dynamically stable structures exist and that the metal binding is directly responsible for initiating misfolding.

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