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Polymorphism of Protein Aggregation: From Amyloid Fibrils to Crystallization[1] MOHAMMAD S SAFARI[2], JACINTA C CONRAD[3], PETER G VEKILOV[4], None — Protein aggregation is commonly observed in neurological diseases and in different types of cancer. Despite the established mechanism of amyloid formation, the polymorphism of aggregation is not very well understood; improved knowledge of mechanisms for aggregation that operate in vivo or under physiological conditions is likely to inform therapeutic design. Here we show that reduction of disulfide bonds in lysozyme can lead to formation of gel-like oligomers that are precursors for protein crystal nucleation events. The growth in size of oligomers follows slow first-order kinetics, suggesting that monomers with free thiol contribute to formation of clusters. Free thiol concentration measurements showed that the thiol concentration was relatively stable over 12 hr, confirming the slow kinetics was due to gelation inside the clusters. We probed the hydrophobicity of the clusters using ANS and ThT assays, and showed that the protein conformation in these clusters differs from that of thermally denatured aggregates. Although partial unfolding aids the formation of precursors to both amyloids and crystals, our results suggest that these pathways exhibit distinct signatures even at the earliest stages.

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