The nucleation precursors in protein crystallization

PETER G. VEKILOV[1,2]

[1]Department of Chemical and Biomolecular Engineering, University of Houston, Houston, TX 77204-4004, USA
[2]Department of Chemistry, University of Houston, Houston, TX 77204-4004, USA
vekilov@uh.edu

Despite a long history of research, nucleation and particularly nucleation of crystals remains one of the most poorly understood processes in natrure. For any system of practical significance, theory predictions diverge from careful experimental determinations by many orders of magnitude. Recently, a two-step mechanism of nucleation of crystals in solution was put forth. This mechanism posits that the first step of crystal nucleation is the formation of disordered protein-rich clusters of mesoscopic size; the second step is the formation of crystal nuclei inside the clusters. This mechanism explained most of the discrepancies between theory and experimental data and has been invoked to explain experimental observations on the nucleation of sickle cell anemia fibers, amyloid fibrils, small-molecule organics colloids, biominerals, polymers, and other materials. The mechanism highlights the significance of the properties of the precursor clusters for nucleation. Results with proteins, by far the best studied solution crystallization system, indicate that the clusters represent a high free energy phase, in which the size of the mesoscopic domains is determined by the formation of transient protein oligomers. The liquid nature of the clusters, postulated in the two-step mechanism, has been verified. Several binding mechanims (Coulomb forces; ion, disulfide, and carbon dioxide bridges; and hydrophobic interaction between non-polar protein molecular patches) have been examined for their role in cluster formation. The results show that only the latter could be a part of the cluster mechanism.