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Time dependent kinetic measurements reveal a metastable intermediate phase during protein crystallization processes

The understanding of protein crystallization is of great interest for many areas of biological research. Examples include drug delivery of crystalline substrates and structural biology, which relies on diffraction-quality crystals. Some crystallization pathways are characterized by a one-step process and can be described by classical nucleation theory (CNT). However, for different systems, several steps are visible in the crystallization process resulting in an insufficient description of the crystallization process by CNT. These cases require a more detailed investigation to obtain a comprehensive picture of the underlying mechanisms. Bovine β-lactoglobulin (BLG) in the presence of the divalent salt $CdCl_2$ is characterized by a rich phase diagram. The protein solutions become turbid after crossing a first threshold salt concentration c^* upon further increasing the salt concentration, the solutions become less turbid but not completely clear again (pseudo-c^{**}). Near pseudo-c^{**}, crystallization follows a nonclassical process with a metastable intermediate phase (MIP). Here we explore the MIP in detail with a focus on the structural evolution and the growth kinetics of the MIP prior to crystal nucleation. We present a systematic study using real-time SANS, optical microscopy and neutron backscattering (NBS) to study the protein crystallization process in the presence of a MIP.
Real-time SANS measurements on D11 show that a correlation peak develops inside the MIP, and its peak position shifts to higher q-values with time (see Figure), finally stabilizing at a characteristic length scale of $d_{MIP} \approx 84$ Å. The area of this peak (proportional to the amount of MIP in the sample) first increases with time, reaches a maximum, and then decreases quickly upon crystallization due to consumption by crystal growth. The evolution of the correlation peak indicates a "preordering" nature of the MIP as precursors of crystal nucleation, which lowers the nucleation barrier for subsequent crystallization. These results on structural evolution and the role of MIPs during a nonclassical crystallization process may be relevant for other fields ranging from structural biology to pharmacology.
Literature: R. Maier et al.: "Protein Crystallization from a Preordered Metastable Intermediate Phase Followed by Real-Time Small-Angle Neutron Scattering" Cryst. Growth Des. 2021, 21, 12, 6971−6980

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