TUNING PROTEIN BEHAVIOR BY MULTIVALENT CHARGES: AGGREGATION, DIFFUSION, AND ADSORPTION

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We discuss concepts for controlling and understanding protein aggregation pathways and the branching between them in aqueous solution by addition of multivalent ions. This route for the tailoring of the interaction potential is exploited for controlling a) crystallization, b) gelation and amorphous aggregation, as well as c) smaller aggregate formation including their dynamics and kinetics. Furthermore, we discuss the connection to and the role of interfaces in this context.

First, we present a real-time study of protein crystallization induced by multivalent ions using small-angle scattering and optical microscopy. Based on the crystallization kinetics, we propose a multistep mechanism. In the first step, an intermediate phase is formed, followed by the nucleation of crystals within the intermediate phase. During this period, the number of crystals increases with time, but the crystal growth is slowed down by the surrounding dense intermediate phase due to the low mobility. In the next step, the intermediate phase is consumed by nucleation and slow growth, and the crystals are exposed to the dilute phase. In this stage, the number of crystals becomes nearly constant, whereas the crystals grow rapidly due to access to the free protein molecules in the dilute phase. This real-time study not only provides evidence for a two-step nucleation process for protein crystallization but also sheds light on the role and the structural signature of the metastable intermediate phase in this process. Furthermore, the competing routes of aggregation are elucidated, as is the role of the general features of the phase diagram including liqiud-liquid phase separation (LLPS).

Second, we present complementary investigations of the dynamics of these systems using quasi-elastic neutron scattering, showing a remarkably universal behavior of the effective diffusion as a function of concentration and salt under suitable conditions.

Third, we show how these concepts can be transferred to protein-interface interations, and how adsorption behavior can be manipulated by multivalent charges. We try to connect the interface and the bulk behavior, including reentrant adsorption and anomalous interface behavior upon approaching bulk phase boundaries.

Finally, we comment on the role of specific ions and attempt a comprehensive discussion of models and theories suitable for a comprehensive explanation of these phenomena.

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