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The potential role of salt bridge formation in the interaction between histatin 5 and polyvalent anions in tris buffer

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Abstract

Re-entrant condensation results in the formation of a condensed protein regime between two critical ion concentrations. The process is driven by neutralization and inversion of the protein charge by oppositely charged ions. Re-entrant condensation of cationic proteins by the polyvalent anions, pyrophosphate and tripolyphosphate, has previously been observed, but not for citrate, which has similar charge and size compared to the polyphosphates. Therefore, besides electrostatic interactions, other specific interactions between the polyphosphate ions and proteins must contribute. Here, we show that additional attractive interactions between arginine and tripolyphosphate determine the re-entrant condensation and decondensation boundaries of the cationic, intrinsically disordered saliva protein, histatin 5. Furthermore, we show by small-angle X-ray scattering (SAXS) that polyvalent anions cause compaction of histatin 5, as would be expected based solely on electrostatic interactions. Hence, we conclude that arginine–phosphate-specific interactions not only regulate solution properties but also influence the conformational ensemble of histatin 5, which is shown to vary with the number of arginine residues. Together, the results presented here provide further insight into an organizational mechanism that can be used to tune protein interactions in solution of both naturally occurring and synthetic proteins.