NTL9 FOLDING AT CONSTANT PH: THE IMPORTANCE OF ELECTROSTATIC INTERACTION AND PH-DEPENDENCE

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There are a large number of theoretical and experimental works that show the importance of the electrostatic interaction in folding and stability of proteins. The conformational arrangements, the salt concentration and the pH condition of the system may alter the charge of the ionizable group of the protein and consequently the electrostatic potential. This pH-dependence has been studied experimentally, but there are no computational studies about this pH-dependence in protein folding. In this work, it was introduced a Debye-Hückel potential into a Cα Structure-Based Model (Ca-SBM)[1,2] with titration of ionizable residues to evaluate the role of interactions during the folding process of the N-terminal domain of the ribosomal protein L9 (NTL9). This small monomeric α+β protein fraction of 56 residues (PDB id: 1CQU) is an interesting system to evaluate the importance of charges during the protein folding. Its folding mechanism is a two-state pathway, and does not interact with any cofactor or foldon containing disulfide bridges. The NTL9 protein is folded in a pH range from 1.0 to 12.0 and its folding is fully reversible. These characteristics make the NTL9 a good system to study the pH-dependence and to verify the consistency of the proposed model [3]. The simulations were performed by Molecular Dynamics (MD) under different pHs and salt concentrations, based on experimental literature available. The charge modification followed the Metropolis Monte Carlo criterion. Initially, the model was validated using the experimental results, and then the free energy profiles, Φ-values and folding routes were calculated for different scenarios. These studies reveal how simplified models can capture physical essential features, reproducing experimental results with a considerable low deviation (mainly due to the high degree of simplification), and presenting the role of electrostatic interactions before, during, and after the transition state.
