



Retention of local conformational compactness in unfolding of barnase; Contribution of end-to-end interactions within quasi-modules

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To understand how protein reduces the conformational space to be searched for the native structure, it is crucial to characterize ensembles of conformations on the way of folding processes, in particular ensembles of relatively long-range structures connecting between an extensively unfolded state and a state with a native-like overall chain topology. To analyze such intermediate conformations, we performed multiple unfolding molecular dynamics simulations of barnase at 498 K. Some short-range structures such as part of helix and turn were well sustained while most of the secondary structures and the hydrophobic cores were eventually lost, which is consistent with the results by other experimental and computational studies. The most important novel findings were persistence of long-range relatively compact substructures, which was captured by exploiting the concept of module. Module is originally introduced to describe the hierarchical structure of a globular protein in the native state. Modules are conceptually such relatively compact substructures that are resulted from partitioning the native structure of a globular protein completely into several contiguous segments with the least extended conformations. We applied this concept of module to detect a possible hierarchical structure of each snapshot structure in unfolding processes as well. Along with this conceptual extension, such detected relatively compact substructures are named quasi-modules. We found almost perfect persistence of quasi-module boundaries that are positioned close to the native module boundaries throughout the unfolding trajectories. Relatively compact conformations of the quasi-modules seemed to be retained mainly by hydrophobic interactions formed between residues located at both terminal regions within each module. From these results, we propose a hypothesis that hierarchical folding with the early formation of quasi-modules effectively reduces search space for the native structure.

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