Insights from Elementary Hydrophobic Interactions into the Activation Enthalpy, Heat Capacity, Volume, and Compressibility of Protein Folding

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Potentials of mean force (PMFs) of two-, three-, and many-body hydrophobic association are investigated to gain insight into the basic energetics of related processes in protein folding. Notably, many features observed in explicit-water simulations are not captured by common implicit-solvent approaches such as solvent accessible surface analysis. For instance, somewhat counter-intuitively, our group first discovered that the two-methane heat capacities of association in water have a prominent maximum in a region that coincides roughly with the PMF desolvation barrier (db). This result explains why the heat capacity signature of a compact denatured state can be experimentally similar to that calculated by assuming an open random-coil-like unfolded state [Shimizu & Chan, 2000; 2002]. Recent simulations of two-methane PMFs at multiple pressures indicate further that the dependence of excess volume on the methane-methane distance is oscillatory for small distances, with the maxima of excess volume and compressibility occurring near db. These features are underpinned by a void volume near db. Taken together, these two-methane properties are consistent with well-corroborated experimental observations of positive activation volumes for protein folding and some experiments suggesting a slightly higher compressibility for the folding transition state than the unfolded state. At high pressures, the volumes at the PMF solvent-separated minimum and the contact-minimum configurations are both smaller than the volume at large distances. This trend rationalizes the compactness of pressure-denatured states of proteins. Taking the packing densities of pure nonpolar phases into consideration, our simulation results suggest that whether the activation volume of unfolding is positive or negative hinges critically on the packing compactness of the folded protein core.