Hydrophilic Interactions Dominate the Inverse Temperature Dependence of Polypeptide Hydration Free Energies Attributed to Hydrophobicity

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We address the association of the hydrophobic driving forces in protein folding with the inverse temperature dependence of protein hydration, wherein stabilizing hydration effects strengthen with increasing temperature in a physiological range. All-atom calculations of the free energy of hydration of aqueous deca-alanine conformers, holistically including backbone and side-chain interactions together, show that attractive peptide–solvent interactions and the thermal expansion of the solvent dominate the inverse temperature signatures that have been interpreted traditionally as the hydrophobic stabilization of proteins in aqueous solution. Equivalent calculations on a methane solute are also presented as a benchmark for comparison. The present study calls for a reassessment of the forces that stabilize folded protein conformations in aqueous solutions and of the additivity of hydrophobic/hydrophilic contributions.