Equilibrium hydrogen-exchange measurements are a powerful tool for investigating the structures, stabilities, and dynamics of native and nonnative states of proteins. Previous analyses of hydrogen-exchange data have provided considerable insight into such properties for a variety of proteins, but the results have generally been qualitative in nature, although more quantitative thermodynamic analyses have been proposed. Here we present a model for the exchange of amide hydrogens with solvent water and determine the structures of species populated during the rare fluctuations of the native state that are required for the exchange. The method is based on an exploration of conformational space using Monte Carlo sampling biased by experimental data. The data involved are the experimental protection (P) factors, which represent the ratios of the exchange rates of amide hydrogens in unstructured polypeptides to those of the same residues in the native protein.

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ln $P^{lim}_{i}$ calculated as described in the text for the native state ensemble (red solid line) of α-lactalbumin. The coefficient of correlation is 0.89. The contribution to $\ln (P^{lim})$ due solely to hydrogen bonds is shown by the thin green line. In the calculation of the coefficient of correlation only those amide hydrogens whose protection factors were measured are included. Secondary structure elements in the native state are shown at the top of the figure.

Due to thermal fluctuations, the native state is an ensemble of many more unfolded conformations that are sampled, but rapidly than in the highly populated species. Residues whose rmsd is larger than 4 Å, and the OH distance is below 2 Å. Contacts between two residues were defined to be present when any pair of their atoms are closer than 8.5 Å. Hydrogen bonds were defined to be present if the angle between the NH vector and the OH vector is below 0.7 rad or if the OH distance is below 2.4 Å. Contacts between two residues were defined to be present when any pair of their atoms are closer than 8.5 Å.

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