Quantitative Description of Backbone Conformational Sampling of Unfolded Proteins at Amino Acid Resolution from NMR Residual Dipolar Couplings - DTU Orbit (13/12/2018)

Quantitative Description of Backbone Conformational Sampling of Unfolded Proteins at Amino Acid Resolution from NMR Residual Dipolar Couplings

An atomic resolution characterization of the structural properties of unfolded proteins that explicitly invokes the highly dynamic nature of the unfolded state will be extremely important for the development of a quantitative understanding of the thermodynamic basis of protein folding and stability. Here we develop a novel approach using residual dipolar couplings (RDCs) from unfolded proteins to determine conformational behavior on an amino acid specific basis. Conformational sampling is described in terms of ensembles of structures selected from a large pool of conformers. We test this approach, using extensive simulation, to determine how well the fitting of RDCs to reduced conformational ensembles containing few copies of the molecule can correctly reproduce the backbone conformational behavior of the protein. Having established approaches that allow accurate mapping of backbone dihedral angle conformational space from RDCs, we apply these methods to obtain an amino acid specific description of ubiquitin denatured in 8 M urea at pH 2.5. Cross-validation of data not employed in the fit verifies that an ensemble size of 200 structures is appropriate to characterize the highly fluctuating backbone. This approach allows us to identify local conformational sampling properties of urea-unfolded ubiquitin, which shows that the backbone sampling of certain types of charged or polar amino acids, in particular threonine, glutamic acid, and arginine, is affected more strongly by urea binding than amino acids with hydrophobic side chains. In general, the approach presented here establishes robust procedures for the study of all denatured and intrinsically disordered states.

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