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Protein Folding and Amyloid Formation: Good Questions for Solid State NMR

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Recent results from two ongoing projects will be described. These projects illustrate the expanding capability of solid state NMR spectroscopy to provide unique information about the molecular structure of complex biochemical systems that are of current interest in the biophysical and biomedical research communities. Methodological advances that facilitate progress on these projects will be discussed briefly. In the area of protein folding, we are using solid state NMR spectroscopy to characterize the distributions of molecular structures in unfolded and partially folded states of relatively simple model proteins. The measurements are carried out on frozen glassy solutions at low temperatures. Initial results for the chemical denaturation of the 35-residue helical protein HP35 show that unfolding does not occur by a simple two-state process and that local conformational distributions in the unfolded state are remarkably non-uniform. In the area of amyloid fibrils, we are using solid state NMR to develop experimentally-based models for the molecular structure of peptide fibrils associated with Alzheimer's disease and other amyloid diseases, and to develop an understanding of the interactions that stabilize amyloid fibril structures in general. The NMR data also reveal molecular-level polymorphism in amyloid fibrils, with implications for biomedical issues such as the etiological role of fibrils in amyloid diseases and the structural basis for strains in prion diseases.