Seeing the Invisible by NMR Spectroscopy

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An understanding of the role played by a protein in cellular function requires a detailed picture of its three-dimensional structure as well as an appreciation of how the structure varies as a function of time due to molecular dynamics. Proteins are not static and often interconvert to states higher in energy than the ground conformation that play important roles in biological function. These so called excited states are often 'invisible' in biophysical studies because of their low population and transient formation. Here I will describe NMR approaches for studying invisible states at atomic resolution. A number of examples will be presented including protein misfolding, where partially folded high energy intermediates have been implicated as the starting points for aggregation and formation of cytotoxic oligomers that are involved in a host of human diseases. In addition, new experimental approaches for 'seeing the invisible' will be discussed.