Telluride Workshop on Protein Dynamics

Prof. Martin J. Stone
Department of Chemistry, Indiana University, Bloomington, Indiana, USA.

From NMR Measurements of Protein Dynamics to Thermodynamics: Recent Advances and Future Challenges

The thermodynamics of protein binding interactions and structural transformations are controlled by an intricate balance between many enthalpic and entropic factors. One important factor is the conformational entropy of the protein chain. However, determining the change in conformation entropy upon binding or folding using classical thermodynamic measurements is generally very difficult because this change is accompanied by substantial changes in other entropic terms such as solvent entropy. NMR relaxation methods that are sensitive to the fluctuations of protein structures offer a complementary approach to estimation of conformation entropy. The strength of this approach is that NMR relaxation parameters (and derived order parameters) can be determined at many sites throughout a protein, providing information not only about the net conformational entropy but also about redistribution of entropic fluctuations across the protein structure. On the other hand, NMR methods are not sensitive to all structural fluctuations and conversion of order parameters to conformational entropy is complicated by the possible existence of correlated (synchronized) motions. By analyzing the covariation of order parameters among many forms of the same protein, one can probe the existence of correlated motions in the protein. We have applied this method to study the backbone amide and side chain methyl fluctuations in a series of mutants of a small protein, the B1 domain from protein G. Data indicate that dynamic correlations are indeed present in this domain and that variations in the internal motions make a substantial contribution to protein stability, although they do not correlate directly with stability or structural properties of the mutated amino acid.