Skills to Develop

- Differentiate between general charge and specific ion-ion pairs and summarize their role in protein stability
- Draw the structure of N-methylacetamide (NMA) and explain why it is a useful small molecule model to study the role of H bonds in protein stability
- Draw a thermodynamics cycle for the transfer of a hydrogen bonded dimer of NMA from water to a nonpolar environment. From the DG0 for steps in the cycle, and extending this model to protein, predict if buried H bond formation drives protein folding
- Explain if studies of low temperature protein denaturation, high temperature protein, and DGo transfer of nonpolar side chains from water to more nonpolar solvents support the hydrophobic effect in protein stability
- Summarize the relationship between the empirical Hofmeister series and preferential binding of reagents into the hydration sphere of protein to explain the effects of denaturants (urea, guanidine salts) and stabilizers (glycerol, ammonium sulfate) on proteins
- Using benzene solubility in water as a model to study the role of hydrophobic effect in protein unfolding and by inference in protein stability, interpret graphs of DG0, DH0, DS0 and DCp for the transfer of benzene to water, as a function of temperature.
- From the above graph, explain if trends in the thermodynamic parameters for benzene transfer into water predict the observed protein unfolding/stability behavior of proteins as a function of temperature?
- Give a molecular interpretation of the observed DCp for the transfer of nonpolar molecules into water.
- Describe chain conformational entropy, relate it to conformational changes in acyl side chains in single and double chain amphiphiles with temperatures, and describe it role in protein stability.
- State which of several given explanations for the observed destabilizing effects of Asn to Ala mutations in protein account for those observation
- Summarize graphically the magnitude and direction of the major contributors (inter- and intramolecular forces and effects) to protein stability

It is clear that proteins are not all that stable, and many contributions of varying magnitudes must sum to give the proteins marginal stability under physiological conditions. Hydrophobic interaction, defined in the new sense, must play a major role in stability. Also, since proteins are so highly packed compared to a lose denatured state, London Forces must also play a significant part. (Remember dispersion forces are short range and become most significant under conditions of closest packing.) Opposing folding is the chain conformational entropy just described. Since proteins are so marginally stable, even one unpaired buried ionic side chain, or 1-2 unpaired buried H bond donors and acceptors in the protein may be enough to "unravel" the native structure, leading to the denatured state.

- **Topic hierarchy**

*Thumbnail: Structure of human hemoglobin. The proteins α and β subunits are in red and blue, and the iron-containing heme groups in green. From PDB: 1GZX. Image used with permission (GNU; Proteopedia Hemoglobin).*

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**Contributors**

- Prof. Henry Jakubowski (College of St. Benedict/St. John's University)