

Lectures 9-10

Protein Architecture: Protein Folding

Thermodynamics of Folding

Remember

Making bonds is enthalpically favorable (-ve ΔH)

An ordered system is entropically unfavorable (+ve $T\Delta S$)

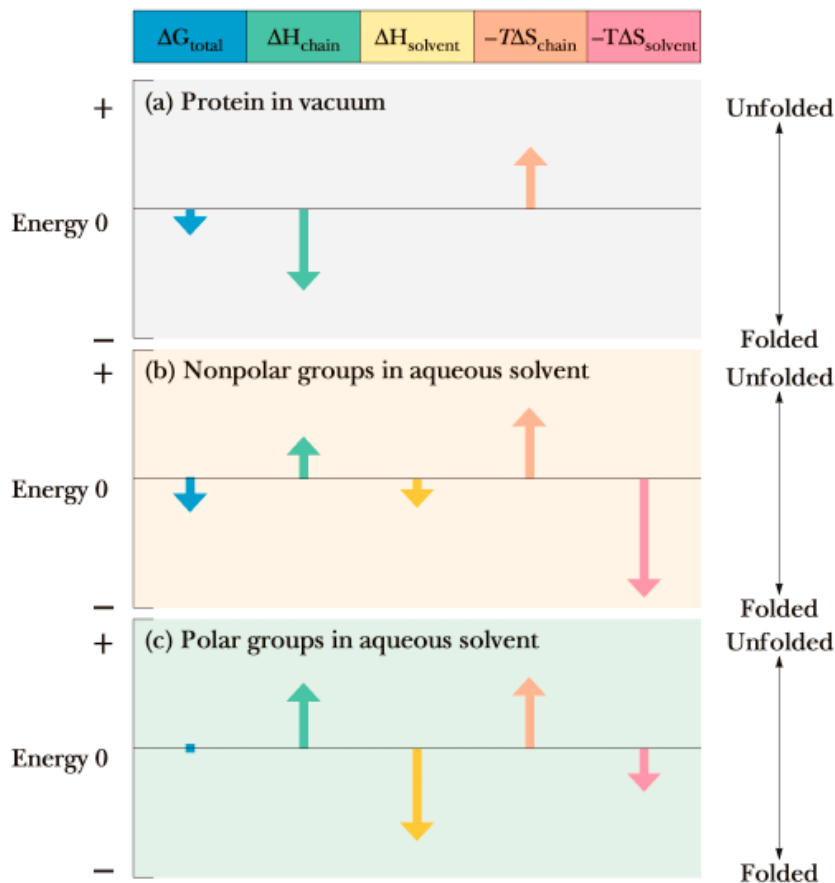
Folding is energetically favorable if the sum of these components

$\Delta G = \Delta H - T\Delta S$, is -ve

Separate the enthalpy and entropy terms for the peptide chain and the solvent

Distinguish polar and nonpolar groups

The largest favorable contribution to folding is the entropy term for the interaction of nonpolar residues with the solvent



Protein Folding: What do We Know?

- Small folding free energies 5-15 kJmol⁻¹
- 3D fold encoded by 1D sequence (Anfinsen)
- Exhaustive conformational search impossible (Levinthal)
- Secondary structural preferences among the amino acids

How do Proteins Recognize and Interpret the Folding Information?

- Consideration of amino acid secondary structure preferences alone gives correct predictions only 50% of the time (Chou and Fasman)
- Stabilizing the folding transition state may be key

Folding Models

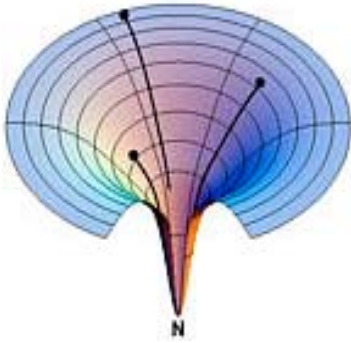
What might the transition states look like?

- Nucleation
 - folding starts with a nucleus of several interacting residues that bring together distant parts of the sequence
- Framework
 - stable secondary structures form first, followed by long-range tertiary interactions
- Diffusion-collision
 - microdomains diffuse through the chain. Some intrachain collisions between these domains serve to increase stability leading ultimately to productive folding

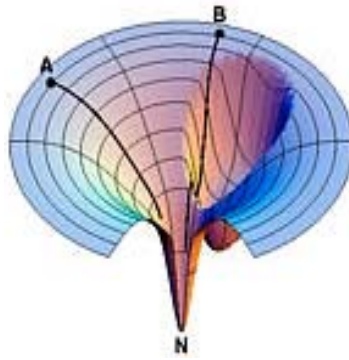
Folding Pathways or Folding Funnels?

- The chemist's picture: reactants pass through identical transition states to become products - a pathway
- The protein's picture: many different transition states may be possible - a family of pathways or a funnel

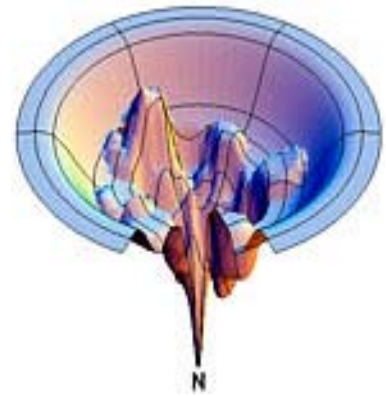
Protein Folding Funnels



Smooth funnel.
All trajectories are equivalent.
Monoexponential folding rates.



Anisotropic funnel.
A few different trajectories have different outcomes.
Biexponential folding rates.



Highly anisotropic funnel.
Most trajectories have different outcomes.
Multiexponential folding rates.

The Molten Globule

- Low energy conformations late in the folding process
- Most secondary structure formed
- Tertiary structure poorly defined
- Hydrophobic core poorly packed