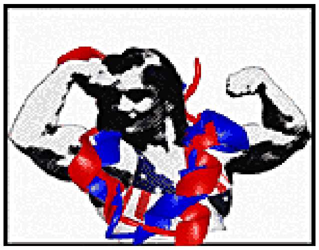
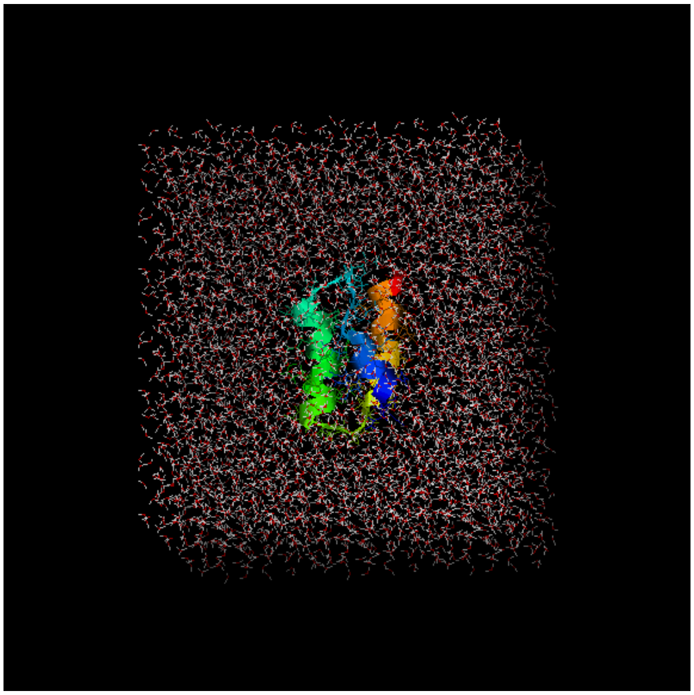
Why Proteins Fold



Proteins are the action superheroes of the body. As enzymes, they make reactions go a million times faster. As versatile transport vehicles, they carry oxygen and antibodies to fight disease. They do a thousand different jobs, and with no complaint. But before a protein can go to work, it must fold into the right shape.

http://www.psc.edu/science/kollman98.html

How Proteins Fold?



Water is key

www.cs.vt.edu/~onufriev

Protein Folding, Nonbonding Forces, and Free Energy

ΔG Gibbs Free Energy

$e^{-\Delta G/kT}$ Boltzman Probability Distribution

Describes the likelihood that a state with a certain free energy will be found

Entropy

- Entropy – a measure of disorder

$$\Delta S_{total} = \Delta S_{system} + \Delta S_{surroundings}$$

$$\Delta S_{total} = \Delta S_{system} - \Delta H_{system} / T$$

H = enthalpy

T = temperature (Kelvins)

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$$\Delta S_{total} = \Delta S_{system} - \Delta H_{system} / T$$

H = enthalpy

T = temperature (Kelvins)

$$-T\,\Delta S_{total} = \Delta H_{system} - T\,\Delta S_{system}$$

Free Energy

$-T\,\Delta S_{total} = \Delta H_{system} - T\,\Delta S_{system} \quad = \Delta G$

- 2nd Law of Thermodynamics – the total entropy of a system and its surroundings always increases for a spontaneous process.

Since we have already seen that:

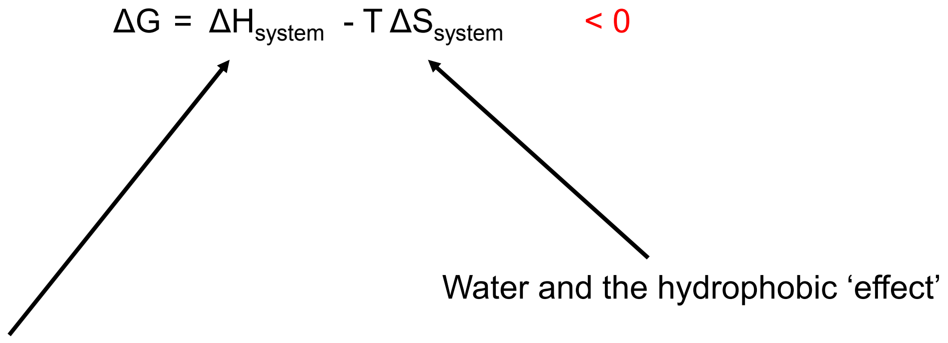
$$\Delta S_{total} = \Delta S_{system} - \Delta H_{system} / T$$

Total entropy will only increase if:

$$\Delta S_{system} > \Delta H_{system} / T \qquad (T\,\Delta S_{system} > \Delta H_{system})$$

Therefore, $\Delta G < 0$ for a spontaneous process

Free Energy and Protein Folding



$$\Delta G = \Delta H_{system} - T\,\Delta S_{system} \quad < 0$$

Water and the hydrophobic ‘effect’

- Bonding Energies
  - Disulfides, bound ions, etc.
- Nonbonding Energies
  - Electrostatic
  - Hydrogen Bonds
  - Van der Waals

Non-Bonding Interactions

Amino acids of a protein are joined by covalent bonding interactions. The polypeptide is folded in three dimension by non-bonding interactions. These interactions, which can easily be disrupted by extreme pH, temperature, pressure, and denaturants, are:

- Electrostatic Interactions (5 kcal/mol)
- Hydrogen-bond Interactions (3-7 kcal/mol)
- Van Der Waals Interactions (1 kcal/mol)
- Hydrophobic Interactions (< 10 kcal/mol)

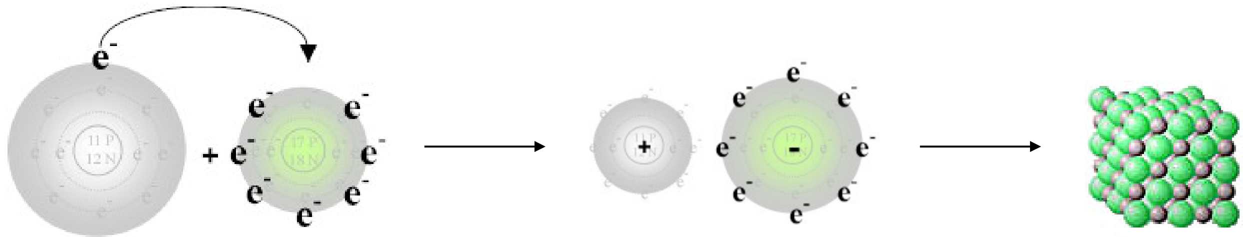
The total inter-atomic force acting between two atoms is the sum of all the forces they exert on each other.

Electrostatic Interactions

Charged groups attract or repel each other. The force F of such an electrostatic interaction is given by Coulomb's law:

$$F = \frac{q_1 q_2}{D r^2}$$

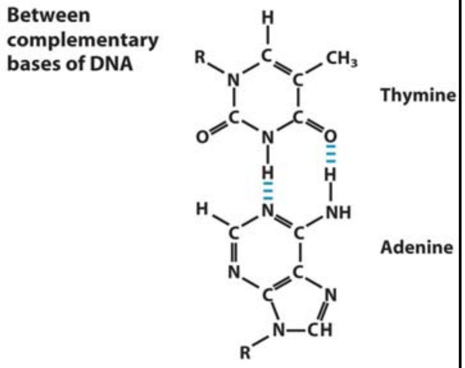
q_1 and q_2 are the charges
r is the distance
D is the dielectric constant

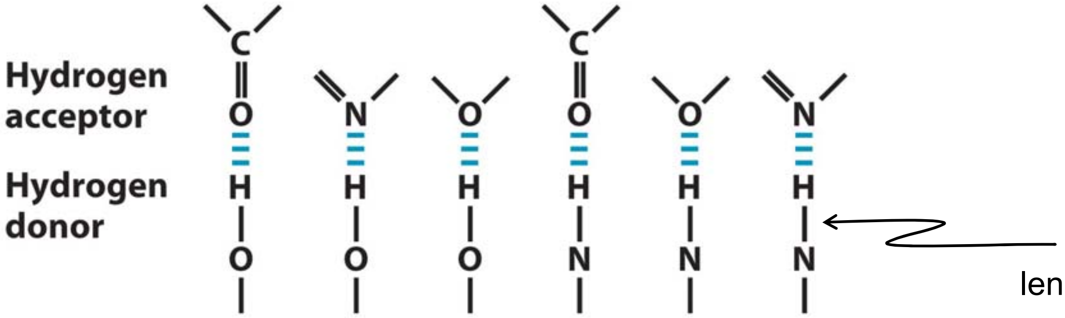


Coulomb's law is also used to determine interactions between uncharged, but polar atoms.

Hydrogen bonds

In a hydrogen bond, a hydrogen atom is shared between two other atoms. The atom to which the hydrogen is more tightly linked is called the hydrogen donor, the other atom is called the hydrogen acceptor.



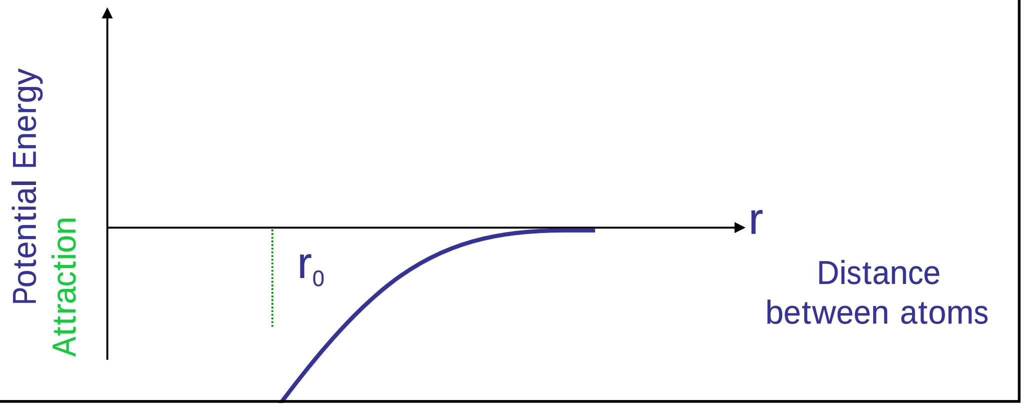


Bond lengthened

Van der Waals Interactions

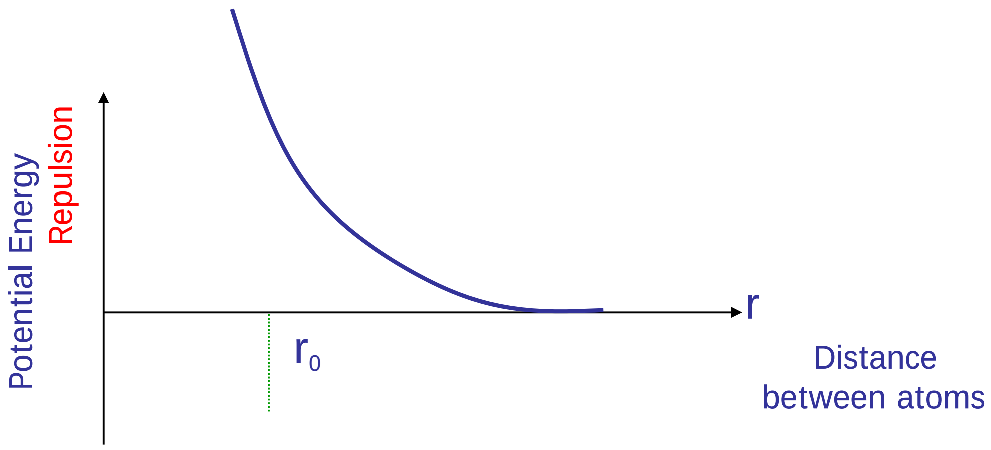
The distribution of electronic charges around an atom changes with time, and a transient asymmetry in the charges around one atom induces a similar asymmetry in the electron distribution around its neighboring atoms.

This is essentially an electrostatic interaction and results in a small distant-dependent (R^{-6}) attractive force.



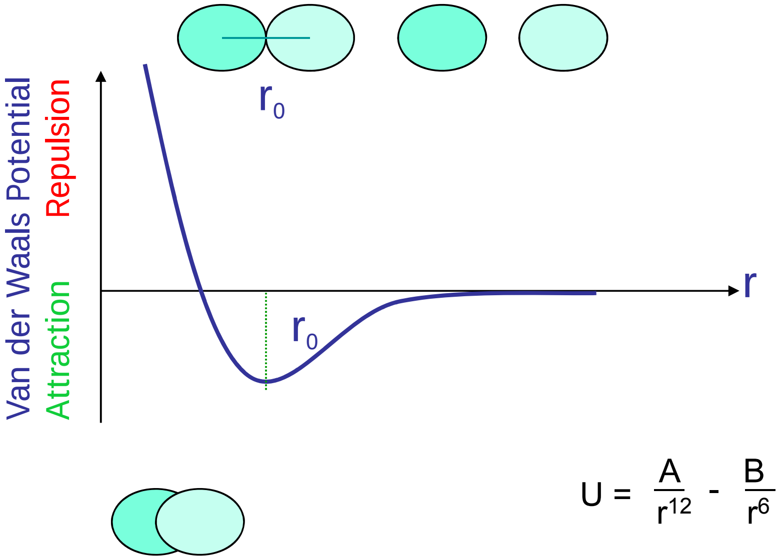
Van der Waals Interactions

As atoms get too close, their electron clouds will clash, resulting i
a distant-dependent (R^{-12}) repulsive potential energy.



Lennard-Jones Potential

The attractive and repulsive terms can be summed together to describe a distance-dependent interatomic potential energy.

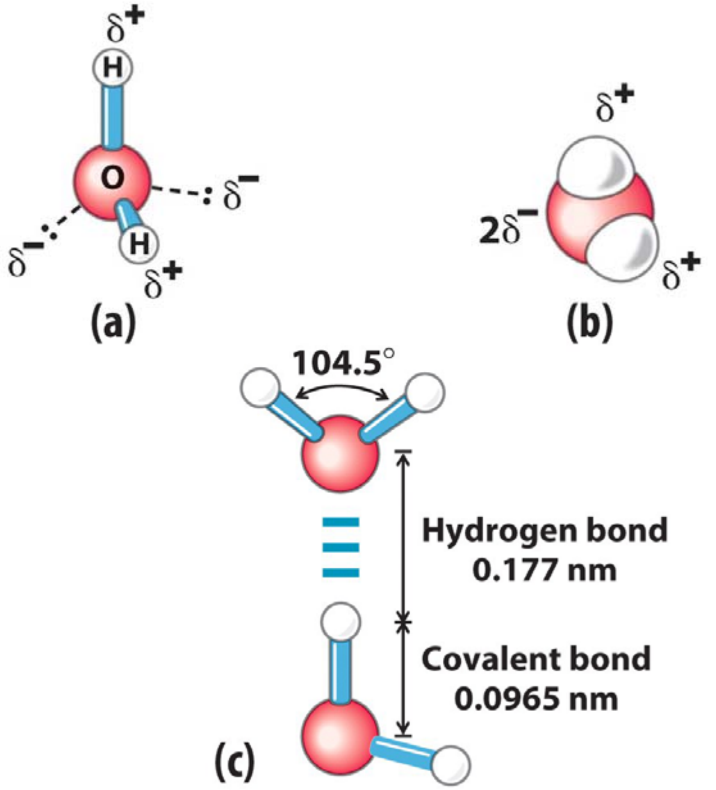


$$U = \frac{A}{r^{12}} - \frac{B}{r^{6}}$$

Hydrophobic Interactions in Proteins

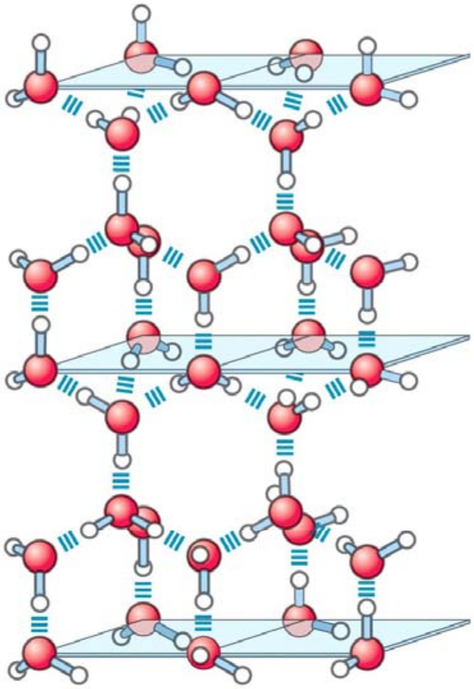
- Hydrophobic interactions minimize interactions of non-polar residues with solvent.
- Non-polar regions of proteins are usually buried in the molecules interior.
- However, non-polar residues can also be found on the surface of a protein. They may participate in protein-protein interactions.
- This type of interaction is entropy driven.

Water

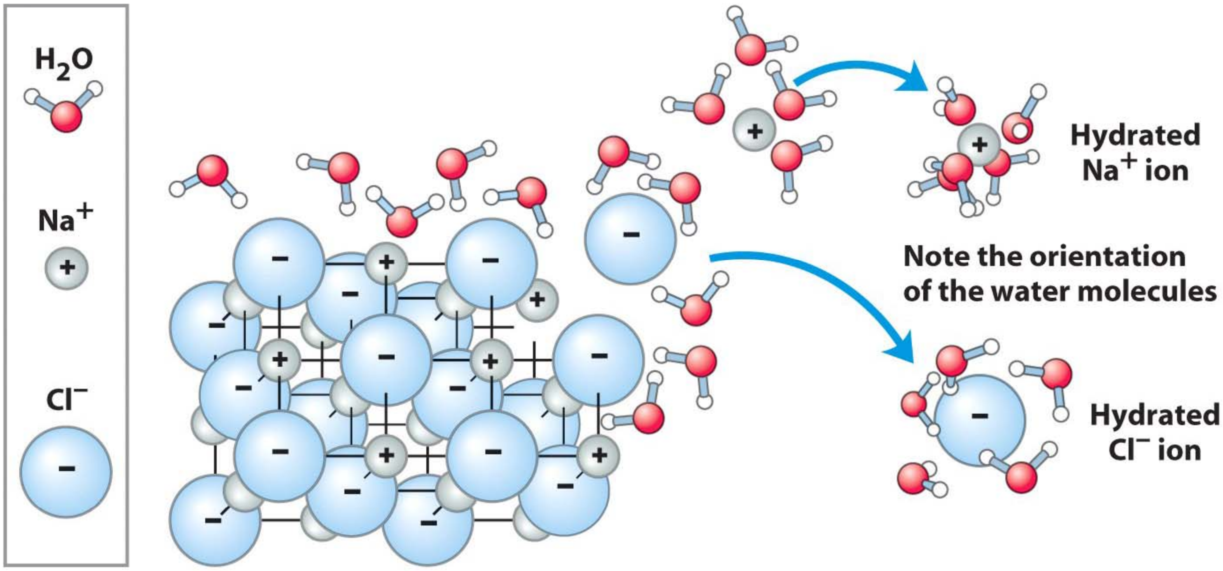


δ+
H
O
δ−
δ−
H
δ+
(a)
δ+
2δ−
δ+
(b)
104.5°
Hydrogen bond
0.177 nm
Covalent bond
0.0965 nm
(c)

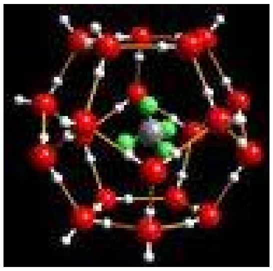
Ice



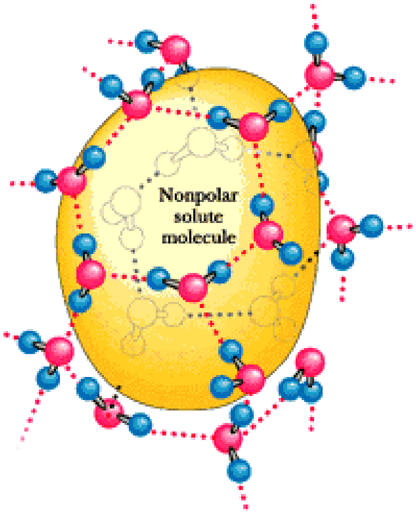
Water as a Solvent



Water Clathrate Cages

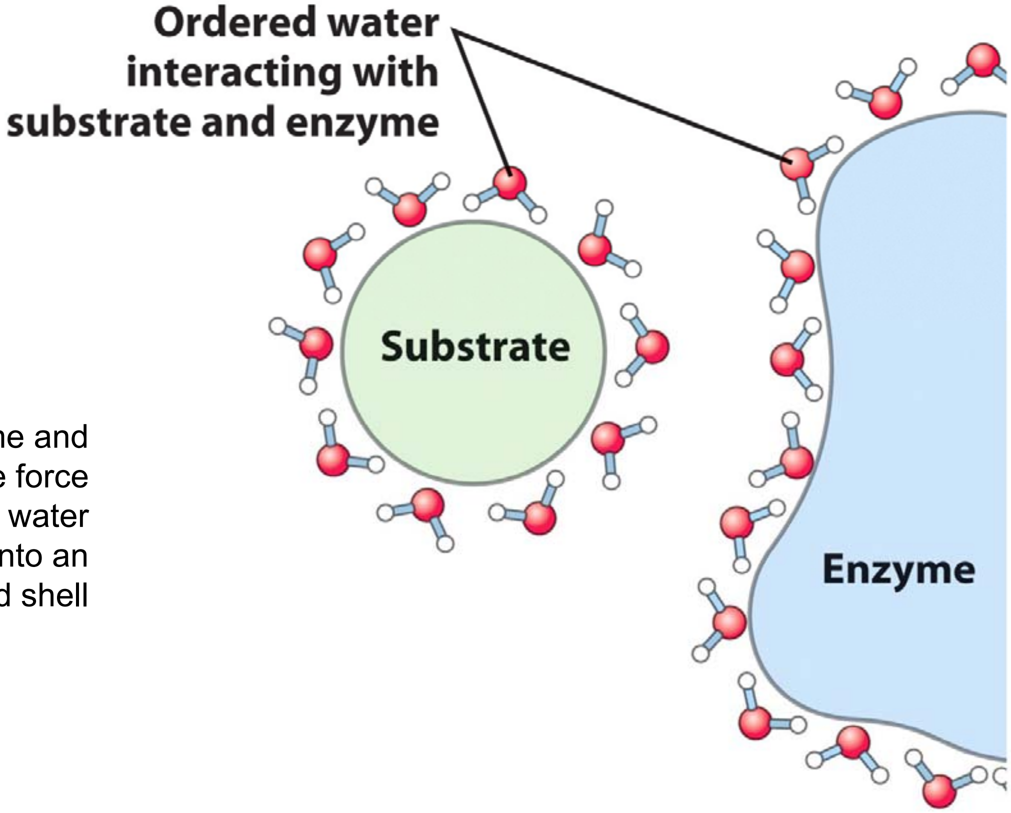


Water clathrate surrounding nonpolar methane molecule



Water molecules have less degrees of freedom in the clathrate cage arrangements because some H-bonds cannot point inside toward the hydrophobic sphere

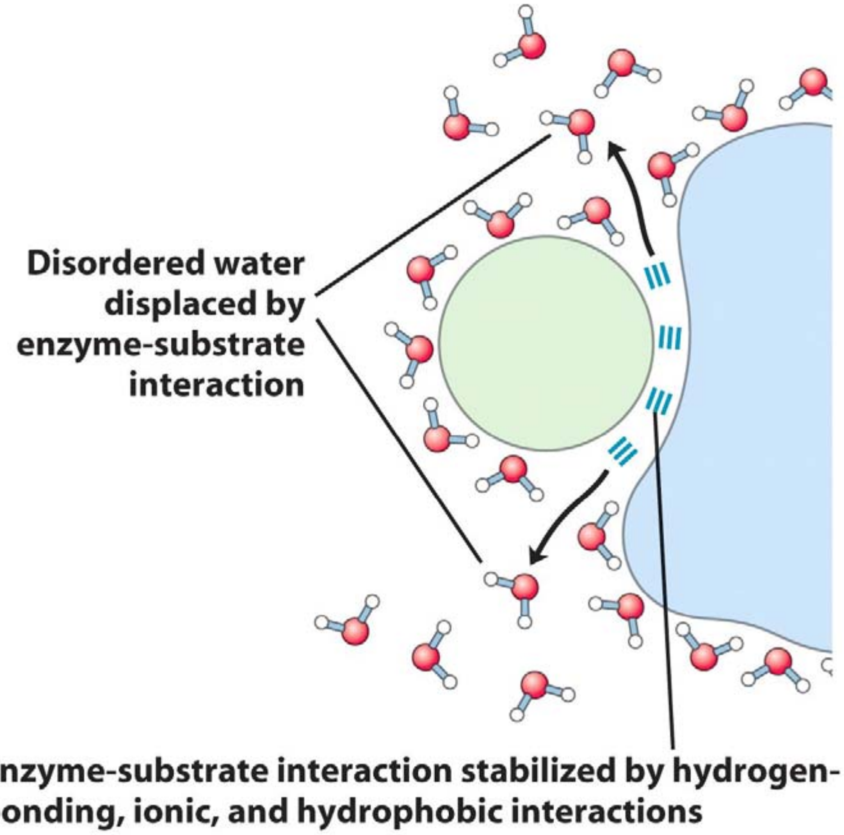
Enzyme-Substrate Binding



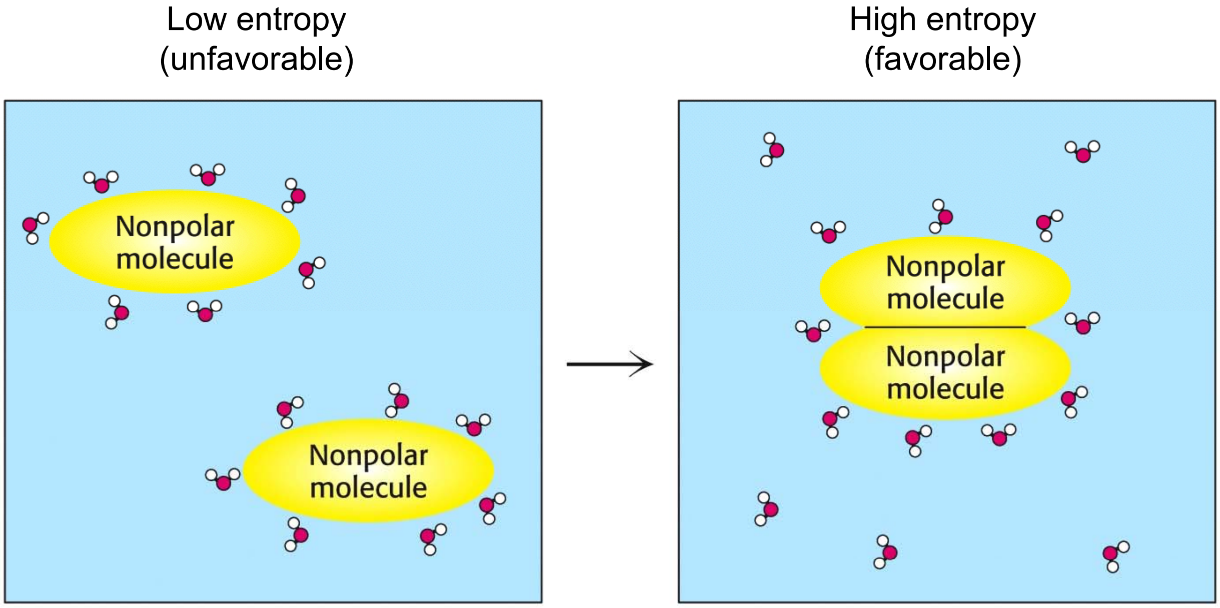
Both enzyme and substrate force neighbouring water molecules into an ordered shell

Enzyme-Substrate Binding

The release of ordered water favors the formation of the enzyme-substrate complex!



The Hydrophobic Effect



$\Delta G = \Delta H - T \Delta S$

Hydrophobic Interactions Recap

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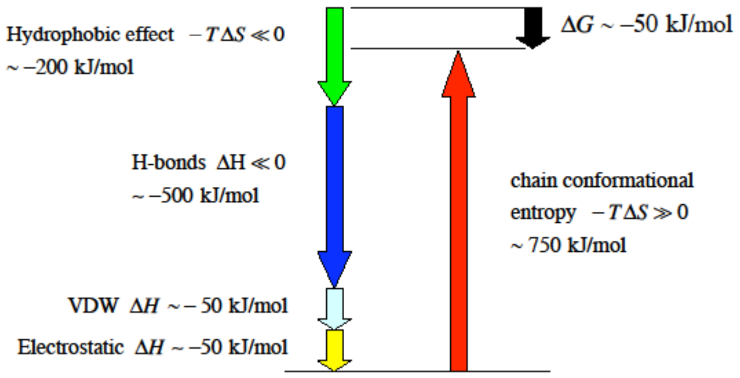
Kcal = 4.18 KJ

Protein Folding Energy

Dissecting the free energy of protein folding

$$\text{Unfolded} \xrightleftharpoons{\Delta G} \text{Folded}$$

$$\Delta G = \Delta H - T\Delta S < 0, \quad \Delta G =\sim -50 \text{ kJ/mol}$$



Hydrophobic effect $-T\Delta S \ll 0$
~ -200 kJ/mol

H-bonds $\Delta H \ll 0$
~ -500 kJ/mol

VDW $\Delta H \sim -50$ kJ/mol

Electrostatic $\Delta H \sim -50$ kJ/mol

$\Delta G \sim -50$ kJ/mol

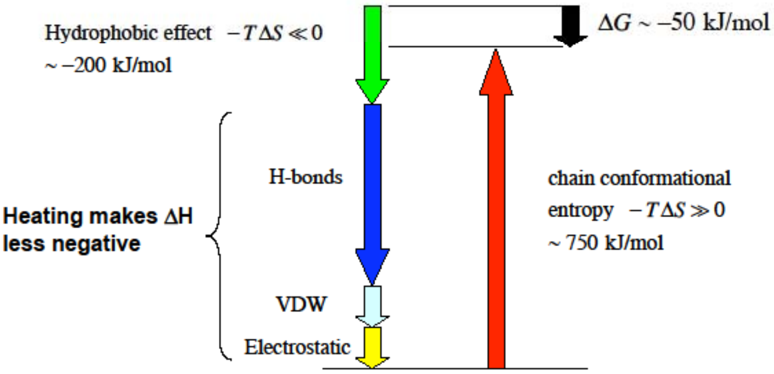
chain conformational
entropy $-T\Delta S \gg 0$
~ 750 kJ/mol

James Chou, Harvard Medical School

Protein Folding Energy

Denaturation by Heat -- break H-bonds and other enthalpically favorable interactions

$$\Delta G = \Delta H - T\Delta S < 0$$



Hydrophobic effect $-T\Delta S \ll 0$
~ -200 kJ/mol

$\Delta G \sim -50$ kJ/mol

Heating makes ΔH less negative

H-bonds

VDW

Electrostatic

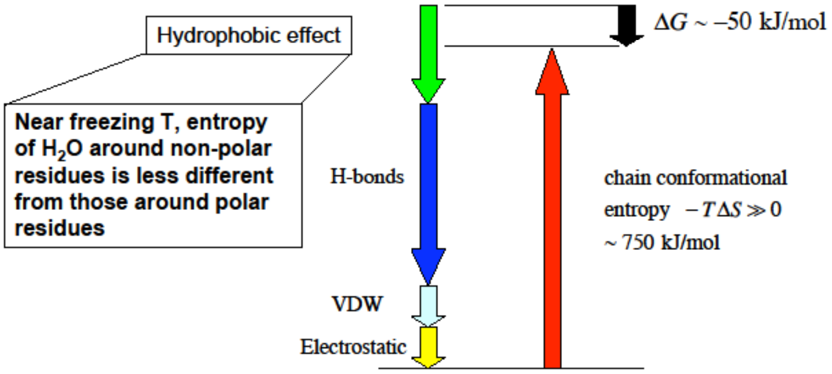
chain conformational
entropy $-T\Delta S \gg 0$
~ 750 kJ/mol

James Chou, Harvard Medical School

Protein Folding Energy

Denaturation by Cold -- reduce the contribution from hydrophobic effect

$$\Delta G = \Delta H - T\Delta S < 0$$



Hydrophobic effect

Near freezing T, entropy of H_2O around non-polar residues is less different from those around polar residues

H-bonds

VDW

Electrostatic

$\Delta G \sim -50$ kJ/mol

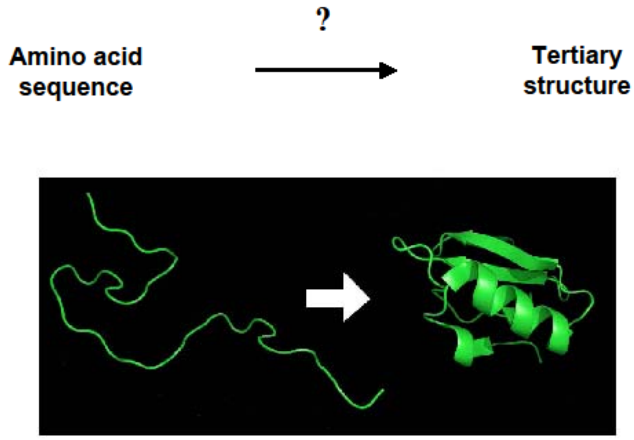
chain conformational entropy $-T\Delta S \gg 0$

~ 750 kJ/mol

James Chou, Harvard Medical School

The Protein Folding Problem

The problem of protein folding



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The Protein Folding Problem

Levinthal paradox

Assume each amino acid backbone can be in 3 conformational states, for 101 residues, there are $3^{100} = 5 \times 10^{47}$ conformations.

If the protein can sample a new conformation at a rate of 10^{13} s^{-1}, it will take 10^{27} years to try them all. Longer than the age of the universe!

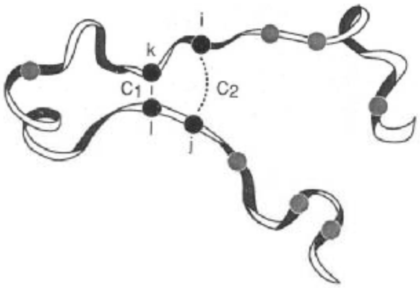
Therefore, proteins must fold in “pre-arranged pathways” and in a cooperative manner.

Levinthal C. *Extrait du Journal de Chimie Physique* 1968; 65:44

Zwanzig et al., *PNAS* 1992; 89:20-22

The Protein Folding Problem

Cooperativity in protein folding : How a globally optimal state can be found without a global search?



Origin of cooperativity -- The probability of forming contact C_2 is much higher if C_1 is formed than in the absence of C_1.

Dill et al., *PNAS* 1993; 90:1942-6

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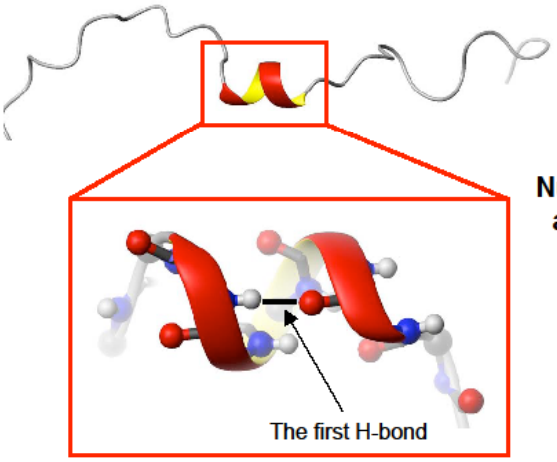
The Protein Folding Problem

Coil-Helix transition -- the paradigm for cooperativity in biopolymers



Nucleation of alpha helix

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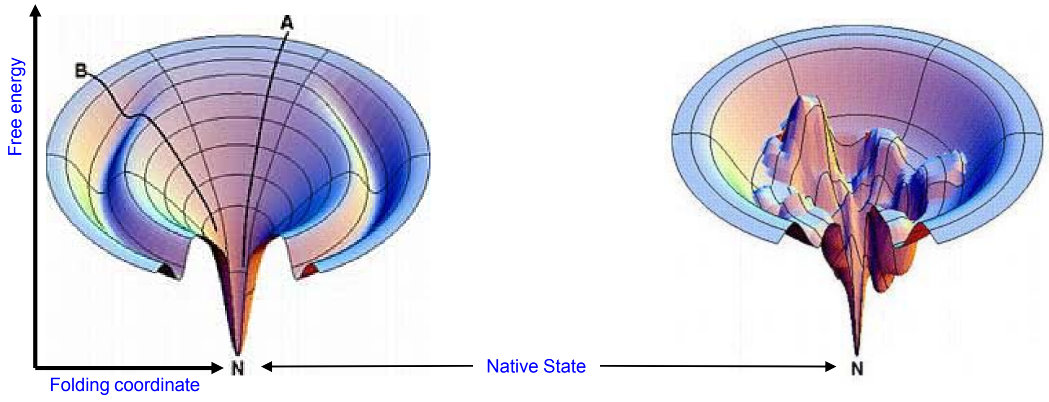
Folding Landscapes



Simple Energy Landscape

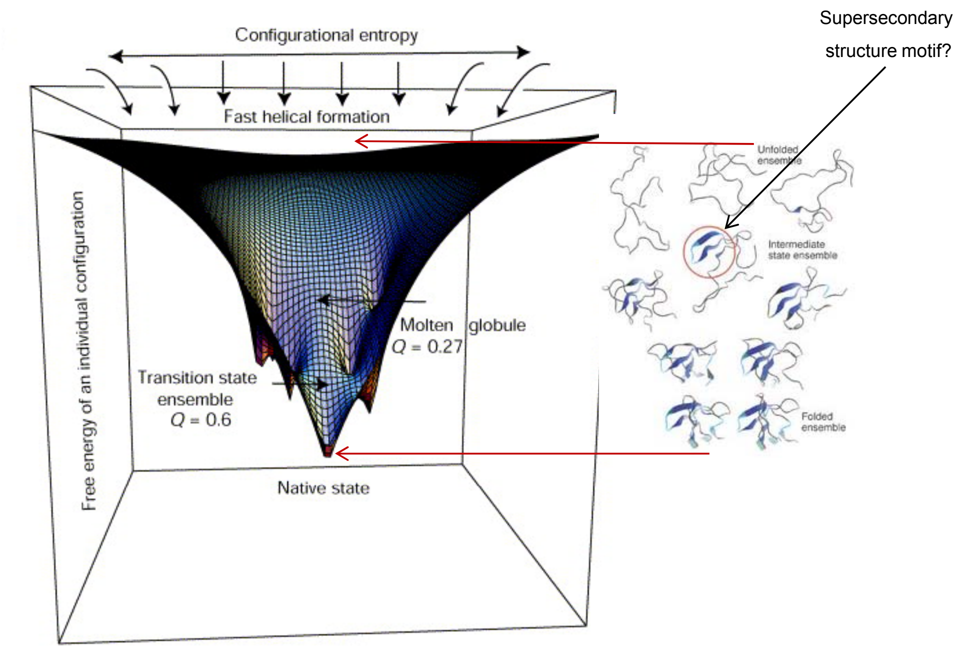
Complex Energy Landscape

Finding a global minimum in a multidimensional case is easy only when the landscape is smooth. No matter where you start (A or B), you quickly end up at the bottom -- the Native (N), functional state of the protein.

Realistic landscapes are much more complex, with multiple local minima – folding traps.

Adopted from Ken Dill's web site at UCSF

Folding Funnels



Supersecondary structure motif?

Folding Funnels