Key points to be covered

1. van der Waals Interaction
2. Hydrogen bond
3. Hydrophilic vs hydrophobic
4. The environment in the cell:

Hydrophobic Bio-molecules

- Hydrocarbon compounds, lipids or fats, etc.
- No charge, non-polar covalent bond
- What are the governing interactions between these molecules?

Molecular Interactions in Bio-molecular Structures - van der Waals Interaction

Attractive force-London force and repulsive force:

- An instantaneous and short-lived imbalance in the electron distribution of an atom that generates a temporary dipole.
- The temporary dipole induces the electron distribution of a neighboring atom to polarize in order to minimize the electron-electron repulsion between the atoms.
- Induced dipole-induced dipole interaction (London dispersion forces).

Energy minimization principle: according to Newton’s first law, \( F = -\frac{\partial V}{\partial r} \). At equilibrium \( \frac{\partial V}{\partial r} = 0 \), meaning that \( F = 0 \).

- The energy minimization methods to find the lowest energy conformation of a

Molecular Interactions in Bio-molecular Structures - van der Waals Interaction

- The London dispersion potential \( V_L \) between two uncharged atoms:
  \[
  V_L = -\frac{3\hbar^2 \alpha^2}{4\pi^2}\frac{1}{r^6}
  \]
  \( \hbar \): Ionizing energy
  \( \alpha \): Polarizability of each atom

- The simplest model to accommodate the repulsive force - Hard sphere approximation:
  - Each atom as an impenetrable spherical volume.
  - A more accurate model:
Molecular Interactions in Bio-molecular Structures - *van der Waals Interaction*

- Van der Waals Interactions:
  - The attractive London dispersion + The repulsive potentials
  
  \[ V_{\text{cdw}} = A \frac{B}{r^6} \]

  - 6-12, Lennard-Jones potential

- An equilibrium distance (The two opposing forces become equal)

  van der Waals radii \( r_{\text{vdw}} \) (Table 3.3)

Watson and Crick demonstrate the complementary of DNA basepairs. The dotted lines denote hydrogen bonds. The shapes and chemical structure of the bases allow hydrogen bonds to form optimal only between adenine (A) and thymine (T) and between guanine (G) and cytosine (C); in these pairings, atoms that are able to form hydrogen bonds can be brought close together without distorting the bases’ geometries.

**Molecular Interactions in Bio-molecular Structures - water and hydrogen bond**

Do you know the fact that...

- Water makes up 70% of your body.
- Why don’t you let it evaporate... leaving those proteins, lipids etc. behind?

**In H₂: H-H are equal.**

The covalent bond is non-polar.

**In H₂O: O takes more of H than it gives.**

So H is dependent on this “partnership”.

In O-H, O \( \delta^- \), H \( \delta^+ \). Polar covalent bond.
Molecular Interactions in Bio-molecular Structures - water and hydrogen bond

- Attraction between water molecules - Hydrogen bond.
- A hydrogen bond is the attraction of a hydrogen atom of a molecule to an atom of another molecule – relatively weak.
- This gives water molecules extra cohesion.

Requirements for formation of hydrogen bonds:
- A polarized D-H (where D is the hydrogen-donating atom)
- A polarized nonbonding orbital of an acceptor (A).
- In most cases, -C-H cannot be used as a donor of a hydrogen bond.

Hydrogen-bond donor:
- O-H, N-H, etc

Hydrogen-bond acceptor:
- :O-the non-bonding electrons of :O, :S, etc.

How to treat hydrogen bond interaction?
- Many of the properties of the hydrogen bond can be accounted for by treating it as a dipole-dipole interaction.
  - Energy: 4-48 kJ/mol (significantly weaker than a typical covalent) or coordinate bond and closer to the magnitude of the potentials for dipole-dipole interactions.
  - The optimum alignment of the three atoms (D-H-A) to give a head-to-tail arrangement of the dipole moments is predicted by the potential function:

\[
V_{dip} = \frac{p_1 \cdot p_2}{D^2} - \frac{2(p_1 \cdot \mathbf{r})(p_2 \cdot \mathbf{r})}{D^3}
\]

In certain ways the hydrogen bond is also similar to a covalent bond:
- An optimum distance separating the donor and acceptor: 0.26 - 0.30 nm (Table 1.3).
- The equilibrium distance is less than the sum of the respective \( r_{vdw} \).
Molecular Interactions in Bio-molecular Structures - water and hydrogen bond

How to treat hydrogen bond interaction?

Hydrogen bonds possess:
- Partial non-bond property
- Partial covalent bond property.

The way to treat hydrogen bonds: The potential energy of a hydrogen bond can be treated in a force field as interaction between the dipoles of the donor and acceptor atoms, along with a potential that accommodates the special structural features of the bond V_{HB}.

\[ V_{HB} = C \frac{D}{r^6} \]

where:
- \( C \): Proportionality constant specific for each donor-acceptor pair.
- \( D \): Proportionality constant specific for each donor-acceptor pair.
- \( r \): Distance between the donor and acceptor atoms.

Positive repulsive term
Negative attractive term

- Short-range interactions
- Typically 2kJ/mol for the dipole-dipole interaction of the hydrogen bond.

The implications of hydrogen bond in the stabilization of biomolecular structure:
- Hydrogen bonding is a stabilizing or destabilizing interaction in macromolecules depending on the solvent environment.
- In water, intramolecular hydrogen-bonding is unfavorable. The donor-acceptor pairs are sequestered from competing interactions with water.
- In the interior of a globular protein or in the stacked bases of nucleic acids, the formation of intramolecular hydrogen-bonding is favored. (Forming the 2nd or tertiary structure.)
- Hydrogen-bonding potential will often overestimate the effect of intramolecular hydrogen bonds.

Hydrogen-bonding interactions stabilize the structures of macromolecules in aqueous solution. Example:
- NMA dimerizes in solution by forming hydrogen bonds between the amino N-H group and the carboxyl oxygen.
- The competing interactions are between NMA and the solvent, and between two NMA molecules to form a dimer. The higher concentration of water favors the fully solvated monomers.

For CCl₄: Dimer formation is favored. The loss in entropy from bringing two NMA molecules together to form hydrogen bonds is nearly identical to that in water. In water this negative \( \Delta S^o \) makes \( \Delta G^o \) positive.
- The enthalpy change is negative (-17 kJ/mol). The negative \( \Delta H^o \) makes \( \Delta G^o \) negative, indicating that a hydrogen bond is inherently stable.

In water: Dimer formation is unfavorable.
- Water competes for the hydrogen-bonding potential of donors and acceptor group of NMA.
- There is a net loss of one hydrogen bond to water.
- \( \Delta H^o \) is of the same order of magnitude for the interaction of NMA to NMA and NMA to water, the higher concentration of bulk solvent greatly favors hydrogen-bonding to water.

**Table 1.5 Energies for Dimerization of NMA**

<table>
<thead>
<tr>
<th>Solvent</th>
<th>( \Delta H^o ) (kJ/mol)</th>
<th>( \Delta S^o ) (J/molK)</th>
<th>( \Delta G^o ) (kJ/mol)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carbon tetrachloride</td>
<td>-17</td>
<td>-45</td>
<td>-3.8</td>
</tr>
<tr>
<td>Dioxane</td>
<td>-3.5</td>
<td>-16</td>
<td>1.6</td>
</tr>
<tr>
<td>Water</td>
<td>0.0</td>
<td>-41</td>
<td>12.8</td>
</tr>
</tbody>
</table>

Hydrophobic vs hydrophilic force

- The general chemical principle: Like dissolves like
  - Polar and charged compounds are soluble in polar solvents such as water.
  - Nonpolar compounds are soluble in nonpolar organic solvents, such as chloroform.
  - Hydrophobic molecules are highly soluble in organic solvents.
  - The favorable interactions between nonpolar molecules come from Van der Waal’s attraction.

Hydrophilic: “water loving”

Hydrophilic forces:
- Electrostatic
- Polar-polar
- Hydrogen bond…

Molecules contain O, S, N,…
Or certain Charged, or polar groups
The strong interaction between the charged ions and polar water. → Energy gain.

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Hydrophobic forces:
- Van der Waals
- Steric
- Configurational…

Molecules contain H, C,… non-polar groups

Hydrophobic vs hydrophilic force

Amphipathic (Amphiphilic) Molecules
Both hydrophilic and hydrophobic

Intmolecular Potential Energy

Hydrophobic molecule
Hydrophilic molecule

A hydrophobic part
A hydrophilic part
Hydrophobic vs hydrophilic force

Amphipathic (Amphiphilic) Molecules

A charged phosphoric acid head group interacts with water.

Long hydrocarbon tails extend and interact with themselves to form an oil-drop like hydrophobic environment.

The environment in cell

- Hydrophilic/hydrophobic environment
- Hydrophilicity and hydrophobicity
- Amphiphilic molecules

The environment in cell: 

Bio-membrane

Amphiphilic (Amphiphilic) Molecules

Protein: polypeptide chain
Some amino acid groups (-R) in a protein are hydrophobic (no charge and non-polar) some are hydrophilic (polar/charged).

Assembly/aggregation

Protein: partially hydrophobic and partially hydrophilic.

The environment in cell:

Amphipathic () Molecules

What about nucleic acids?

- Answer: Both, amphipathic
- Nucleic acids: hydrophobic bases and negative charged phosphates.
The environment in cell:
- The structure of macromolecules is strongly influenced by their surrounding environment.
- The mass of a cell: 70% Water- biological systems- Primarily as aqueous solutions.

Attention:
- $\text{H}_2\text{O}$ can be part of a solvent to dissolve $\text{NaCl} \rightarrow \text{Na}^+ + \text{Cl}^-$
- $\text{H}_2\text{O}$ can be part of a macromolecule (mediating the interaction between protein and DNA)

The environment in cell
- Aqueous environment: dominant solvent system
- A dominant role in defining the structures and functions of many bio-macromolecules

The environment in cell
- The energies associated with long-range interaction (charge-charge, charge-dipole and dipole-dipole) are dependent on the intervening medium.
  
  $\rho \sim 1/(\varepsilon \varepsilon_0)$

- Dielectric constant $\varepsilon$: An environmental factor in stabilizing the conformation of a macromolecule

The environment in cell
- Cell membranes: a very important non-aqueous environment where many bioprocesses occur.

Membrane Proteins:
- Hydrophobic bilayer

The environment in cell
- Significant Differences:
  - That part of a molecule residing within the hydrocarbon tail of the membrane bilayer must be hydrophobic.
  - The structure of an integral membrane protein can be thought of as being inverted in relation to the structure of a water-soluble protein.
  - Hydrophobic groups exposed to the non-polar solvents, while hydrophilic atoms form the internalized core.

Key Message
- van der Waals Interaction is responsible for hydrophobic interaction.
- Hydrogen bond plays a very important role in determining the intra molecules interactions and structures.
- Hydrophobic environment will be in favor of the formation of intra molecular hydrogen bond while hydrophilic environment will deteriorate the formation of H bond.
- Amphiphilic molecules tend to assemble at the surface