Physical Interactions that Determine the Properties of Proteins
Intra- and Intermolecular Forces

- Intramolecular forces
  - Covalent bonds
  - Ionic bonds
  - Disulfide bonds
- Intermolecular (nonbonding) Forces
  - Charge-charge interaction
  - Charge-dipole interaction
  - Dipole-dipole interaction
  - H-binding
  - Van der Waals interaction
  - Salt bridge
  - Hydrophobic interaction
Orbitals

- Electrons has some of the properties of a particle, and some of the properties of a wave motion.

- As a result, the position of an electron at a given time cannot be precisely located, but only the region of space where it is most likely to be.

- These regions are referred to as orbitals or electron shells with a particular energy level.
Structure of Atoms

Atomic weight of 1 = $1 \times 10^{-23}$ g

Atomic wt $\sim 0$

Figure 2–1. Molecular Biology of the Cell, 4th Edition.
Sketches of the electron density for the first three shells

1s: 2 electrons
2s: 2 electrons
2p: 6 electrons, $m_l = \pm 1$
3s: 2 electrons
3p: 6 electrons, $m_l = \pm 1$
Quantum Numbers

• 4 quantum numbers

• Principal quantum number: n
  – Describes the energy level within the atom.
  – The principal quantum number (n) cannot be zero.
  – n must be 1, 2, 3, etc.

• The second *(azimuthal) quantum number: l (l = n-1).
  – s, p, d, f
  – Govern the shape of the orbital

• The third quantum number: m (magnetic quantum number).
  – Describes the orbital within a sublevel. s has 1 orbital p has 3 orbitals d has 5 orbitals f has 7 orbitals
  – Orbitals contain 1 or 2 electrons, never more

• The 4th quantum number: spin quantum number: ½, -1/2
Graphical Representation of Allowable Combinations of Quantum Numbers

<table>
<thead>
<tr>
<th>Shell of n</th>
<th>Subshell l</th>
<th>Subshell notation</th>
<th>Orientation m</th>
<th>Number Orbitals</th>
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<td>0</td>
<td>1s</td>
<td>0</td>
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</tr>
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<td>2</td>
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<td>2p</td>
<td>-1 0 +1</td>
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<td>-1 0 +1</td>
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<td>2</td>
<td>4d</td>
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<td>3</td>
<td>4f</td>
<td>-3 -2 -1 0 +1 +2 +3</td>
<td>7</td>
</tr>
</tbody>
</table>
Two Types of Atomic Interaction

Covalent Bonds
(make molecules)

Non-covalent Bonds
(make molecules come alive)
Covalent Bonds

The most stable bond type: involves electron sharing

Each type of atom forms a characteristic number of covalent bonds with other atoms; shortest bond lengths

Covalent bonds are strong and require a lot of energy to break

Thermal energy at 25°C (i.e. in cell) is 1 kcal/mol

C-C bond requires 83 kcal/mol to break
Bond Preferences

Hydrogen: 1 covalent bond
Oxygen: 2 covalent bonds
Nitrogen: 3 covalent bonds
Carbon: 4 covalent bonds

(a)

(b)

Hydrogen chloride (HCl)
Water (H₂O)
Ammonia (NH₃)
Methane (CH₄)
Octet Rule

- Atoms tend to combine to have eight electrons in their valence shells, giving them the same electronic configuration as a noble gas.
- The rule is applicable to the main-group elements, especially carbon, nitrogen, oxygen, and the halogens, but also to metals such as sodium or magnesium.
- Molecules or ions tend to be most stable when the outermost electron shells of their constituent atoms contain eight electrons.

The bonding in carbon dioxide (CO₂): all atoms are surrounded by 8 electrons, fulfilling the octet rule.
## Atoms and Bonds: Electronic Shell

### Figure 2–4. Molecular Biology of the Cell, 4th Edition.

<table>
<thead>
<tr>
<th>element</th>
<th>I</th>
<th>II</th>
<th>III</th>
<th>IV</th>
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<td>Helium</td>
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<tr>
<td>Carbon</td>
<td>●●●</td>
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<tr>
<td>Nitrogen</td>
<td>●●●●</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Oxygen</td>
<td>●●●●●</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neon</td>
<td>●●●●</td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Sodium</td>
<td>●●●●●</td>
<td></td>
<td>●</td>
<td></td>
</tr>
<tr>
<td>Magnesium</td>
<td>●●●●●</td>
<td></td>
<td>●●</td>
<td></td>
</tr>
<tr>
<td>Phosphorus</td>
<td>●●●●●●</td>
<td></td>
<td>●●●</td>
<td></td>
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<tr>
<td>Sulfur</td>
<td>●●●●●●●</td>
<td></td>
<td>●●●●</td>
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</tr>
<tr>
<td>Chlorine</td>
<td>●●●●●</td>
<td></td>
<td>●●●●</td>
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<tr>
<td>Argon</td>
<td>●●●●●</td>
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<td>Potassium</td>
<td>●●●●●●●</td>
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<td></td>
<td>●</td>
</tr>
<tr>
<td>Calcium</td>
<td>●●●●●</td>
<td></td>
<td></td>
<td>●</td>
</tr>
</tbody>
</table>

- **atomic number**
- **element**
- **electron shell**
- **valency**
- **stable**
Exceptions to the Octet Rule

- **Paramagnetic** – containing 1 or more unpaired e⁻
  - Cannot have a total spin equal to zero
  - Examples are organic free radicals and gaseous nitric oxide

- **Diamagnetic** – contain only paired e⁻
  - $O_2$
    - Recently discovered it’s paramagnetic
    - Suggesting unpaired e-. Resonance is suggested
Double & Triple Covalent Bonds

- Double covalent bonds share two pairs of electrons.
  - $\text{CO}_2 \quad \text{O}=\text{C}=\text{O}$

- Triple covalent bonds share three pairs of electrons.
  - $\text{N}_2 \quad :\text{N}=\text{N}:$
Coordinate Covalent Bonds

- Two nuclei are attracted to a lone pair of electrons (e⁻)
- A bond in which one atom shares an entire pair of electrons (lone pair) with another atom.
- Typically forms polyatomic ions
- In structural formula, coordinate covalent bonds are shown as arrows that point from the atom donating the pair of electrons to the atom receiving them.
\[
\text{H}:\text{N} \text{H} + \text{H}^+ \rightarrow \left[ \text{H}:\text{N} \text{H} \right]^+
\]

\[
\text{H} \quad \text{N} \quad \text{H} \quad \text{H} \quad \text{H} \quad \text{O} \rightarrow \text{H} \quad \text{H}
\]

\[
\left[ \text{NH}_4^+ \right] \quad \text{H}_3\text{O}^+
\]
Resonance

- Bond lengths are an average of possible bond lengths.

- Bonds become a hybrid of all the possible bonds.

- Increases stability within the atom

Examples of resonance - ozone, benzene and the allyl cation
Polar and Nonpolar Covalent Bonds

\[ \delta^+\text{H} - \delta^-\text{Cl} \]

A polar covalent bond.
The bonding electrons are attracted more strongly by Cl than by H.

\[ \text{Cl} : \text{Cl} \]

A nonpolar covalent bond
Polar Bonds

• When e- pairs are not shared equally between atoms
• Due to differences in electronegativity
• Polar covalent bond – an uneven sharing of e- between 2 nonmetals
• Non-polar covalent bond – an even sharing of e- between 2 nonmetals
Polar Bonds (cont)

- The lower case Greek letter delta shows that atoms involved in the covalent bond acquire only partial charges, much less than 1+ or 1-

- The polarity of a bond may also be represented with an arrow pointing to the more electronegative atom
Polar Molecules

- In a polar molecule, one end of the molecule is slightly negative and the other end is slightly positive.
- The electrically charged regions are called poles.
- A molecule that has two poles is called a dipolar molecule or dipole.
- The effect of polar bonds on the polarity of a molecule depends on its shape.
  - \( \text{CO}_2 \)
  - \( \text{H}_2\text{O} \)
• Water has two polar covalent bonds, but the polar covalent bonds pull electrons to the oxygen's region of the molecule, to make the molecule polar.
• The reason for this is the molecule's bent geometry: The electrons are not pulled in equal and opposite directions, despite the bonds being identical.
• Despite having two polar covalent bonds, carbon dioxide is non-polar.
• The reason for this is the molecule's linear geometry: The electrons are pulled in equal but opposite directions, causing them to cancel one another.
Nonpolar

Two identical polar bonds pointing in opposite directions will cancel. The molecule is non-polar.

Nonpolar

Three identical polar bonds at 120° from each other will cancel. The molecule is non-polar.

Polar

Three polar bonds in a trigonal pyramidal arrangement (109.5°) will not cancel. The molecule is polar.

Polar

Two polar bonds with an angle of less than 180° between them will not cancel. The molecule is polar.

Nonpolar

Four identical polar bonds in a tetrahedral arrangement (109.5° from each other) will cancel. The molecule is non-polar.

Note: In all cases where the polar bonds cancel, the bonds are assumed to be identical. If one or more of the bonds are different than the other(s), the bonds will not cancel and the molecule is polar.
VSEPR Theory

• Valence Shell Electron Pair Repulsion Theory

• Because electrons repel, molecules adjust shape so the electron pairs are as far apart as possible.

• Unshared pairs of e\(^{-}\) are also important when trying to predict shape.

• Methane forms a tetrahedron with angles of 109.5° (tetrahedral angle): nonpolar
VSEPR Theory

• A method that chemists use to predict the shapes of molecules.
• This theory predicts that electron pairs, whether involved in bonds or as non-bonding pairs, will adopt a geometry in which they maximize the distance from one another in order to minimize repulsions.
• This will result in a geometry with the lowest possible energy.
VSEPR Theory (cont)

Some common shapes:
- linear triatomic,
- trigonal planar,
- bent triatomic,
- pyramidal,
- tetrahedral,
- trigonal
- bipyramidal
Trigonal planar
Formaldehyde
Bent structure

Water $105^\circ$
Ammonia

107°

Pyramidal structure
Tetrahedral Methane
Trigonal bipyramidal
Sulfur Hexafluoride

Octahedral

Electron Pair Geometry

Bond Angles

Octahedral

Molecular Geometry
Disulfide Bonds

- Side chain of cysteine contains highly reactive thiol group
- Two thiol groups form a disulfide bond
- Contribute to the stability of the folded state by linking distant parts of the polypeptide chain
Cross links (disulfide bridges)

Prevalent mainly in extracellular proteins

\[
\text{Oxidation} \quad \text{Reduction}
\]

\[
\text{Cysteine} \quad \text{Cysteine}
\]

\[
\text{Cystine}
\]

\[
+ 2 \text{H}^+ + 2 \text{e}^-
\]
Disulfide Bridge –
Linking Distant Amino Acids
Ionic Bonds

- A type of chemical bond that involves a metal and a nonmetal ion.
- Formed by the attraction between two oppositely charged ions.
- *Pure* ionic bonding is not known to exist.
- All ionic compounds have a degree of covalent bonding.
- Ionic compounds conduct electricity when molten or in solution.
- Generally have a high melting point and tend to be soluble in water.
- In covalent bonding, the molecular geometry around each atom is determined by VESPER rules, whereas, in ionic materials, the geometry follows maximum packing rules.
Ionic Bonds

‘strong’ covalent bond

ionic bond Weaker than covalent bond

Figure 2–5. Molecular Biology of the Cell, 4th Edition.
Atoms and Bonds of Sodium Chloride

sodium atom (Na)  chlorine atom (Cl)
(A)

sodium ion (Na⁺)  chloride ion (Cl⁻)

sodium chloride (NaCl)

(B)

(C)

Figure 2–6. Molecular Biology of the Cell, 4th Edition.
Non-covalent Bonds

Much weaker than covalent bonds

- these bonds break and reform at Room Temperature (RT)
  ‘Transient Bonds’

- however, **cumulatively** they are very effective e.g. α helix for proteins and double helix for DNA
Weak Chemical Interactions

- Weak chemical interactions or non-covalent bonds are key to life
- They can form and break with minimal energy costs
- They allow for very dynamic systems as observed in living organisms

- nearly all of the interactions between macromolecules in the cell are highly dynamic
Nature of Intermolecular Forces

• The force between molecules is a physical or intermolecular force
• Weaker than Intramolecular Forces
• The properties of matter result from the properties of the individual molecule (resulting from chemical bonding) and how the molecules act collectively (resulting from intermolecular forces).
Structure-Stabilizing Interactions

• Non-covalent Interactions
  – Van der Waals forces: ubiquitous attractions between atoms and molecules
    • Between two permanent dipoles
    • Between a permanent and an induced dipole
    • Between two induced dipoles
  – Electrostatic forces
    • Point charges: between charged ions
    • Dipoles: dipole moment
  – Hydrogen bonds
<table>
<thead>
<tr>
<th>Type of Interaction</th>
<th>Model</th>
<th>Example</th>
<th>Dependence of Energy on Distance</th>
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</thead>
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<tr>
<td>(a) Charge–charge</td>
<td><img src="#" alt="Diagram" /></td>
<td><img src="#" alt="Example" /></td>
<td>(1/r)</td>
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<td>Longest-range force, nondirectional</td>
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<tr>
<td>(b) Charge–dipole</td>
<td><img src="#" alt="Diagram" /></td>
<td><img src="#" alt="Example" /></td>
<td>(1/r^2)</td>
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<td>Depends on orientation of dipole</td>
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<td>(c) Dipole–dipole</td>
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<td>(1/r^3)</td>
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<td>Depends on mutual orientation of dipoles</td>
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<td>(d) Charge–induced dipole</td>
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<td>(1/r^4)</td>
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<td>Depends on polarizability of molecule in which dipole is induced</td>
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<td>(e) Dipole–induced dipole</td>
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<td>(1/r^5)</td>
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<td>Depends on polarizability of molecule in which dipole is induced</td>
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<td>(f) Dispersion</td>
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<td>Involves mutual synchronization of fluctuating charges</td>
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<td>(g) van der Waals repulsion</td>
<td><img src="#" alt="Diagram" /></td>
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<td>(1/r^{12})</td>
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<td>Occurs when outer electron orbitals overlap</td>
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<td>(h) Hydrogen bond</td>
<td><img src="#" alt="Diagram" /></td>
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<td>Length of bond fixed</td>
</tr>
<tr>
<td>Charge attraction + partial covalent bond</td>
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</table>
Charge – Charge Interactions

- electrostatic interactions between a pair of charges
- in a vacuum (or in a crystal) very strong interactions
- as strong as some covalent bonds.

**Force** between a pair of charges ($q_1$ and $q_2$, separated by distance $r$):

$$F = k \frac{q_1 \times q_2}{\varepsilon \times r^2}$$  \hspace{1cm} \text{Coulomb’s law}

If $F$ is $+$, corresponds to repulsion ($q_s$ have same charge)
If $F$ is $-$, corresponds to attraction ($q_s$ have different charge)
higher $\varepsilon$ (Dielectric Constant) = weaker force between particles

<table>
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<th>Dielectric constants</th>
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<td>H$_2$O</td>
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<tr>
<td>organic solvents</td>
<td>1-10</td>
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</table>
Dipole interactions

- Charge-dipole
- Dipole-dipole
- Charge-induced dipole
- Dipole-induced dipole

Interactions involving permanent dipoles depend on the orientation of the dipole and they are shorter range than charge-charge interactions. Some dipoles are induced in polarizable molecules.
**Dipole interactions-permanent and induced**

- Molecules with **no net charge** but with asymmetric distribution of charge (e.g., CO)
  - Polar (permanent dipole)
- Dipole moment \( m \)
  - expresses a molecule’s polarity
  - A vector always directed towards the positive charge \( q^+ \)
  - Molecules with large dipole moments are highly polar
Dipole Moments

\[ \mu = qx \]

\( \mu \), dipole moment

\( q \), charge (or fractional charges)

\( x \), distance between charges

Dipole moment

\[ \begin{array}{c}
O \equiv C \\
q^- \quad q^+
\end{array} \]

\[ \begin{array}{c}
O \equiv C \equiv O \\
q^- \quad q^+ \quad q^-
\end{array} \]

\[ \begin{array}{c}
O \\
q^-
\end{array} \]

\[ \begin{array}{c}
H \downarrow \ H \\
q^+ \quad q^+
\end{array} \]

Glycine

\[ \begin{array}{c}
H_3N-\text{CH}_2-\text{COO}^- \\
^+
\end{array} \]

Because the distance between charges is so great

0.12

0

16.7

Equal in magnitude but opposite direction, cancel each other out
Charge-dipole forces

- When salt is dissolved in water, the ions of the salt dissociate from each other and associate with the dipole of the water molecules.
- The force is decomposed into two equal but opposite charges and adding up the resulting charge-charge forces.
- Charge-Dipole Forces depend on relative molecular orientation.
- This means that the forces can be *attractive or repulsive* depending on whether like or unlike charges are closer together.
- Many charge-dipole interactions overcome the ion pair interactions within the crystal - Allows solvation of ions.
Note the orientation of the water molecules.
Dipole-Dipole forces

• Exist between neutral polar molecules
• This force produced by decomposing each of the dipole into two equal but opposite charges and adding up the resulting charge-charge forces
• Allows solvation of polar molecules (e.g. sugar)
Induced Dipoles

• Electric fields can induce a dipole in a molecule which does not have a dipole
• A molecule in which a dipole can be induced is said to be polarizable
• Interactions of polarizable molecules are called induced dipole interactions.
Charge-induced dipole force

- When a charged molecule (ion) induces a dipole moment in a nearby neutral molecule, the two molecules stick together, even though the neutral molecule was initially round and uncharged.
The movement of the electrons, even in the He atom, cause an instantaneous dipole to be formed.

The time-averaged dipole moment of the atom is still zero.

This dipole fleeting can *induce* a dipole in a neighboring atom, causing a force.
Van der Waals Force (Interaction)

• The attractive or repulsive force between molecules (or between parts of the same molecule) other than those due to covalent bonds or to the electrostatic interaction of ions with one another or with neutral molecules

• Attractive – induced dipole interaction: short range \((R^{-6})\)

• Repulsive – electron-electron: very short range \((R^{-12})\)
van der Waals Interaction

- A short-range repulsions: Pauli’s exclusion principle
  - No two identical fermions (particles with half-integer spin) may occupy the same quantum state simultaneously.

- 3 attractive components: A group of intermolecular attractive forces including
  - dipole-dipole forces
  - dipole-induced dipole forces
  - dispersion forces: mutual synchronization of fluctuating charges
van der Waals repulsion

- When molecules or atoms come so close together their outer electron orbitals begin to overlap, there is a *mutual repulsion*.

- This repulsion increases very rapidly as the distance between centers (r) decreases.

- This repulsive force increases so drastically at small distances it acts as a ‘wall’, effectively barring approach closer than distance $r_v$ - defines the so-called *van der Waals radius*.

- The energy minimum is where the attractive forces are the strongest: *van der Waals radius*.

- The balance between these forces is important in biologymediate binding of enzymes with substrates and antibodyantigen interactions and base stacking in DNA.
van der Waals forces

Note: Covalently – and H-bonded atoms are closer than the van der Waals distance
Van der Waals volume

- The van der Waals volume ($V_w$, the atomic volume or molecular volume) is the atomic property most directly related to the van der Waals radius.
- It is the volume "occupied" by an individual atom (or molecule).
- The van der Waals volume may be calculated if the van der Waals radii (and, for molecules, the inter-atomic distances and angles) are known.
- For a spherical single atom, it is the volume of a sphere whose radius is the van der Waals radius of the atom.
Hydrogen bonds

• Special case of dipolar interactions involving molecules having H bound to small electronegative atoms. *In biomolecules, that means N or O.*

• The highly polar bond N-H or O-H bond results in a partially unshielded H.

• Interaction between such a H atom and the lone pair of an O or N atom.

• This attraction is directed along the donor-H axis and the lone pair of the acceptor.

• This results in a shortening of the distance between the H and the H-bond acceptor.
Rules for H-bonds

1. Donor atom must be N or O and have a H attached to it
2. Acceptor atom must be N or O and have a lone pair of electrons
3. The lone pair should be pointing at the H
4. Ideal geometry would be a straight line between donor-H-acceptor
Hydrogen Bonds

- **VERY** important in biochemistry.
- An interaction between a covalently bonded hydrogen atom on a *donor group* and a pair of non-bonded electrons on an *acceptor group*.

![Diagram of Hydrogen Bond](image)

- **sufficiently electronegative**
  - *donor groups*: O-H, N-H
  - *acceptor groups*: N, O, (S) (nonbonded electron pair)

Shares features with covalent and non-covalent interactions

N-H \cdots O=C, predict H-O distance of **0.26 nm**; actually **0.19 nm**
Hydrogen bonds

hydrogen atom partly shared

Hydrogen-bond donor  Hydrogen-bond acceptor

\[
\begin{align*}
\text{N} & \equiv \text{H} & \equiv \text{N} \\
\delta^- & \delta^+ & \delta^-
\end{align*}
\]

Electrostatic interactions,

\[
\begin{align*}
\text{N} & \equiv \text{H} & \equiv \text{O} \\
\delta^- & \delta^+ & \delta^-
\end{align*}
\]

Energies of 1-3 kcal mol\(^{-1}\)

\[
\begin{align*}
\text{O} & \equiv \text{H} & \equiv \text{N} \\
\delta^- & \delta^+ & \delta^-
\end{align*}
\]

\[
\begin{align*}
\text{O} & \equiv \text{H} & \equiv \text{O} \\
\delta^- & \delta^+ & \delta^-
\end{align*}
\]
Strength of Hydrogen Bonds

- F—H···F (155 kJ/mol or 40 kcal/mol)
- O—H···N (29 kJ/mol or 6.9 kcal/mol)
- O—H···O (21 kJ/mol or 5.0 kcal/mol)
- N—H···N (13 kJ/mol or 3.1 kcal/mol)
- N—H···O (8 kJ/mol or 1.9 kcal/mol)
- HO—H···OH+3 (18 kJ/mol or 4.3 kcal/mol)
<table>
<thead>
<tr>
<th>Type of hydrogen bond</th>
<th>Typical distance between donor and acceptor atom (nm)</th>
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<tbody>
<tr>
<td>Hydroxyl-hydroxyl</td>
<td>0.28</td>
</tr>
<tr>
<td>Hydroxyl-carbonyl</td>
<td>0.28</td>
</tr>
<tr>
<td>Amide-carbonyl</td>
<td>0.29</td>
</tr>
<tr>
<td>Amide-hydroxyl</td>
<td>0.30</td>
</tr>
<tr>
<td>Amide-imidazole nitrogen</td>
<td>0.31</td>
</tr>
</tbody>
</table>
Examples of hydrogen bond donating (donors) and hydrogen bond accepting groups (acceptors)

\[
\text{H}_2\text{O} - \text{H} \cdot \text{H} - \text{NH}
\]

hydrogen bond donor  hydrogen bond acceptor

\[
\text{H}_2\text{O} - \text{H} \cdot \text{H} - \text{NH}
\]

hydrogen bond acceptor  hydrogen bond donor

\[
\text{H} \cdot \text{H} - \text{N} - \text{H} - \text{O} - \text{N}
\]

hydrogen bond acceptor  hydrogen bond acceptor and/or donor

\[
\text{H} \cdot \text{H} - \text{N} - \text{H} - \text{O} - \text{N}
\]

hydrogen bond acceptor  hydrogen bond donor

prozac

\[
\text{H} \cdot \text{H} - \text{N} - \text{H} - \text{O} - \text{N}
\]

hydrogen bond acceptor
Hydrogen Bonds in DNA
An example of a protein α-helix (a common structural element in proteins) 
Structure is maintained by 

\[
\begin{align*}
\text{N} & \quad \text{H} \cdots \text{O} \equiv \text{C} \\
\end{align*}
\]

Hydrogen bonds along the backbone.
H₂O

- The biological solvent
- [H₂O] = 55.5 M

- Can dissolve many compounds
  - Acids: can release H⁺
  - Bases: can accept H⁺
    - pH = - log [H⁺]
    - Pure H₂O pH = 7
    - [H⁺] = [OH⁻] = 10⁻⁷ M

- Why are reactions so pH sensitive?
  - Amino acid functional groups can change state based on pH
Atoms and Bonds: 3 representations

(A) H – O – H

(B) 104.5°

(C) van der Waals radius of O = 1.4 Å

van der Waals radius of H = 1.2 Å

O–H covalent bond distance = 0.96 Å

Figure 2–12. Molecular Biology of the Cell, 4th Edition.
Dominating characteristic:

- H-bond donor/acceptor
- Can form 4 hydrogen bonds
  - High energy barrier to liquid --> gas phase transition
- $sp^3$-hybridized $\rightarrow$ tetrahedral arrangement of orbitals
- Dipole due to more electronegative O
- Both in solid and liquid forms, exists as extensive H-bonded network
- High density, high boiling point, high heat capacity, high dielectric constant, etc.
Hydrogen bonds

104.5°

Hydrogen bond 0.177 nm

Covalent bond 0.0965 nm
Structure of Water

(a)

(b) ice

(c) water
Water

Water is actually a rather remarkable chemical!

Comparing water with chemicals of similar Molecular Weight, reveals several obvious differences.

Why is water unique?

- Strong Hydrogen Bonding
Hydrogen Bond Exchange

Probably helps to dissolve macromolecules
Sphere of hydration surrounding proteins is important; high concentrations of certain salts (e.g., ammonium sulfate) make the proteins become less soluble and precipitate.

Polar (dipolar) nature of water makes it ideal for solubilizing salts and other macromolecules (breaks ionic bonds):

\[
\begin{align*}
q^- & \quad \text{Cl}^- \\
O & \quad H \\
q^+ & \quad q^+ 
\end{align*}
\]
Salt Bridges

• A combination of two noncovalent interactions: hydrogen bonding and electrostatic interactions.

• Contribute stability to the entropically unfavorable folded conformation of proteins.

• Most often arises from the anionic carboxylate (RCOO\(^{-}\)) of aspartic acid or glutamic acid and the cationic ammonium (RNH\(_3\)\(^{+}\)) from lysine or the guanidinium (RNHC(NH\(_2\))\(_2\)\(^{+}\)) of arginine
Salt Bridge between glutamic acid and lysine demonstrating electrostatic interaction and hydrogen bonding.
Salt Bridges

- Ionizable side chains such as histidine, tyrosine, and serine can also participate.
- The distance between the residues participating in the salt bridge is important (less than 4 Å).
- The pH at which a protein is placed is crucial to its stability.
- At pH extremes, two amino acids participating in a salt bridge could lose their ability because one will lose its charge.
Hydrophobic Interactions

• The property that non-polar molecules tend to form aggregates of like molecules in water and analogous intramolecular interactions.

• The apparent repulsion between water and hydrocarbons.

• An important driving force for biological structures and responsible for protein folding, protein-protein interactions, formation of lipid bilayer membranes, nucleic acid structures, and protein-small molecule interactions.
Hydrophobic Interactions

- Driven by the loss of hydrogen bonding and the higher entropic cost of forming a cavity around nonpolar molecules.
- These losses can be minimized by forcing nonpolar molecules together.
- The effect does not involve forces of repulsion between the components; hydration of hydrophobic substances is enthalpically favorable.
Hydrophobic "forces"

• Not really a *force* — rather, the hydrophobic effect is driven by entropic considerations of water.

• Water molecules surrounding apolar molecules (e.g. alkanes) form a tightly H-bonded network, which restricts their orientation and motion. Thus, there is a net decrease in entropy ($\Delta S < 0$).

• By clustering hydrophobic molecules together, the amount of water molecules in this network is decreased ($\Delta S$ is maximized). Basically, this is a case of minimizing surface:volume.
Clathrate Hydrate

- Crystalline water-based solids physically resembling ice, in which small nonpolar molecules (typically gases) are trapped inside "cages" of hydrogen bonded water molecules.

- Clathrate hydrates are clathrate compounds in which the host molecule is water and the guest molecule is typically a gas.

- Without the support of the trapped molecules, the lattice structure of hydrate clathrates would collapse into conventional ice crystal structure or liquid water.
Hydrophobic molecules in aqueous solution

- Molecules that cannot form hydrogen bonds have limited solubility in water ie. non-polar, non-ionic substances that cannot form H bonds (eg. hydrocarbons)

- When *hydrophobic* molecules dissolve in water, ‘ice-like’ Clathrate structures ‘cage’ the molecules; highly ordered, so not energetically favoured

- Less energy is required to encage 2+ molecules than each alone-so they tend to cluster and form aggregates
Clathrate Hydrate Structure

• Most low molecular weight gases (including \( \text{O}_2 \), \( \text{HH}_2 \), \( \text{NN}_2 \), \( \text{CO}_2 \), \( \text{CH}_4 \), \( \text{H}_2\text{S} \), \( \text{Ar} \), \( \text{Kr} \), and \( \text{Xr} \)), as well as some higher hydrocarbons and freons and will form hydrates at suitable temperatures and pressures.

• Clathrate hydrates are not chemical compounds as the sequestered molecules are never bonded to the lattice.

• Clathrates have been found to occur naturally in large quantities.

• Around 6.4 trillion (i.e. \( 6.4 \times 10^{12} \)) tonnes of methane is trapped in deposits of methane on the deep ocean floor.
Hydrophilic and Hydrophobic "forces"

- Hydrophilic – "water-loving", relatively polar molecules, miscible with water
- Hydrophobic – "water-hating", relatively nonpolar molecules, immiscible with water
- Amphiphilic – molecules having both hydrophilic and hydrophobic regions
- Most biomolecules are amphiphilic (phospholipids, polypeptides, nucleic acids)
Micelles
All hydrophobic groups are sequestered from water; ordered shell of H\textsubscript{2}O molecules is minimized, and entropy is further increased.
Enthalpy and Entropy

Enthalpy

• A thermodynamic property of a thermodynamic system.
• Used to calculate the heat transfer during a quasistatic process taking place in a closed thermodynamic system under constant pressure.
• Change in enthalpy $\Delta H$ is equal to the change in the internal energy of the system, plus the work that the system has done on its surroundings.
• $\Delta H$ is the heat absorbed by a chemical reaction.

Entropy

• “A measurement of the disorder or randomness of a system" or measuring "the spontaneous dispersal of energy — at a specific temperature."
Amphipathic molecules

- Includes phospholipids, fatty acids and detergents
- Form monolayers, micelles or bilayer vesicles
  - Basis of cellular membrane bilayers
- Polar or ionic head groups become hydrated

Hydrophilic head groups

Hydrophobic tail groups

fatty acid  detergent
"Flickering clusters" of H₂O molecules in bulk phase

Highly ordered H₂O molecules form "cages" around the hydrophobic alkyl chains
Dispersion of lipids in H₂O

Each lipid molecule forces surrounding H₂O molecules to become highly ordered.
Clusters of lipid molecules

Only lipid portions at the edge of the cluster force the ordering of water. Fewer H\textsubscript{2}O molecules are ordered, and entropy is increased.
H-bonding & hydrophobic effect

• The two major determinants of biomolecular structure
  – Membranes – Hydrophobic effect creates the lipid bilayer
  – Proteins – Hydrophobic effect drives creation of protein core, where hydrophobic sidechains are segregated. Internal H-bonds determine structure.
  – DNA – Hydrophobic effect drives formation of double helix, with aromatic bases in interior and polar/charged sugar-phosphate backbone exposed to water. Internal H-bonds between bases determine which strands can pair with each other.
## Range of Intermolecular Interactions

<table>
<thead>
<tr>
<th>Biomolecule</th>
<th>H-bonds</th>
<th>Hydrophobic effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>carbohydrate</td>
<td>major</td>
<td>minor</td>
</tr>
<tr>
<td>lipid</td>
<td>minor</td>
<td>major</td>
</tr>
<tr>
<td>protein</td>
<td>major</td>
<td>major</td>
</tr>
<tr>
<td>nucleic acid</td>
<td>major</td>
<td>major</td>
</tr>
</tbody>
</table>

(Just a generalization -- do not take too seriously.)
# Interamolecular Forces

<table>
<thead>
<tr>
<th>Force</th>
<th>Model</th>
<th>Basis of Attraction</th>
<th>Energy (kJ/mol)</th>
<th>Example</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Bonding</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ionic</td>
<td><img src="image" alt="Ionic Model" /></td>
<td>Cation–anion</td>
<td>400–4000</td>
<td>NaCl</td>
</tr>
<tr>
<td>Covalent</td>
<td><img src="image" alt="Covalent Model" /></td>
<td>Nuclei–shared e\textsuperscript{-} pair</td>
<td>150–1100</td>
<td>H–H</td>
</tr>
<tr>
<td>Metallic</td>
<td><img src="image" alt="Metallic Model" /></td>
<td>Cations–delocalized electrons</td>
<td>75–1000</td>
<td>Fe</td>
</tr>
</tbody>
</table>
Intermolecular Forces

**Nonbonding (Intermolecular)**

- **Ion-dipole**
  - Ion charge–dipole charge
  - Range: 40–600
  - Example: Na⁺⋯⋯O⁻

- **H bond**
  - Polar bond to H–dipole charge
  - (high EN of N, O, F)
  - Range: 10–40
  - Example: ⋮O–H⋯⋯O–H

- **Dipole–dipole**
  - Dipole charges
  - Range: 5–25
  - Example: I–Cl⋯⋯I–Cl

- **Ion–induced dipole**
  - Ion charge–polarizable e⁻ cloud
  - Range: 3–15
  - Example: Fe²⁺⋯⋯O₂

- **Dipole–induced dipole**
  - Dipole charge–polarizable e⁻ cloud
  - Range: 2–10
  - Example: H–Cl⋯⋯Cl–Cl

- **Dispersion (London)**
  - Polarizable e⁻ clouds
  - Range: 0.05–40
  - Example: F–F⋯⋯F–F
Summary of Types of Intermolecular Forces

- Are polar molecules involved?
  - NO
  - Are hydrogens atoms bonded to N, O, or F atoms?
    - NO
    - London forces only (induced dipoles)
      - Examples: Ar(l), I_2(s)
    - YES
      - Dipole-dipole forces
        - Examples: H_2S, CH_3Cl
    - YES
      - Hydrogen bonding
        - Examples: liquid and solid H_2O, NH_3, HF
  - YES
    - Are ions involved?
      - NO
      - Are polar molecules and ions both present?
        - NO
        - ion-dipole forces
          - Example: KBr in H_2O
        - YES
          - Ionic bonding (Section 8.2)
            - Examples: NaCl, NH_4NO_3
Bond Dissociation Energies

• Bond dissociation energy is the total energy required to break the bond between two covalently bonded atoms.

• A typical carbon-carbon single bond has a bond dissociation energy of 347 kJ. The ability of carbon to form strong bonds helps to explain its stability.

• They are unreactive partly because the dissociation energy of these bonds is high
Most biologically relevant covalent bonds are strong (stable) but not so strong as to be impossible to break. These bonds are continuously broken and reformed.

All biologically relevant noncovalent bonds include hydrogen bonds, charge-charge interactions, and other noncovalent interactions.