Lecture 2- Nucleic Acid Structure

Forces stabilizing DNA

Van der Waals Interactions
- Electrostatic interaction between two mutually induced dipoles

Lennard-Jones Potential
\[ \Delta E = -\frac{B}{r^6} + \frac{A}{r^{12}} \]

B is a function of polarizability

Benzene crystal VdW Energy
-9.9 kcal/mol

Van der Waals radius

\[ \text{VdW distance} = \sum \text{VdW radii} \]

<table>
<thead>
<tr>
<th>Atom</th>
<th>VdW radii (Å)</th>
</tr>
</thead>
<tbody>
<tr>
<td>RO-H</td>
<td>1.5</td>
</tr>
<tr>
<td>R₁R₂O</td>
<td>1.5</td>
</tr>
<tr>
<td>R₁R₂O⁻</td>
<td>1.55</td>
</tr>
<tr>
<td>R₁⁻⁰⁺NH₃⁺</td>
<td>1.65</td>
</tr>
<tr>
<td>CH (tet)</td>
<td>1.85</td>
</tr>
<tr>
<td>CH (tri)</td>
<td>1.7</td>
</tr>
<tr>
<td>R₁⁻S⁻R₂</td>
<td>1.8</td>
</tr>
</tbody>
</table>

Forces stabilizing DNA

Hydrophobic Effect
- Describes tendency of hydrophobic molecules to transfer from aqueous phase to organic phase

1. Iceberg-like structure of water around organic solute: All four hydrogen bonds formed/ high order-entropic rerdty
   (In liquid water: roughly 1/2 hydrogen bonds formed)

2. Poor polarizability of oxygen
   Decreased VdW interaction between water and organic solute
   Also drives hydrophobic effect

- Measurement of hydrophobicity is partitioning of molecule between n-octanol and H₂O

\[ \Delta G = \text{RT} \log \frac{P}{P_0} \]

- Energetic contribution due to substituent
- R groups have a constant additive effect on hydrophobicity of parent compound in absence of strong resonance/inductive effects

<table>
<thead>
<tr>
<th>Group</th>
<th>( \Delta G ) (kcal/mol)</th>
</tr>
</thead>
<tbody>
<tr>
<td>-CH₄</td>
<td>0.68</td>
</tr>
<tr>
<td>-Et</td>
<td>1.36</td>
</tr>
<tr>
<td>-propyl</td>
<td>2.05</td>
</tr>
<tr>
<td>-isopropyl</td>
<td>1.77</td>
</tr>
<tr>
<td>-benzyl</td>
<td>3.6</td>
</tr>
<tr>
<td>-OH</td>
<td>-1.58</td>
</tr>
<tr>
<td>-NHO</td>
<td>-1.65</td>
</tr>
</tbody>
</table>

1 Å² of hydrophobic surface ca. 24 cal/mol stabilization when removed from H₂O

- Hydrophobic Effect can be relatively non-specific when molecules bind to protein or DNA
Lecture 2 - Nucleic Acid Structure

Forces stabilizing DNA

Electrostatic Interaction

- Proportional to 1/r; Long distance interaction compared to VdW

\[ E = \frac{e_1 e_2}{D r} \]

- Point charge induces dipoles in solvent which together with counterions induce field to neutralize charge

\[ D \text{ water} \approx 80 \rightarrow -1.3 \text{ kcal/mol (very small)} \]

\[ D \text{ pentane} \approx 2 \rightarrow -50 \text{ kcal/mol} \]

- So electrostatic interactions are far more important in organic solvent than water.

\[ \text{HN} \text{ NH} \]

\[ pK_{a1} \approx 8.8 \]

\[ pK_{a2} \approx 3 \]

\[ \Delta pK_{a} \approx 6 \Rightarrow \Delta G = -RT \log K \]

\[ \Delta G \approx 8.4 \text{ kcal/mol} \]

\[ \Delta G = -RT \log K = -1.4 \log K \text{ kcal/mol (room temp)} \]

\[ = -1.4 \text{ kcal/mol for Product/Substrate} = 10 \]

Environmental Effect on pK$_a$s

<table>
<thead>
<tr>
<th>% Dioxane in H$_2$O</th>
<th>pK$_a$ Values</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>4.76</td>
</tr>
<tr>
<td>20</td>
<td>5.29</td>
</tr>
<tr>
<td>45</td>
<td>6.31</td>
</tr>
<tr>
<td>70</td>
<td>8.34</td>
</tr>
</tbody>
</table>

acetic acid (CH$_3$CO$_2$H) 4.76 5.29 6.31 8.34

glycine (NH$_3^+$) 9.8 9.3 8.5 7.42

- Leveling Effect

Metal ion coordination stabilizes DNA

- Hard: Mg$^{2+}$, Co$^{2+}$, Ni$^{2+}$, Mn$^{2+}$, Zn$^{2+}$
- Soft: Cd$^{2+}$, Cu$^{2+}$

- Bind $-\text{OH/-PO}_4^-$
- Bind Bases

Duplex DNA

- Always specify directionality of DNA sequence

\[ \Delta G^\dagger = -1.4 \log(K_2/K_1) \text{ at room temp} \]

\[ = -1.4 \text{ kcal/mol for a 10 fold difference in rate} \]
Lecture 2 - Nucleic Acid Structure

Duplex DNA (continue)

**G-C pair:**

- Wide major groove - binds peptides
- Narrow minor groove - binds planar molecules

**B form DNA (dominant form)**
- Right handed under physiological conditions
- 10 bp/turn
- 3.3 Å/bp
- Helix axis through center of bp
- Anti
- C'2 endo

**A form DNA**
- Right handed (more contact)
- 11 bp/turn
- 2.3 Å/bp (short/broader)
- 24 Å/turn
- Major groove (deep narrow)/minor groove (broad shallow)
- Anti
- C'3 endo

**Z form DNA**
- Left handed
- 12 bp/turn
- 3.8 Å/bp
- Anti C/Syn G
- No major groove/minor groove (deep narrow)

**A form RNA**
- C'3 endo
- RNA can adapt more distinct structures than DNA

- Single-stranded RNA: A form
- DNA-RNA duplexes: A form
- DNA duplexes: A form

**Helix formation is cooperative**

- Helix-coil transition is highly cooperative and nucleates by 3 bps

**Tm calculator**

- Tm characterizes the stability of double helix
- Melting duplex to single-stranded is accompanied by an increase in absorbance
- Tm depends on length, ionic strength and GC/AT ratio

- Tm calculator:
  + 2 °C A-T pair
  + 4 °C A-T pair

**RNA secondary structure**

- Secondary RNA structure can be predicted
- Tertiary RNA structure is hard to be predicted

- Single strand
- A-form double helix
- Single nt bulge
- Three nt bulge
- Hairpin loop
- Mismatch pair
- Symmetric internal loop
- Asymmetric internal loop
**Lecture 2- Nucleic Acid Structure**

**Higher order of DNA structure**
- Supercoiling
  - -2 supercoil (neg) ~ 2 linear base
  - Enzymes to control winding and unwinding of DNA
  - Topoisomerase (wind and unwind DNA)
  - target for cancer drug

**Packing of chromosomal DNA**
- DNA is packaged into chromatin in mammalian cells
- duplex DNA tightly binds to 5 histones
  - packing ratio is $10^4$ in human genome
  - 680 Å into ~110 Å leads to packing ratio of 7
  - Modulate duplex DNA and histone Interaction
  - acetylation of lysine (positive charge of histone proteins~ neutralized)
  - other post-translational modifications (PTMs) exist for modulating histone/DNA interaction
  - DNA is a popular target for cancer drugs as rapidly proliferating cells need to replicate DNA faster

**DNA-binding small molecules**
- Electrostatic Interaction
  - target phosphated sugar backbone
  - Electrosic Interaction
    - spermine

- Intercalation
  - targets G-C rich regions
  - $K_d 10^{-6} \text{M}^{-1}$
  - binds DNA from the narrow groove

- Cancer drug - Doxorubicin
  - binds DNA from minor groove
  - cancer drug
  - when Topo unwinds DNA, dox stabilizes single strand DNA intermediate