Lecture 23: Noncovalent Interactions

Reading: Anslyn & Dougherty, Chapter 3
Announcements

• Problem Set 6 due now. Answer Key will be posted immediately.
• Final Exam: Mon, 12/12, 7-10pm, 207 BRL
  – Comprehensive
Today: Weak, Noncovalent Interactions

• Although usually weak, multiple noncovalent interactions can add up to BIG influence on reactivity or selectivity.

• Observed in solvent effects, enzymes, small molecule catalysis, etc.
Types of Noncovalent Interactions

• Steric hindrance (repulsive) – not today
• Hydrogen bonds
• $\pi$-Interactions
  – Cation–$\pi$
  – $\pi$-$\pi$
• Hydrophobic effect

(Note: This is not an inclusive list.)
Hydrogen Bonds

- Generally between a heteroatom & heteroatom–H:
  
  $X \cdots \cdots H - Y$

- Complicated
- Short range
- Energy of interaction proportional to $-1/r^2$
## Different Strengths of H-bonds

<table>
<thead>
<tr>
<th>Strength</th>
<th>A–H····B interaction</th>
<th>Relative bond lengths</th>
<th>Bond angle</th>
<th>Bond energy (kcal/mol)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Strong</td>
<td>Mostly covalent</td>
<td>A–H ≈ H–B</td>
<td>175–180°</td>
<td>14–40</td>
</tr>
<tr>
<td>Medium</td>
<td>Mostly electrostatic</td>
<td>A–H &lt; H–B</td>
<td>130–180°</td>
<td>4–15</td>
</tr>
<tr>
<td>Weak</td>
<td>Electrostatic</td>
<td>A–H &lt;&lt; H–B</td>
<td>90–150°</td>
<td>&lt;4</td>
</tr>
</tbody>
</table>

Examples of H-bonds in Nature

in water

in DNA/RNA
(ex: thymine–adenine)
H-Bonds in Small-Molecule Catalysis


Published in: Takahiko Akiyama; Chem. Rev. 2007, 107, 5744-5758.
DOI: 10.1021/cr068374j
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H-Bonds in Small-Molecule Catalysis


Yong Huang, Aditya K. Unni, Avinash N. Thadani and Viresh H. Rawal
*Nature* **424**, 146
Solid-state structures of TADDOL 4a–c.

Avinash N. Thadani et al. PNAS 2004;101:5846-5850
A proposed working model for the TADDOL-catalyzed Diels–Alder reactions.

Avinash N. Thadani et al. PNAS 2004;101:5846-5850

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Many Other Types of H-Bonds in Small-Molecule Catalysis


• Dual H-bond donors:
  • Jacobsen Nature 2009, 461, 968
  • Jacobsen JACS 2009, 131, 15358

• H-bonding in Lewis acidic catalysts:
  • Corey JACS 2002, 124, 9992
  • Fadden-Row, Sherburn ACIE 2008, 47, 7013
Cation–π Interactions

Recall:

\[ M^+ = H^+, \text{ Lewis acid, etc.} \]
Cation–π Interactions

- Linear correlation between strength of cation–π interaction & electrostatic potential of arene.
- Predominantly electrostatic (but not exclusively, also some hydrophobic effects, etc.). EDG’s strengthen cation–π interactions.
Cation-\(\pi\) Interaction Strengths

\[
\text{K}^+ + \text{H}_2\text{O} \rightarrow \text{K}^+\cdot\text{H}_2\text{O}
\]
\[
\text{K}^+ + \text{C}_{6\text{H}}\text{H}_6 \rightarrow \text{K}^+\cdot\text{C}_{6\text{H}}\text{H}_6
\]

Gas Phase Binding Energy (kcal/mol)

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Size of cation also matters... Li\(^+\) is bound more tightly than Rb\(^+\) or NMe\(_4^+\).

Cation–π in Nature: Acetyl Choline Binding Proteins: Brain vs. Muscle

\[ \pi-\pi \text{ Interactions} \]

- Due to electrostatic & dispersion & other forces

**stacked or sandwich**

**T-shape or edge-face**

**slip-stack**
A proposed working model for the TADDOL-catalyzed Diels–Alder reactions.

Avinash N. Thadani et al. PNAS 2004;101:5846-5850

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Hydrophobic Effect

• “Observation that hydrocarbons & related ‘organic’ compounds are insoluble in water.”
• Aggregation of organics in H₂O
• *Not* electrostatic
• Not well understood in quantitative sense
• Related to surface area of organics
• Important in protein structure, binding substrates to enzymes, micelles, bilayers, and organic chemistry!
Hydrophobic Effect: Surface Area Importance

<table>
<thead>
<tr>
<th>Medium</th>
<th>Anti : Gauche</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gas phase or liquid butane</td>
<td>70 : 30</td>
</tr>
<tr>
<td>$H_2O$</td>
<td>55 : 45</td>
</tr>
</tbody>
</table>
Hydrophobic Effect: Effect on Reactivity

\[
\text{Isooctane} + \text{MeOH} \rightarrow \text{MeOH}
\]

(mixture of endo & exo isomers)

<table>
<thead>
<tr>
<th>Solvent</th>
<th>(K_{rel})</th>
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<tbody>
<tr>
<td>Isooctane</td>
<td>1</td>
</tr>
<tr>
<td>MeOH</td>
<td>12</td>
</tr>
<tr>
<td>H(_2)O</td>
<td>730</td>
</tr>
</tbody>
</table>
Origin of the Hydrophobic Effect

First consider H$_2$O...

At room temperature: liquid
- high cohesive energy/surface tension, but dynamic (more disordered, higher entropy)

At 0 °C: solid (ice)
- 4 H-bonds for each H$_2$O molecule
- enthalpically favorable (lots of good H-bonding)
- entropically costly (very ordered)
Origin of the Hydrophobic Effect

- Around “hole”, H-bonds are lost.
- To compensate, remaining H-bonds get stronger → Enthalpically neutral!
- But, results in “ice-like” structure around hole → Entropy decreases (costly).
- Because 2 “holes” have more surface area than 1 “hole”, aggregation of organics in water is less entropically costly.

organic in H$_2$O => "hole"
Thanks for a great semester!!