Physical Organic Chemistry

• The key to understanding organic reactions lies in gaining an understanding of:
  – the structure and bonding of stable organic compounds.
  – reactivity of organic compounds.
  – reactive intermediates and transition states.
  – mechanisms through which organic compounds transform into other organic compounds.
  – kinetics, thermodynamics and the relationship between the two.

Revision: Structure and Bonding

• Electropositive elements tend to lose electrons to form an octet
• Electronegative elements tend to gain electrons to form an octet

Types of bonds:
• ionic bonds
• covalent bonds
• polar covalent bonds

The type of bonding in a molecule affects:
• shape
• physical properties
• reactivity
Models for Bonding

- **Lewis structures:** valence bond theory
  - Atoms interact to form discrete chemical bonds

- **Molecular orbital theory**
  - Nuclei interact, electrons are placed in molecular orbitals
  - Discrete bonds are not formed between atoms; electrons may “roam” over multiple nuclei.

Hybridization models: sp³, sp², sp orbitals

- Valence shell electron pair repulsion (VSEPR) theory rationalises the tetrhedral shape of methane without the use of atomic or molecular orbitals

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Models for Bonding

- Connection between hybridization of an atom and the arrangement in space of bonds around that atom:
  
  **sp³ hybridization** occurs for atoms having four groups in a tetrahedral arrangement (note: a “group” may be an electron pair)

  **sp² hybridization** occurs for atoms having three groups in a trigonal (planar) arrangement

  **sp hybridization** occurs for atoms having two groups in a linear arrangement

- **Hybridization and molecular geometry are closely correlated**

- **The covalent bond has a definite direction in space (compare to ionic bonds)**

- **The directionality of covalent bonding is responsible for molecular shape**
Models for Bonding

- **Molecular orbital theory: methane**

  ![Molecular orbitals of carbon](image1)
  ![Molecular orbitals of hybridized carbon](image2)

  molecular orbitals of carbon
  molecular orbitals of hybridized carbon
  (as in methane)

Models for Bonding

- **Molecular orbital theory: ethane**

  - Three of the carbon sp\(^3\) orbitals combine with one hydrogen 1s orbital each to form C-H bonds
    *sp\(^3\)-1s \(\sigma\) bonds* (shown shaded in pink below)

  - The remaining carbon sp\(^3\) bonding orbital from each carbon is used to form the C-C- bond in ethylene
    *sp\(^3\)-sp\(^3\) \(\sigma\) bond* (shown shaded in blue below)

  ![Molecular orbitals of carbon in ethane](image3)
Models for Bonding

**Molecular orbital theory: ethylene**

- Two carbon sp\(^2\) orbitals combine with one hydrogen 1s orbital each to form C-H bonds: \(sp^2 - 1s \sigma\) bonds (shaded in pink)
- The remaining carbon sp\(^2\) bonding orbital from each carbon is used to form the C-C- bond in ethylene: \(sp^2 - sp^2\sigma\) bond (shaded in blue)
- One half-occupied, unhybridized \(2p_z\) orbital left over on each carbon combine to form two new \(p\) orbitals (one bonding and one antibonding orbital).
- Each carbon atom contributes one electron to occupy the bonding orbital to form a: \(\pi\) bond (shaded in green)

![Molecular orbitals of carbon in ethylene](image)

**Molecular orbital theory: acetylene**

- One carbon sp orbital combines with one hydrogen 1s orbital to form one C-H bond \(sp - 1s \sigma\) bond
- The remaining carbon sp bonding orbital from each carbon is used to form the C-C- bond in ethylene \(sp - sp\sigma\) bond
- In acetylene, there are two left-over, half-occupied p orbitals: \(p_y\) and \(p_z\). These can form two sets of p orbitals. Two mutually perpendicular \(\pi\) bonds are formed from these orbitals.

![Molecular orbitals of carbon in acetylene](image)
Acids and Bases

**Lewis acids and bases**

- A *Lewis acid* is an **electron acceptor**
- A *Lewis base* is an **electron donor**

**Bronsted acids and bases**

- A *Bronsted acid* is a **proton donor**
- A *Bronsted base* is a **proton acceptor**

**Electrophiles and Nucleophiles**

This terminology is used almost interchangeably with that of Lewis acids and Lewis bases
- Electrophile (*electron-loving*) = Lewis acid
- Nucleophile (*nucleus-loving:* ) = Lewis base

Relative Strengths of Bronsted Acids

- The relative strengths of Bronsted acids are determined by how well they transfer a proton to a Bronsted base.
- In order to have a basis for comparison, reactions of different acids with the base are compared.

What base is used for comparison? | water

The transfer of a proton from an acid, HA, to H₂O is a reversible reaction. An acid and a base react to form a base and an acid. In general, these are called conjugate acid-base pairs.

\[
K_{eq} = \frac{a_{A^-} a_{H^+}}{a_{AH} a_{H_2O}}
\]
Definition of pK_a

- The quantity "activity" may be thought of as an effective mole fraction. When reactions are carried out with very highly dilute acids in water, the activity of water approaches unity.

- We call this equilibrium constant for dissociation $K_a$.

$$K_{eq} = \frac{a^- a_{H^+}}{a_{AH} a_{H_2O}} \approx \frac{a^- a_{H^+}}{a_{AH}}$$

$K_a = \frac{[A^-][H^+]}{[AH]}$

In terms of concentrations and activity coefficients

When we work in very dilute solutions, activity coefficients approach unity, and we can approximate the expression for $K_a$ using concentrations.

Definition of pK_a

Bronsted acids exhibit a huge variation in strength, over many powers of 10. Therefore a log scale is used to describe acidity.

$$pK_a = -\log(K_a) = \left\{-\log\left(\frac{[A^-]}{[HA]}\right) + \log\left([H^+]\right)\right\}$$

From this we see how the quantity used to measure acidity in Bronsted acids ($pK_a$) is related to aqueous acidity ($pH$)

$$pH = -\log\left([H^+]\right)$$

$$pK_a = -\log(K_a) = -\log\left(\frac{[A^-]}{[HA]}\right) + pH$$
Using $pK_a$

- Reaction is driven forward from the strong acid side to the weak acid side. This means that the equilibrium favors the side with the weaker acid and weaker base.
- This means that if we know the $pK_a$ values of the acids on either side of the reaction equation, we can predict which direction will be favored.

$$\text{HCN} + \text{OH}^- \rightleftharpoons \text{CN}^- + \text{H}_2\text{O}$$

$pK_a = 9.4$

$$\text{HCN} + \text{NH}_3 \rightleftharpoons \text{CN}^- + \text{NH}_4^+$

$pK_a = 9.4$

\[ pK_a(\text{H}_2\text{O}) - pK_a(\text{HCN}) = 15.7 - 9.4 = 6.3 \]

\[ K_q = 10^{6.3} = 2 \times 10^6 \]

*The equilibrium lies far to the right*

\[ pK_a(\text{NH}_4^+) - pK_a(\text{HCN}) = 9.25 - 9.4 = -0.15 \]

\[ K_q = 10^{-0.15} = 0.71 \]

*The equilibrium is lies slightly to the left*

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The influence of Organic Solvents on $pK_a$

- $pK_a$ values are defined and compiled for aqueous solutions.
- Most of our reactions in organic chemistry are carried out in organic solvents!
- We must adjust our thinking about $pK_a$

![Table 3: Ionization constants of neutral acids of type HA in water, amphiprotic and cyclic aprotic solvents, respectively](image-url)

<table>
<thead>
<tr>
<th>Acid</th>
<th>$pK_a$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acetic</td>
<td>4.73</td>
</tr>
<tr>
<td>Chloroacetic</td>
<td>2.81</td>
</tr>
<tr>
<td>Dichloroacetic</td>
<td>1.30</td>
</tr>
<tr>
<td>Benzene</td>
<td>4.21</td>
</tr>
<tr>
<td>3,4-DMc benzene</td>
<td>4.4</td>
</tr>
<tr>
<td>3,5-benzene</td>
<td>3.81</td>
</tr>
<tr>
<td>3,4-DCI benzene</td>
<td>3.6</td>
</tr>
<tr>
<td>4-NO$_2$ benzene</td>
<td>3.45</td>
</tr>
<tr>
<td>3,5-NO$_2$ benzene</td>
<td>2.82</td>
</tr>
<tr>
<td>2,4,6-triNO$_2$ benzene</td>
<td>0.3</td>
</tr>
</tbody>
</table>

The influence of Organic Solvents on pK\(_a\)

- Acid pK\(_a\) values are affected more than weak bases are by organic solvents.

Table 4
Ionization constants of cation acids (monoproticated bases) of type HB

<table>
<thead>
<tr>
<th>Acid</th>
<th>pK(_a)</th>
<th>MeOH</th>
<th>EtOH</th>
<th>DMSO</th>
<th>ACN</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ammonium</td>
<td>9.2</td>
<td>10.6</td>
<td>10.5</td>
<td>16.5</td>
<td></td>
</tr>
<tr>
<td>Ethylammonium</td>
<td>10.6</td>
<td>11.0</td>
<td>18.4</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diethylammonium</td>
<td>11.0</td>
<td>10.5</td>
<td>18.8</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Triethylammonium</td>
<td>10.7</td>
<td>10.9</td>
<td>9.0</td>
<td>18.5</td>
<td></td>
</tr>
<tr>
<td>Tri-n-Propylammonium</td>
<td>10.6</td>
<td>11.1</td>
<td>18.5</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Di-n-Butylammonium</td>
<td>11.3</td>
<td>10.0</td>
<td>18.3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tri-n-Butylammonium</td>
<td>10.8</td>
<td>8.4</td>
<td>18.1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anilinium</td>
<td>4.6</td>
<td>5.7</td>
<td>3.6</td>
<td>10.6</td>
<td></td>
</tr>
<tr>
<td>Pyridinium</td>
<td>5.2</td>
<td>5.2(^{+})</td>
<td>3.4</td>
<td>12.3</td>
<td></td>
</tr>
<tr>
<td>4-Ethylpyridinium</td>
<td>6.1(^{+})</td>
<td></td>
<td>13.6(^{+})</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Using pK\(_a\)

- Reaction is driven forward from the strong acid side to the weak acid side. This means that the equilibrium favors the side with the weaker acid and weaker base.
- This means that if we know the pK\(_a\) values of the acids on either side of the reaction equation, we can predict which direction will be favored.

\[
pK_a(\text{Et}_3\text{NH}^+) - pK_a(\text{PhCOOH}) = 9.2 - 4.21 \\
\log K_{eq} = 5 \quad K_{eq} = 10^5
\]

\[
pK_a(\text{Et}_3\text{NH}^+) - pK_a(\text{PhCOOH}) = 18.5 - 20.7 \\
\log K_{eq} = -2.2 \quad K_{eq} = 10^{-2.2}
\]

*The equilibrium lies far to the right*  
*The equilibrium lies to the left*
Factors Affecting pK\textsubscript{a} in Organic Solvents

- **Dielectric constant:** this parameter takes into account electrostatic interactions of the ions in solution.

<table>
<thead>
<tr>
<th>High $\epsilon$</th>
<th>Low $\epsilon$</th>
</tr>
</thead>
<tbody>
<tr>
<td>H-bonded</td>
<td>H-bonded</td>
</tr>
<tr>
<td>Water (W)</td>
<td>Acetonitrile (ACN)</td>
</tr>
<tr>
<td>Methanol (MeOH)</td>
<td>$N,N$-Dimethylformamide (DMF)</td>
</tr>
<tr>
<td>Ethylene glycol</td>
<td>$N,N$-dimethylacetamide (DMA)</td>
</tr>
<tr>
<td>Formamide</td>
<td>Dimethylsulfoxide (DMSO)</td>
</tr>
<tr>
<td>Acetamide</td>
<td>$n$-Butanol ($n$-BuOH)</td>
</tr>
<tr>
<td>$N$-Methylformamide</td>
<td>$i$-Butanol ($i$-BuOH)</td>
</tr>
<tr>
<td>$N$-Methylacetamide</td>
<td></td>
</tr>
</tbody>
</table>

Table 1
Classification of solvents for potential use in CE, according to Ref. [21]

$pK_a$ of benzoic acid in:
- DMF 12.3
- DMSO 11.0
- MeCN 20.7

Water and methanol have similar properties

Clearly, dielectric constant is not telling the whole story!

Factors Affecting pK\textsubscript{a} in Organic Solvents

- **Solute-solvent interactions:** looking at dielectric constant alone neglects the effects of interactions between solute and solvent (sometimes called "medium effects" as opposed to the "solvent effect" described by $\epsilon$).

- An important characteristic is the ability of the medium to solvate ions.

- Solvation ability in a given solvent can be significantly different for cations compared to anions.

<table>
<thead>
<tr>
<th>Solvation ability</th>
<th>Solvent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anion</td>
<td>Very high</td>
</tr>
<tr>
<td>Cation</td>
<td>Very high</td>
</tr>
</tbody>
</table>

Table 2
Ability of solvents to solvate anions and cations
Factors Affecting pK\textsubscript{a} in Organic Solvents

- Organic solvents are generally worse as solvators of anions than they are of cations.
- This helps explain why the pK\textsubscript{a} values for bases such as Et\textsubscript{3}N are less affected by solvent than are neutral acids.
- pK\textsubscript{a} is affected more in MeCN because it is much less basic than the other non-H-bonding solvents of similar dielectric constant.
- Medium effects must also consider the role of the other charged species present (A\textsuperscript{-} and HB\textsuperscript{+}).

<table>
<thead>
<tr>
<th>Solvation ability</th>
<th>Solvent</th>
<th>Water</th>
<th>MeOH</th>
<th>DMSO</th>
<th>ACN</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anion</td>
<td>Very high</td>
<td>Medium</td>
<td>Low</td>
<td>Very low</td>
<td></td>
</tr>
<tr>
<td>Cation</td>
<td>Very high</td>
<td>Very high</td>
<td>Very high</td>
<td>Very low</td>
<td></td>
</tr>
</tbody>
</table>

Table 8
Ability of solvents to solvate anions and cations