What is meant by "biological emphasis"?
As in Chem 303, emphasis is on **reaction mechanism**. But examples will be taken from biochemistry whenever appropriate.

Biology can be understood in terms of basic organic mechanisms operating in complex systems.

New emphasis: **MOLECULAR ASSOCIATION**—weak interactions between organic molecules:
- structure of proteins, DNA
- enzyme-substrate
- hormone-receptor
- lipid membranes
- etc.
  - ionic, H-bonding, dipole-dipole, van der Waals interactions

NMR and IR spectroscopy will be important in solving problems


Polarity influences many properties: **mp, BP, solubility** "LIKE DISSOLVES LIKE"

Extreme: Na+ Cl−

<table>
<thead>
<tr>
<th>Compound</th>
<th>MW</th>
<th>mp</th>
<th>bp</th>
<th>Solubility</th>
</tr>
</thead>
<tbody>
<tr>
<td>Na+ Cl−</td>
<td></td>
<td>801°</td>
<td>1413°</td>
<td>soluble in water</td>
</tr>
</tbody>
</table>

n-butane CH₃-CH₂-CH₂-CH₃

<table>
<thead>
<tr>
<th>Compound</th>
<th>MW</th>
<th>mp</th>
<th>bp</th>
<th>Solubility</th>
</tr>
</thead>
<tbody>
<tr>
<td>CH₃-CH₂-CH₂-CH₃</td>
<td>58</td>
<td>-138°</td>
<td>-0.5°</td>
<td>insoluble in water</td>
</tr>
</tbody>
</table>

acetone CH₃-C( CH₃)₂-O

<table>
<thead>
<tr>
<th>Compound</th>
<th>MW</th>
<th>mp</th>
<th>bp</th>
<th>Solubility</th>
</tr>
</thead>
<tbody>
<tr>
<td>CH₃-C( CH₃)₂-O</td>
<td>58</td>
<td>-94°</td>
<td>56°</td>
<td>soluble in water</td>
</tr>
</tbody>
</table>

isopropyl alcohol CH₃-C( CH₃)₂-OH

<table>
<thead>
<tr>
<th>Compound</th>
<th>MW</th>
<th>mp</th>
<th>bp</th>
<th>Solubility</th>
</tr>
</thead>
<tbody>
<tr>
<td>CH₃-C( CH₃)₂-OH</td>
<td>60</td>
<td>-89°</td>
<td>82°</td>
<td>soluble in water</td>
</tr>
</tbody>
</table>

1. Ionic bonds involve full charges **STRONG** electrostatic attraction Cl− Na+ Cl− Na+
   boiling, melting: means breaking apart the electrostatic attraction (bond).

2. Polar covalent bonds involve partial charges (permanent dipole), **MODERATE** electrostatic attraction
   DIPOLE-DIPOLE ATTRACTION (0.1-1.0 kcal/mol)

acetonene:
3. Special case of dipole-dipole attraction: HYDROGEN BOND  1.0-10 kcal/mol
   X--H  (X = strongly electronegative atom such as F, O, N)
   Intense dipole as pull charge from H atom
   self association of isopropyl alcohol (MW 60)

4. Induced dipole: Van der Waals attraction: polarizibility of electron clouds: temporary dipole
   Consider series of molecules with similar MW, no highly polarized bonds,
   but very different boiling points/
   \[ \begin{array}{|c|}
   \hline
   \text{molecule} & \text{bp} \\
   \hline
   \text{n-heptane} & 98^{\circ} \\
   \text{n-octane} & 126^{\circ} \\
   \text{n-nonane} & 151^{\circ} \\
   \text{2,2,4-trimethylpentane} & 99^{\circ} \\
   \text{ethyl iodide} & 100^{\circ} \\
   \hline
   \end{array} \]
   van der Waals can add up:
   \textbf{cholesterol  mp 150^{\circ}}  large non-polar molecule with a polar functional group

Overall: FOUR ATTRACTION MECHANISMS:
(a) ionic
(b) dipole-dipole
(c) hydrogen bond
(d) van der Waals

Consider effects on solubility: Now must consider solvent-solvent interactions
solute-solute interactions
solute-solvent interactions

How do they add up? [Like dissolves like?]
Dissolving means slipping solute molecules in between solvent molecules: remove some solvent-solvent and solute-solute interactions and replace with solute-solvent interactions.

SOLVENT EFFECTS

**Note:** polar **molecule** measured by dipole moment, due to summation of bond dipoles polar **solvent** measured by dielectric constant, ability to stabilize charge

For polar effects of solvents, apply the Electrostatic Law: $E = \frac{q_1 q_2}{\varepsilon r_{1,2}}$  
$E =$ attraction between charges
$q =$ charges on particles
$r_{12} =$ distance between particles
$\varepsilon =$ dielectric constant

Stabilizing the ions means reducing $E$;
higher $\varepsilon =$ smaller $E$

**TABLE OF SOLVENT PROPERTIES**

**Water is a "polar, protic" solvent**  High dielectric constant (78), Strong H-bonding  
dissolves ions by dipole/dipole interactions with ions  
specifically stabilizes anions by H-bond donation  
great for solubilizing ionic compounds

**Dimethyl sulfoxide is a "polar, aprotic" solvent.**  
High dielectric constant (47)  
NO H-bond donation  
dissolves ions by dipole/dipole interactions, especially with cations  
not strongly stabilize anions

**Hexane is a non-polar solvent:** (also diethyl ether, benzene, etc)

Consider solutes:

- [glucose](#)
- [naphthalene](#)

**A.** Highly associated solute (eg, glucose) requires strong interactions with solvent to break up molecular association.

Highly associated (H **bonding**, dipole-dipole) solvent such as water must find similar strong interactions with solute to favor separating water molecules from each other

DMSO can also **accept** H-bonds and dissolve glucose
Polar solute requires polar solvent: Like dissolves like!

B. Non-polar solvent cannot provide the molecular association necessary to separate molecules of a polar solute. Polar solute does not dissolve in non-polar solvent

C. Non-polar solutes cannot break up polar solvents--do not dissolve

D. Non-polar solvents dissolve non-polar solutes (no special attractions to overcome)

Cholesterol is insoluble in water and hexane: mainly a non-polar molecule even though a polar group

How about CH₂Cl₂ vs CCl₄?
Consider Acidity and Basicity          Recall carboxylic acids and amines (base).
Jones: p 237-8; 149, 291, 822-826, 1086-1090, 958-963, 878-882

General terms:
Lewis acid: capable of accepting an electron pair to form a covalent bond.
prototype example: \( \text{BF}_3 \) empty orbital in valence shell

Lewis base: capable of donating an electron pair to form a covalent bond.
prototype example: \( :\text{NH}_3 \) low energy non-bonding electrons

In simplest case, non-bonding electron pair on Lewis base engages in overlap with empty atomic orbital on Lewis acid to form a "coordinate covalent bond".

Bronsted acid: capable of delivering a proton (special acid)
e.g., \( \text{HCl} \)

Bronsted base: capable of accepting a proton
e.g., \( \text{NaOH} \) and \( \text{NH}_3 \)

In general: How does the structure of a molecule affect its acidity/basicity?

Define: equilibrium acidity:
\[
\begin{align*}
\text{H-A} & \rightleftharpoons \text{H}^+ + \text{A}^- \\
K_{\text{eq}} &= K_a = \frac{[\text{H}^+][\text{A}^-]}{[\text{HA}]}
\end{align*}
\]

If the free energy \( (\Delta G) \) of the products is equal to the free energy of the reactants, \( K_{\text{eq}} = 1 \)
If the products have a larger \( -\Delta G \), more stable, and \( K_{\text{eq}} > 1 \)
If the reactants have a larger \( -\Delta G \), reactants are more stable and \( K_{\text{eq}} < 1 \)

Usually express acidity in terms of \( pK_a \), negative log of \( K_a \).

What are the factors which influence the \( pK_a \)?

Remember Hess's law?
\[
\begin{align*}
\text{H-A} & \rightarrow \text{H}^+ + \text{A}^- \quad \text{(bond dissociation energy)} \\
\text{A}^+ + e^- & \rightarrow \text{A}^- \quad \text{electron affinity} \\
\text{H}^+ + e^- & \rightarrow \text{H-A} \quad \text{ionization potential}
\end{align*}
\]
add up:
\[
\text{H-A} \rightarrow \text{H}^+ + \text{A}^-
\]
more electronegative: higher electron affinity (more easily form \( \text{A}^- \); less easily add \( \text{H}^+ \) to \( \text{A}^- \))
stronger H-A bond: higher BDE and less easy to ionize
Compare acidity (ease of ionization):

<table>
<thead>
<tr>
<th></th>
<th>H-F</th>
<th>H-OH</th>
<th>H-NH₂</th>
<th>H-CH₃</th>
</tr>
</thead>
<tbody>
<tr>
<td>pKa</td>
<td>3.2</td>
<td>15.7</td>
<td>ca 35</td>
<td>&gt;55</td>
</tr>
<tr>
<td>EN</td>
<td>4.0</td>
<td>3.4</td>
<td>3.0</td>
<td>2.5</td>
</tr>
</tbody>
</table>

Electronegativity has a big effect
(bond energies are similar, except the H-F bond is unusually strong)

Bond dissociation energies can dominate:

<table>
<thead>
<tr>
<th></th>
<th>H-F</th>
<th>H-Cl</th>
<th>H-Br</th>
<th>H-I</th>
</tr>
</thead>
<tbody>
<tr>
<td>BDE</td>
<td>135</td>
<td>103</td>
<td>88</td>
<td>71</td>
</tr>
<tr>
<td>EN</td>
<td>4.0</td>
<td>3.2</td>
<td>3.0</td>
<td>2.7</td>
</tr>
<tr>
<td>pKa</td>
<td>3.2</td>
<td>-7</td>
<td>-9</td>
<td>-9.5</td>
</tr>
</tbody>
</table>

H-OH \[\rightleftharpoons\] H⁺ + HO⁻ pKa 15.7

CH₃CH₂O-H \[\rightleftharpoons\] CH₃CH₂O⁻ + H⁺ pKa 15.9 (a little less acidic)

ethoxide anion, the conjugate base of ethyl alcohol

Therefore: If mix NaOH with CH₃CH₂OH,
get approx. equal amounts of NaOH, NaOCH₂CH₃, H₂O, CH₃CH₂OH

Consider:

| acidity: CF₃CH₂OH \(>\) CF₃CH₂CH₂OH \(>\) CF₃CH₂CH₂CH₂OH \(>\) CH₃CH₂OH |
|------|------|------|------|------|
| pKa  | 12.4 | 14.6 | 15.4 | 15.9 |

CH₃CH₂OH \[\rightleftharpoons\] CH₃CH₂O⁻ + H⁺ pKₐ 15.9

CF₃CH₂OH \[\rightleftharpoons\] CF₃CH₂O⁻ + H⁺ pKₐ 12.4
\[ \Delta G_1 > \Delta G_2 \]

Therefore, \( pK_a(1) \) is > \( pK_a(2) \)

ethyl alcohol is a weaker acid compared to 2,2,2-trifluoroethyl alcohol

\[ \Delta \Delta G = 2.3RT [pK_a(1) - pK_a(2)] = (2.3) (2.0 \text{ cal mol}^{-1} \text{ K}^{-1}) (300^\circ \text{K}) (15.9-12.4) = \]

ca 5000 cal/mol or 5 kcal/mol

\( R = 8.31 \text{ J mol}^{-1} \text{ K}^{-1} \text{ or 2.0 cal mol}^{-1} \text{ K}^{-1} \) Assume room temperature, 300\(^\circ\)K

Now: Why? What is responsible for the 5 kcal/mol lower energy difference?

Approximation: the concentration of charge in the anion is a dominant factor in determining whether proton loss is more-or-less favorable.

Analyze factors which influence the product after de-protonation: inductive effects electronegativity

Focus on the ALKOXIDE ANION. (other differences are parallel--
breaking O-H bond in both cases, no serious structural change, etc)

CF\(_3\)CH\(_2\)OH is more acidic than CH\(_3\)CH\(_2\)OH due to the inductive effect of the F substituent:

Very electronegative F draws electrons from adjacent carbon, transmitted to second carbon, and then to O\(^-\).