# Chemistry 304B with Biological Emphasis

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Check the 304B Webpage for information regarding the administration of the course.
Key points: notes are available for each lecture; need to be "filled in."
exams are "open everything"
grading will be approximately parallel with 304X
First exam: March 1st, 7:30-9:30 pm

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

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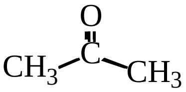
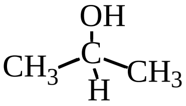
Reading assignment: Handout on molecular association; Jones: p 863, 820, 107-108, 236,
Problem set 1.

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

| | | | | | |
|---|---|---|---|---|---|
| Extreme: | $Na^+$ $Cl^-$ | MW 58 | mp 801° | bp 1413° | soluble in water |
| n-butane | $CH_3$-$CH_2$-$CH_2$-$CH_3$ | MW 58 | mp -138° | bp -0.5° | insoluble in water |
| acetone |  $CH_3C(=O)CH_3$ | MW 58 | mp -94° | bp 56° | soluble in wate |
| isopropyl alcohol |  $CH_3CH(OH)CH_3$ | MW 60 | mp -89° | bp 82° | soluble in wate |

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)

**acetone:**

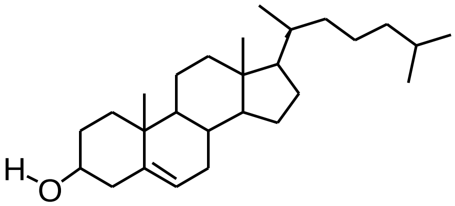
3. Special case of dipole-dipole attraction: HYDROGEN BOND 1.0-10 kcal/mol
X--H (X = strongly electronegative atom such as F, O, N)
Intense dipole as pull charge from H atom

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/

| | **bp** |
|---|---|
| n-heptane | 98° |
| n-octane | 126° |
| n-nonane | 151° |
| 2,2,4-trimethylpentane | 99° |
| ethyl iodide | 100° |

van der Waals can add up:
**cholesterol mp 150°** 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 <u>solubility</u>: 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

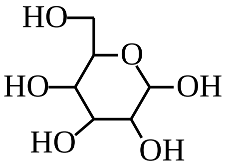
**Water is a "polar, protic"** solvent High dielectric constant (78), Strong H-bonding
dissolves ions by dipole/dipole interactions with ions
specifically stabilizes anions by H-bond donation
great for solubilizing ionic compounds

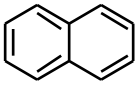
**Dimethyl sulfoxide is a "polar, aprotic"** solvent.
High dielectric constant (47)
NO H-bond donation
dissolves ions by dipole/dipole interactions, especially with cations
not strongly stabilize anions

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

Consider solutes:

glucose



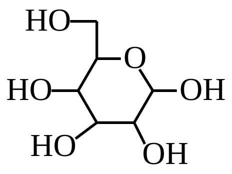


naphthalene

**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



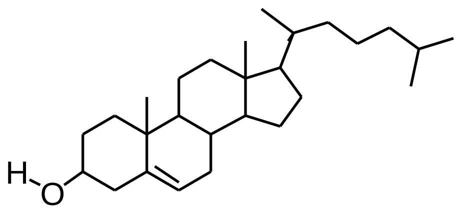
**Polar solute requires polar solvent:** Like dissolves like!

**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 $CH_2Cl_2$ vs $CCl_4$?

**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: $\mathbf{BF_3}$ empty orbital in valence shell

Lewis base: capable of donating an electron pair to form a covalent bond.
prototype example: $\mathbf{:NH_3}$ 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., **HCl**

Bronsted base: capable of accepting a proton
e.g., **NaOH** and $\mathbf{NH_3}$

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

Define: equilibrium acidity:

$$\text{H-A} \rightleftharpoons \text{H}^+ + \text{A}^- \qquad K_{eq} = K_a = \frac{[\text{H}^+][\text{A}^-]}{[\text{HA}]}$$

If the free energy ($\Delta G$) of the products is equal to the free energy of the reactants, $K_{eq} = 1$

If the products have a larger $-\Delta G$, more stable, and $K_{eq} > 1$

If the reactants have a larger $-\Delta G$, reactants are more stable and $K_{eq} < 1$

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?

$$\begin{array}{rlll} & \text{H-A} \longrightarrow & \text{H}\bullet + \text{A}\bullet & \text{(bond dissociation energy)} \\ & \text{A}\bullet + e^- \longrightarrow & \text{A}:^- & \text{electron affinity} \\ & \underline{\text{H}\bullet \longrightarrow} & \underline{\text{H}^+ + e^-} & \text{ionization potential} \\ \text{add up:} & \text{H-A} \longrightarrow & \text{H}^+ + \text{A}^- & \end{array}$$

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):**

| | H-F | H-OH | $H-NH_2$ | $H-CH_3$ |
|---|---|---|---|---|
| pKa | 3.2 | 15.7 | ca 35 | >55 |
| EN | 4.0 | 3.4 | 3.0 | 2.5 |

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

**Bond dissociation energies can dominate:**

| | H-F | H-Cl | H-Br | H-I |
|---|---|---|---|---|
| BDE | 135 | 103 | 88 | 71 |
| EN | 4.0 | 3.2 | 3.0 | 2.7 |
| pKa | 3.2 | -7 | -9 | -9.5 |

$$H\text{-}OH \rightleftharpoons H^+ + HO^- \quad pKa\ 15.7$$

$$CH_3CH_2O\text{-}H \rightleftharpoons CH_3CH_2O^- + H^+ \quad pKa\ 15.9 \quad \text{(a little less acidic)}$$

ethoxide anion, the conjugate base of ethyl alcohol

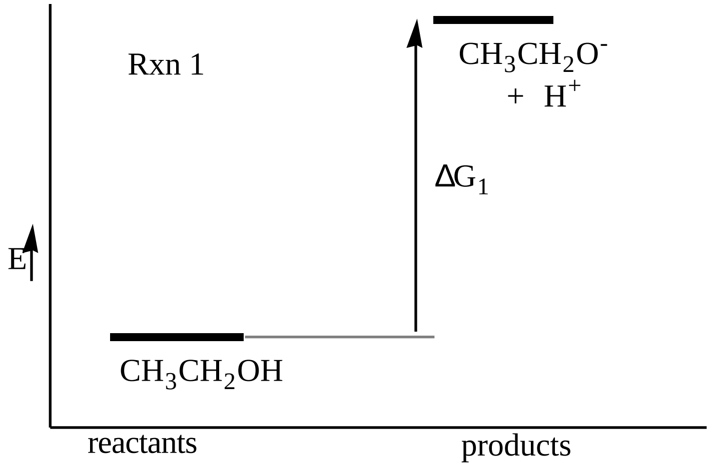
Therefore: If mix NaOH with $CH_3CH_2OH$,
get approx. equal amounts of NaOH, $NaOCH_2CH_3$, $H_2O$, $CH_3CH_2OH$

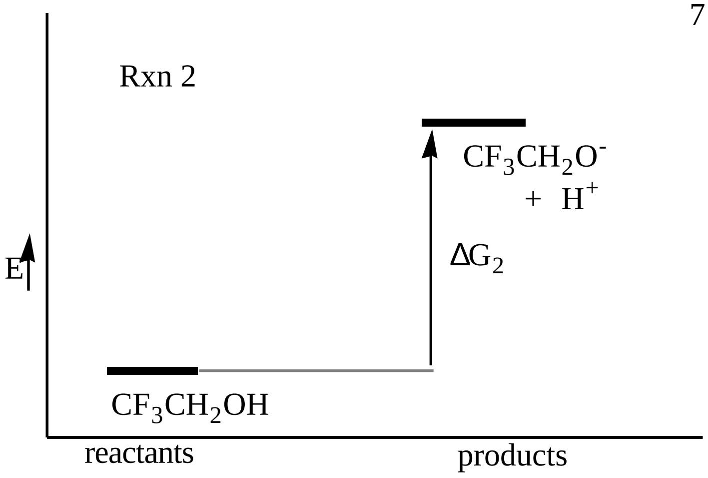
**Consider:**

| acidity: | $CF_3CH_2OH$ | > | $CF_3CH_2CH_2OH$ | > | $CF_3CH_2CH_2CH_2OH$ | > | $CH_3CH_2OH$ |
|---|---|---|---|---|---|---|---|
| pKa | 12.4 | | 14.6 | | 15.4 | | 15.9 |

$$CH_3CH_2OH \rightleftharpoons CH_3CH_2O^- + H^+ \quad pK_a\ 15.9$$

$$CF_3CH_2OH \rightleftharpoons CF_3CH_2O^- + H^+ \quad pK_a\ 12.4$$





$\Delta G_1 > \Delta G_2$ Therefore, $pK_a(1)$ is > $pK_a(2)$

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

$$\Delta\Delta G = 2.3RT\,[pK_a(1) - pK_a(2)] = (2.3)\,(2.0 \text{ cal mol}^{-1}\text{ K}^{-1})\,(300^{0}\text{K})\,(15.9-12.4) =$$

**ca 5000 cal/mol or 5 kcal/mol**

$R = 8.31$ J $mol^{-1}$ $K^{-1}$ or 2.0 cal $mol^{-1}$ $K^{-1}$ Assume room temperature, $300^{0}$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)

$CF_3CH_2OH$ is more acidic than $CH_3CH_2OH$ due to the inductive effect of the F substituent:

Very electronegative F draws electrons from adjacent carbon, transmitted to second carbon, and then to $O^-$