Exam III, 80 pts = 68 pts (MCQs) + 12 pts (Daily assignments)

- 68 pts (MCQs) covers the first 5 (not 6) lectures
- The final, 40 pts (MCQs)
- Bring your calculator to the lectures and exams
Daily assignments (12 pts)

1. Individual work (Problem sets)
   - Submit a printed copy in class
   - 1.5 pts/assignment × 7 = 10.5 pts
   - No makeup/class attendance
   - Helps from some LGs for homework collection

2. Team (Learning Group) work
   - Post the team answers at “Go Maroon” at the Blackboard [http://maroon2012.wikispaces.com](http://maroon2012.wikispaces.com)
   - Posted one day after the due day
   - Concisely
     - A few key words → helpful hints
     - Two questions/LG (including Problem Set #8)
     - 0.75/per question; 1.5 pts/each member

3. Constructive comments and suggestions are appreciated
   - E-mails
   - In-class anonymous notes

Required textbook:
- Principles of Medicinal Chemistry by William O. Foye, Thomas L. Lemke and David A. Williams, 6th edition, Lippincott Williams & Wilkins
  - Chapters 2, 3, 9, 10, 11

Recommended textbooks:
  - Chapters 1-3

Recommended articles:
- Footnotes in slides

Basic chemistry background
- On-line resources (e.g., Wikipedia.com)
- Chemistry textbooks
Today’s outline

I. General course information
   □ Definition of medicinal/pharmaceutical chemistry
   □ Drug discovery process

II. Drug acidity and basicity
   A. Acidity/basicity and drug design and development
   B. Concept of acids and bases
   C. Relative strengths of acids and bases
   D. Quantitatively evaluation of the relative acid/base strength
   E. Acidity, basicity, and chemical structure
   F. The acidity and basicity of common functional groups
   G. Buffer capacity
   H. pH of polyprotic compounds
   I. pH of amphiprotic compounds

Definition of Medicinal Chemistry by the International Union of Pure and Applied Chemistry (IUPAC):

“Medicinal chemistry concerns the discovery, the development, the identification, and the interpretation of the mode of action of biologically active compounds at the molecular level. Emphasis is put on drugs, but the interests of the medicinal chemist are not restricted to drugs but include bioactive compounds in general. Medicinal chemistry is also concerned with the study, identification, and synthesis of the metabolic products of these drugs and related compounds.”
Medicinal/pharmaceutical chemistry

- The chemistry of drug design and development
- How the drug is prepared and dispensed
- Important aspects
  - Lead discovery and modification
  - Structure/activity relationships
  - Structure/pharmaceutical property relationships
  - Drug stereochemistry
  - Drug-drug interactions
  - Drug transport and metabolism
  - Safe and practical standards to both dosage and quality

General steps of drug discovery

1. Assess the biological and biochemical processes of the diseases and/or its causes
2. Identify a necessary medical intervention
3. Decide the structure of a suitable lead compound
4. Pharmacological and toxicological testing
5. Synthesis of analogues (Lead modification)
II. Drug acidity and basicity
A. Acidity/basicity and drug design and development

Drug acidity and basicity play important roles in:

- Drug solubility and bioavailability
- Different pH values at different parts of the GI tract
- Different pKa values of drugs
- Drug bioavailability
- Duration time
- On-set time
- Drug stability

B. Concept of acids and bases

1. By observation

- **Acid**
  - Turns blue litmus **Red**
  - Neutralizes **Bases**
  - React with active metals with evolution of **Hydrogen**
  - Tastes **Sour**

- **Bases**
  - Turns blue litmus **Blue**
  - Neutralizes **acids**
  - Tastes **Bitter**
  - Feels **Soapy**
(2). Svante Arrhenius (1887) concept

\[ \text{H}_2\text{O} \leftrightarrow \text{H}^+ + \text{OH}^- \]

- Acid - Water solution contains an excess of H\(^+\)
- Base - Water solution contains an excess of OH\(^-\)

(3). Bronsted-Lowry (1923) concept

- Acid - Any substance that can donate a proton to any other substance
- Base - Any substance that can accept a proton from any other substance

(4). G.N. Lewis (1875-1946, UC Berkeley) concept

- Acid - An electron-pair accepter
- Base - An electron-pair donor
- It focuses on the acid-base reactions
  - The sharing of an electron pair with an acid by a base
    - Neutralization
      - Formation of a coordinate covalent bond between an acid (Electron-pair acceptor) and a base (Electron-pair donor)
      - Acid + Base $\rightarrow$ Coordinated complex
Examples:

Acid + Base $\rightarrow$ Coordinated complex

\[
\begin{array}{c}
\text{F} \\
\text{B} \\
\text{F} \\
\end{array}
+ 
\begin{array}{c}
\text{O} \\
\text{H} \\
\text{H} \\
\end{array}
\rightarrow 
\begin{array}{c}
\text{F} \\
\text{B} \\
\text{F} \\
\end{array}
\]

Boron Trifluoride

\[
\begin{array}{c}
\text{O} \\
\text{S} \\
\text{O} \\
\end{array}
+ 
\begin{array}{c}
\text{O} \\
\text{O} \\
\text{O} \\
\end{array}
\rightarrow 
\begin{array}{c}
\text{O} \\
\text{S} \\
\text{O} \\
\end{array}
\]

Sulfur trioxide

(5). Definition of conjugate bases and conjugate acids

\[
\begin{align*}
\text{Acid} & \rightarrow \text{H}^+ + \text{Conjugate base} \\
\text{Base} + \text{H}^+ & \rightarrow \text{Conjugate acid} \\
\text{Acid} + \text{Base} + \text{H}^+ & \rightarrow \text{Conjugate base} + \text{Conjugate acid} + \text{H}^+ \\
\text{Acid} + \text{Base} & \rightarrow \text{Conjugate base} + \text{Conjugate acid}
\end{align*}
\]
Practice problem #1 - Acid, base, or amphoteric?

Warfarin (Beta-dicarbonyl group)

Prostaglandin

Propanolol

Tyrosine 
Zwitterion

Phenytoin 
(Acidic imide)

Warfarin 
(Beta-dicarbonyl group)

C. Relative strengths of acids and bases

The stronger an acid the weaker its conjugate base.

\[
\begin{align*}
\text{HCl} + \text{H}_2\text{O} & \rightleftharpoons \text{Cl}^- + \text{H}_3\text{O}^+ \\
\text{HA} + \text{H}_2\text{O} & \rightleftharpoons \text{A}^- + \text{H}_3\text{O}^+
\end{align*}
\]
The stronger a base the weaker its conjugate acid.

\[
\text{NH}_3 + \text{H}_2\text{O} \rightleftharpoons \text{NH}_4^+ + \text{OH}^-
\]

\[
\begin{array}{c}
\text{H} \\ \\
\text{N} \\ \\
\text{H} \\
\end{array}
\rightleftharpoons \left\{ \begin{array}{c}
\text{H} \\ \\
\text{N} \\ \\
\text{H} \\
\end{array} \right\}^+ + \left\{ \begin{array}{c}
\text{O} \\ \\
\text{H} \\
\end{array} \right\}^-
\]

\[
\text{B} + \text{H}_2\text{O} \rightleftharpoons \text{BH}^+ + \text{OH}^-
\]

\[
\begin{array}{c}
\text{B} \\
\text{H} \\
\end{array}
\rightleftharpoons \begin{array}{c}
\text{B} \\
\text{H} \\
\end{array}^+ + \begin{array}{c}
\text{O} \\
\text{H} \\
\end{array}^-
\]

D. Quantitatively evaluation of the relative acid/base strength

1. Definition (the Brønsted-Lowry theory)
   - Acid \rightarrow H^+ + Conjugate base
   - Base + H^+ \rightarrow Conjugate acid
   - Acid + Base + H^+ \rightarrow Conjugate base + Conjugate acid + H^+
   - Acid + Base \rightarrow Conjugate base + Conjugate acid \ (Rx.1)

The equilibrium constant \( K_{eq} \) of Rx.1 is

\[
K_{eq} = \frac{[\text{Conjugate acid}][\text{Conjugate base}]}{[\text{Acid}][\text{Base}]}
\]
2. Is water an acid or a base?
Both acid and base

\[
\text{H}_2\text{O} + \text{H}_2\text{O} \rightleftharpoons \text{H}_3\text{O}^+ + \text{OH}^-
\]

Weaker acid + weaker base \rightleftharpoons Stronger acid + stronger base

Thus, H\text{H}_2\text{O} is an amphiprotic substance
Or, \ H\text{H}_2\text{O} \rightleftharpoons \text{H}^+ + \text{OH}^-

\[
\text{H}_2\text{O} \rightleftharpoons \text{H}^+ + \text{OH}^-
\]

The equilibrium constant \(K\)

\[
K = \frac{[\text{H}^+][\text{OH}^-]}{[\text{H}_2\text{O}]}
\]

The concentration of H\text{H}_2\text{O} is

\[
[\text{H}_2\text{O}] \text{ (mole/liter)} = \frac{\text{Weight of 1L H}_2\text{O}}{\text{Molecular weight of H}_2\text{O}}
\]

Thus, the equilibrium constant \(K\)

\[
K = \frac{[\text{H}^+][\text{OH}^-]}{[\text{H}_2\text{O}]} = \frac{[\text{H}^+][\text{OH}^-]}{55.5 \text{ M}}
\]
The equilibrium constant $K$

$$K = \frac{[H^+] [OH^-]}{[H_2O]} = \frac{[H^+] [OH^-]}{55.5 \text{ M}}$$

At 25°C

$$[H^+] [OH^-] = 1 \times 10^{-14} \quad \text{And} \quad [H^+] = [OH^-]$$

$$\therefore [H^+] \text{ in H}_2\text{O} =$$

$$\therefore \text{pH of H}_2\text{O} = -\log_{10} [H^+] = \log_{10} \frac{1}{[H^+]}$$

Finally, the pH of water is?

Alkalines: $[H^+] < 1 \times 10^{-7}$ mole/liter
Acids: $[H^+] > 1 \times 10^{-7}$ mole/liter

3. Dissociation of weak acids and bases

(a) Dissociation of weak acids

For weak acids, $HA + H_2O \rightarrow H_3O^+ + A^-$

Or $HA \rightleftharpoons H^+ + A^-$

$$Ka = \frac{[H^+] [A^-]}{[HA]}$$

The greater the value of $Ka$, the stronger is the acid.

$$\log Ka = \log [H^+] + \log \frac{[A^-]}{[HA]}$$

$$-\log Ka = -\log[H^+] - \log \frac{[A^-]}{[HA]}$$

$$pKa = pH - \log \frac{[A^-]}{[HA]} \quad \text{For weak acid} \quad pH = pKa + \log \frac{[A^-]}{[HA]}$$
(b) Dissociation of weak bases

For weak bases, \( \text{B} + \text{H}_2\text{O} \rightleftharpoons \text{BH}^+ + \text{OH}^- \)

\[
K_b = \frac{[\text{BH}^+] \times [\text{OH}^-]}{[\text{B}]}
\]

The greater the value of \( K_b \), the stronger is the base.

\[
\log K_b = \log [\text{OH}^-] + \log \frac{[\text{BH}^+]}{[\text{B}]}
\]

\[
-pK_b = -\log[H^+] - \log \frac{[\text{BH}^+]}{[\text{B}]}
\]

\[
pK_b = p\text{OH} - \log \frac{[\text{BH}^+]}{[\text{B}]}
\]

\[
p\text{OH} = pK_b + \log \frac{[\text{BH}^+]}{[\text{B}]}
\]

\[
pH + p\text{OH} = ?
\]
E. Acidity, basicity, and chemical structure

- A type of structure/pharmaceutical property relationship
- What structural features confer proton-donating or proton-accepting tendencies?

(a). Relationships of acidity and basicity to charge

Conjugate acid

Conjugate base

Increasing acidity

Increasing basicity

(b). Relationships of acidity and basicity to electronegativities

Order of increasing electronegativities

Order of increasing acidity

Order of increasing acid strength

Order of decreasing base strength
Order of increasing electronegativities

Li < Be < B < C < N < O < F

Order of increasing acidity

LiH < BeH₂ < CH₄ < NH₃ < H₂O < HF

Order of increasing basicity

\[
\begin{align*}
\text{H} & \text{=} & \text{H} \\
\text{H} \cdot \text{N} \cdot \text{H} & > & \text{H} \cdot \text{O} \cdot \text{H} > \text{H} \cdot \text{F} \\
\text{H} \cdot \text{N} \cdot \text{H} & > & \text{H} \cdot \text{O} \cdot \text{H} > \text{H} \cdot \text{F}
\end{align*}
\]

Order of decreasing acidity

\[
\begin{align*}
\left( \text{H} \cdot \text{N} \cdot \text{H} \right)^+ & < \left( \text{H} \cdot \text{O} \cdot \text{H} \right)^+ < \left( \text{H} \cdot \text{F} \right)^+
\end{align*}
\]

F. The acidity and basicity of common functional groups (a). Common acidic organic functional groups and their ionized (conjugate base) forms (Table 2-1, From Foye's)

- **Sulfonic acid and sulfonate** (0-1)
  \[
  \text{O} \cdot \text{SO}_3 \cdot \text{OH} \hspace{1cm} \text{O} \cdot \text{SO}_3 \cdot \text{O}^-
  \]

- **Sulfonamide and sulfonimide** (5-6)
  \[
  \text{O} \cdot \text{SO} \cdot \text{NH} \cdot \text{R} \hspace{1cm} \text{O} \cdot \text{SO} \cdot \text{N} \cdot \text{R}
  \]

- **Sulfonyl chloride** (9-10)

- **N-arylsulfonamide and N-arylsulfonimidate** (6-7)

\[
\begin{align*}
\text{SO}^+ & \rightarrow \text{SO}^2- & \text{SO}^+ & \rightarrow \text{SO}^2- \\
\text{SO}^+ & \rightarrow \text{SO}^2- & \text{SO}^+ & \rightarrow \text{SO}^2-
\end{align*}
\]
(b). Common basic organic functional groups and their ionized (conjugate acid) forms (Table 2-2, From Foye’s)

- **Alkylthiol and thiolate (10-11)**
  - $R\text{-SH}$
  - $R\text{-S}^-$

- **Thiophenol and thiophenolate (9-10)**
  - $\text{SH}$
  - $\text{S}^-$

- **Phenol (9-11) and phenolate**
  - $\text{OH}$
  - $\text{O}^-$

- **Arylcarboxylic acid (5-6) and arylcarboxylate**
  - $\text{COOH}$
  - $\text{COO}^-$

- **Alkylcarboxylic acid (5-6) and alkylcarboxylate**
  - $R\text{-C}^=\text{OH}$
  - $R\text{-C}=\text{O}$

- **Imine (3-4) and Iminium**
  - $\text{HC}=\text{NN}$
  - $\text{HC}^+=\text{NN}^+$

- **Aromatic amine (9-11) and aromatic ammonium**
  - $\text{NH}_2$
  - $\text{NH}_3^+$

- **1° alkylamines (9-10) and 1° alkylammonium**
  - $R\text{-NH}_2$
  - $R\text{-NH}_3^+$

- **2° alkylamines (9-10) and 2° alkylammonium**
  - $R\text{NH}_2$
  - $R\text{NH}_3^+$

- **Arylamine (9-11) and arylammonium**
  - $\text{NH}_2$
  - $\text{NH}_3^+$

- **Guanidine (12-13) and guanidinium**
  - $R\text{-NH}_2$
  - $R\text{-NH}_2^+$

- **Amidine (10-11) and amidinium**
  - $\text{NH}_2$
  - $\text{NH}_2^+$

- **Guanidine (12-13) and guanidinium**
  - $R\text{NH}_2$
  - $R\text{NH}_2^+$
(c). Common organic functional groups that are considered neutral under physiologic conditions (Table 2-3 From Foye's)

<table>
<thead>
<tr>
<th>Functional Group</th>
<th>Structure</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nitrile</td>
<td>R≡C≡N</td>
</tr>
<tr>
<td>Akyl alcohol</td>
<td>R−CH₂−OH</td>
</tr>
<tr>
<td>Thioether</td>
<td>R−S−R'</td>
</tr>
<tr>
<td>Ether</td>
<td>R−O−R'</td>
</tr>
<tr>
<td>Ketone and aldehyde</td>
<td>R−C=O</td>
</tr>
<tr>
<td>Sulfoxide</td>
<td>R−S=O</td>
</tr>
<tr>
<td>Amide</td>
<td>R−N=O</td>
</tr>
<tr>
<td>Ester</td>
<td>R−O−R'</td>
</tr>
<tr>
<td>Quaternary ammonium</td>
<td>R−N−R''R'''</td>
</tr>
<tr>
<td>Sulfone</td>
<td>R−SO−R'</td>
</tr>
<tr>
<td>Sulfonic acid ester</td>
<td>R−SO₂−R'</td>
</tr>
<tr>
<td>Diarylamine</td>
<td>Ar−Ar</td>
</tr>
</tbody>
</table>

Practice problem #2 (From Foye's)

Codeine phosphate (a morphine analogue)

Quaternary amine

Aromatic hydrocarbon

Ether

Cycloalkane

Alcohol
G. Buffer capacity

(a) The buffer systems of the body

a. Sodium bicarbonate-carbonic acid system (H2CO3 and HCO3-),
b. Phosphate system (H2PO4--:HPO4--)
c. Protein system

(b) Henderson-Hasselbalch equation for weak acidic buffer systems

\[
\text{Ka} = \frac{[\text{H}^+] \times [\text{A}^-]}{[\text{HA}]}
\]

\[
\log \text{Ka} = \log [\text{H}^+] + \log \frac{[\text{A}^-]}{[\text{HA}]}
\]

\[
-\log \text{Ka} = -\log [\text{H}^+] - \log \frac{[\text{A}^-]}{[\text{HA}]}
\]

\[
p\text{Ka} = \text{pH} - \log \frac{[\text{A}^-]}{[\text{HA}]}
\]

\[
\text{pH} = p\text{Ka} + \log \frac{[\text{A}^-]}{[\text{HA}]}
\]