What you should remember from the last lecture

- **Acids** and **Bases**, and the pKₐ’s of some common organic compounds. You should be able to calculate Kₑq for a simple acid-base reaction, given the pKₐ’s involved.
- **Nucleophiles** and **Electrophiles**
- The mechanism of **Markovnikov** addition of H-X to an alkene;
- The mechanism of **electrophilic aromatic substitution**.

![Chemical structure](image)
How might these be made *in vivo*?

**Phenylalanine**

**Tyrosine**

**Tryptophan**

Powerful Lewis acidic conditions are NOT COMPATIBLE with wet (aqueous) conditions.
The aromatic core is built around the substituents.

Pyruvic acid (pyruvate) → Phosphoenolpyruvate → Erythrose-4-phosphate → Erythrose → Shikimic Acid
The aromatic core is built around the substituents

Shikimic Acid

Chorismate

Prephenate
What you should do before the next lecture

Finish reading Chapter 19 and do as many problems as you can.
Maleic Acid

\[ \text{pK}_a(1) = 2 \]
\[ \text{pK}_a(2) = 6 \]

Fumaric Acid

\[ \text{pK}_a(1) = 3 \]
\[ \text{pK}_a(2) = 4 \]

Why is the first ionization (proton loss) more favorable in maleic acid? Why is the second ionization more favorable in fumaric acid?
What you should remember from the last lecture

**Carboxylic Acids** – You should know the structure and the typical pK\(_a\) of this common functional group.

**Preparation of Acids** - Oxidation of alcohols (Cr(VI) reagents) or benzylic C-H’s (KMnO\(_4\)).

**Substituent Effects** – You should understand how different groups nearby (electron-donating and electron-withdrawing groups) will affect the pK\(_a\) of a carboxylic acid.

**Other Acids** – You should be familiar with common acids that are not carboxylic acids. Ammonium ions, sulfur acids, and phosphoric acids are common acids throughout biology.
How do you explain this?

Why is the first ionization (proton loss) more favorable in maleic acid? Why is the second ionization more favorable in fumaric acid?

**Fumaric Acid**
- \( pK_a(1) = 3 \)
- \( pK_a(2) = 4 \)

**Maleic Acid**
- \( pK_a(1) = 2 \)
- \( pK_a(2) = 6 \)
How do you explain this?
What you should remember from the last lecture

• **Carbonyl Groups**
  • Electrophilic at the carbonyl carbon
  • Somewhat basic at the carbonyl oxygen
  • Protons on the $\alpha$-carbon are acidic ($pK_a \sim 20$)

• **Addition reactions:** nucleophiles add to ketones and aldehydes

• **Addition-Elimination reactions:** nucleophiles add to acid chlorides, esters, and amides to form a tetrahedral intermediate which then eliminates a leaving group.
What you should do before the next lecture

- Finish reading Chapter 20. Skip 20.6
- Be able to draw the mechanism and the products of **addition reactions** and **addition-elimination** reactions involving carbonyl groups;
- Understand how the **rate** of addition-elimination reactions depends upon the leaving group present;
- Be able to identify a nucleophile that has added to a carbonyl;
- Understand the **selectivity** of NaBH₄ and LiAlH₄ toward different carbonyl groups;
- Understand the preparation and reactivity of **Grignard** reagents and other carbon anions reagents
Let’s play ‘SPOT THE NUCLEOPHILE’!

“H−” was the nucleophile
Carbonyl Reductions

1. NaBH₄
2. H₂O, HCl

1. NaBH₄
2. H₂O, HCl

1. NaBH₄
2. H₂O, HCl

1. LiAlH₄
2. H₂O, HCl

No Reaction

OH

OH
Carbonyl Reductions

1. LiAlH₄
2. H₂O, HCl

1. NaBH₄
2. H₂O, HCl
Carbonyl Reductions

1. LiAlH₄
2. H₂O, HCl

1. NaBH₄
2. H₂O, HCl

1. LiAlH₄
2. H₂O, HCl
What you should remember from the last lecture

The reduction of carbonyl-containing functional groups with $\text{NaBH}_4$ and $\text{LiAlH}_4$

- Aldehydes $\rightarrow$ primary alcohols (with either reagent)
- Ketones $\rightarrow$ secondary alcohols (with either reagent)
- Acids $\rightarrow$ primary alcohols (with LAH)
- Esters $\rightarrow$ primary alcohols (carbonyl side) and alcohols (with LAH)
- Amides $\rightarrow$ amines (with LAH)

The stereochemistry of reduction

- Happens from both sides of carbonyl group.
What you should do before the next lecture

**Finish reading Chapter 20.** Do the suggested problems. *Please* look for the common patterns of reactivity and understand how each reagent supplies a particular nucleophile.

**Begin reading Chapter 21.** Please notice that this chapter is an extension of Chapter 20. The same common themes prevail.
Carbonyl Reductions

1. LiAlH₄
   2. H₂O, HCl

1. LiAlH₄
   2. H₂O, HCl

1. NaBH₄
   2. H₂O, HCl

H₂, Pd/C
What reagents are needed?

1. LiAlH₄
2. H₂O, HCl

(LAH would also work)
What reagents are needed?

1. "CH$_3^-$"
2. H$_3$O$^+$

1. NaBH$_4$
2. H$_2$O, HCl
What is the product?
What you should remember from the last lecture

Hydride reducing agents, specifically NaBH₄ and LAH, but also DIBAL. You should know the functional groups that these reagents will reduce (and which they don’t).

Carbon nucleophiles, specifically

- Grignard reagents (RMgBr) and alkyl lithium reagents (RLi) add to carbon carbons.
- Dialkyl cuprates (R₂CuLi) and add to enones (α,β-unsaturated ketones) in a 1,4 manner.
Review **nucleophiles**, **nucleophilic addition to carbonyls**, and the **reduction of ketones**.

Understand the mechanism and result of the **Wittig** reaction.

Understand the mechanism and result of the addition of amines to ketones/aldehydes to produce **imines** (Schiff bases) and **enamines**.
What is the product?
What is the product?

Watch out for elimination of a leaving group β to anion.
What you should remember from the last lecture

**Carbon nucleophiles**, specifically **dialkyl cuprates** ($R_2CuLi$)
These are prepared from Cu(I) and 2 eq. of RLi, and are much milder carbon nucleophiles than are Grignards or alkyl lithium reagents. Dialkyl cuprates add ONCE to acid chlorides (to give ketones) and add to enones ($\alpha,\beta$-unsaturated ketones) in a 1,4 manner

**Protecting Groups**, specifically the use of silyl ethers to protect alcohols and render them unreactive toward powerful bases like carbanions.

**Oxidation of alcohols** to make aldehydes, ketones, and carboxylic acids. **Ozonolysis** of alkenes.
What you should do before the next lecture

Read though 21. Understand the (reversible) formation of acetals.
Synthesis

\[ \text{AlCl}_3 + \text{CH}_3\text{Cl} \rightarrow \text{CH}_3\text{Cl} \]

\[ \text{Br}_2 + \text{hv} \rightarrow \text{Br} \]

\[ \text{Mg} + \text{MgBr} \]

\[ \text{CrO}_3 \]

\[ 1. \text{CHO} + \text{HCl, H}_2\text{O} \]

\[ 2. \text{HCl, H}_2\text{O} \]

\[ \text{BrMg} \]
Carbanions are strong bases, and cause E2 elimination (rather than ‘cross coupling’) with alkyl halides.
Skinning cats.....
And more ways.....
Other Electrophiles

\[
\begin{align*}
\text{MgBr} & \xrightarrow{1. \text{ CO}_2} \text{H}_3\text{O}^+ \\
\text{OH} & \xrightarrow{\text{HBr}} \text{Br} \xrightarrow{1. \text{ Mg}} \xrightarrow{2. \text{ CO}_2} \\
\end{align*}
\]
What you should remember from the last lecture

**Carbonyl group reactivity** – specifically that these are electrophilic at the carbonyl carbon (which you knew) and they are weakly acidic ($pK_a$ 20) at the $\alpha$-carbon. Anions at the $\alpha$-carbon are known as *enolate* anions, and are nucleophilic.

**The Wittig reaction** involves reaction of a phosphorous *ylide* with a ketone or aldehyde to form a new alkene, via a 4-membered ring intermediate. Mixtures of $E$ and $Z$ result (often more $Z$ than you might think).
A few notes on the Wittig reaction
Finish Reading Chapter 21. Be an **ace** with acetals and hemiacetals, and the mechanisms by which these form. Acetals and hemiacetals are central to the structure of carbohydrates (sugars) and polysaccharides (starch, glycogen, cellulose), as well cell-surface oligosaccharides.
Biperidin synthesis

1. Mg

2.

Biperidin
(an antispasmodic drug)
More practice.....

\[
\text{[Chemical structure images]}
\]
Some Practice

\[ \text{CH}_3\text{I} \xrightarrow{1. \text{Ph}_3\text{P}} \text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{H} \xrightarrow{2. \text{BuLi}} \text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{H} \]

\[ \text{Br} \xrightarrow{1. \text{Ph}_3\text{P}} \text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{H} \xrightarrow{2. \text{BuLi}} \text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{H} \]

\[ \text{same as} \]

\[ E \text{ and } Z \text{ (preference for } Z! \text{)} \]
Some Practice

1. Ph₃P
2. BuLi
3. ????
What you should do before the next lecture

Finish Reading Chapter 21. Be an **ace** with acetals and hemiacetals, and the mechanisms by which these form. Acetals and hemiacetals are central to the structure of carbohydrates (sugars) and polysaccharides (starch, glycogen, cellulose), as well cell-surface oligosaccharides.
What you should remember from the last lecture

The *reversible* addition of nucleophiles to carbonyls. Specifically, the addition of cyanide ion (formation of cyanohydrins) and the addition of primary amines to form **imines** and the addition of secondary amines to produce **enamines**.

The mechanism of acid-catalyzed reactions. These proceed by $H^+$ on, (something happens), $H^+$ off (or a variation on this theme.)
What you should remember from the past.....

Acid-catalyzed dehydration of alcohols
What you should remember from the past.....

Formation of a *hydrazone*, the first step in the Wolff-Kishner reduction.
Carbohydrates

Glucose

(α-pyranose form)

(β-pyranose form)
What you should remember from the last lecture

The *reversible* addition of amines and alcohols to aldehydes and ketones:

Acetals, hemiacetals,

\[
\begin{align*}
\text{ketone} & \quad \text{hydrate} & \quad \text{hemiacetal} & \quad \text{acetal} \\
\end{align*}
\]
Carbohydrates

\[
\xrightarrow{\text{dry CH}_3\text{OH}} \]
\[ \alpha\text{-methylglucoside} \]
\[ \beta\text{-methylglucoside} \]
Carbohydrates

Sucrose

Lactose
Notes on the upcoming exam

- Bring photo ID. **This is required.**
- Be in your seat before 12:00.
- Be sure that you devote to each problem an appropriate amount of time. The exam is 100 points and you have 50 minutes. You can afford to spend ~ 5 minutes on each 10 point problem.
- Tomorrow night – Get to bed at a decent hour. Studying all night is usually counterproductive. Get a solid 8 hours of sleep.
- Wednesday AM – have a good breakfast and have a snack before the exam (if not lunch).
- **Answer the question – Don’t just restate it.**
Material covered on Exam 2

Everything from class or reading through through the end of Chapter 21. No material from Chapter 22.

Emphasis will be on recent material (since Exam 1), but you are responsible for all older material (back to general chemistry).

Remember – There is more chemistry than what is in the book. There is more in the book than we can cover in lecture. There is more in the lecture than we can put on an exam...
Write a viable, stepwise mechanism

Advice: Take it slowly. One step at a time. Lone pairs, resonance forms are often extremely helpful.
How does this happen?

All oxygens can be (and will be) protonated, but only the protonation of one site leads to products. Protonation of the other site leads to a dead end. **It’s all reversible and it’s one big equilibrium!**
What reagents are needed here?

\[
\begin{align*}
\text{H}_3\text{N} & \quad \text{O} \\
\text{O} & \quad \text{H}_2 \\
\text{H}_2\text{O} & \quad 1. \text{LiAlH}_4 \\
\text{L} & \quad \text{Al} \\
\text{H}_4 & \quad 2. \text{HCl}, \text{H}_2\text{O} \\
\text{H}_2 & \quad \text{Pd/C} \\
\text{Pd} & \quad \text{C} \\
\text{NaBH}_4 & \quad \text{NaBH}_4 \\
\text{OH} & \quad \text{OH}
\end{align*}
\]
What you should remember from the last lecture

**Acetals and hemiacetals**, including their presence in mono-saccharides (simple sugars) and in di- (and poly) saccharides, such as sucrose and starch.

**Reagents, reactions, and selectivity.** Oxidations, reductions, Grignards, organolithiums, lithium dialkylcuprates, Wittig reagents, amines, cyanide ion, and many others.
Carbohydrates

α-methylglucoside

β-methylglucoside

Dry CH₃OH
Polysaccharides

Starch

Cellulose
Oligosaccharides

- Fructose
- Glucose
- Galactose

**Raffinose**

- Fructose
- Glucose
- Galactose

- Glucose
- Galactose

**Stachyose**

- Fructose
- Glucose
- Galactose
What reagents are needed here?

1. CH₃OH, H⁺
2. LiAlH₄
3. HCl, H₂O

via

1. LiAlH₄
2. HCl, H₂O

NaBH₄

via

CH₃O

OCH₃

O

via

H
Mannose is reduced by NaBH₄, yet there is no C=O group in mannose. How does this happen?

Mannose is a hemiacetal, in equilibrium with the aldehyde form. Reduction is irreversible.
Write a viable, stepwise mechanism
Write a viable, stepwise mechanism
What reagents are needed here?

\[
\text{Ph} \xrightarrow{\text{Cl, } \text{AlCl}_3} \text{PhCOCH}_2\text{CH}_2\text{CH}_2\text{CH}_3 \xrightarrow{\text{TsOH (cat)}} \text{PhNCH}_2\text{CH}_2\text{CH}_2\text{CH}_3
\]
How would this be made?

From benzene and reagents of 5 carbons or less
How would this be made?

\[
\text{CH}_2\text{OH} \xrightarrow{\text{HBr or PBr}_3} \text{CH}_2\text{Br}
\] 

\[
\text{CO}_2\text{H} \xrightarrow{\text{Br}_2, h\nu} \text{CH}_3
\]
How would this be made?

苯环

CH₃Cl  

AlCl₃  

CH₃

Br₂, hν

CH₂Br

PPh₃

BuLi

PPh₃

O

酮

CH⁻
How would this be made?

1. LiAlH₄
2. H₂O, HCl

1. CH₃Cl
2. H₂O, HCl

1. MgBr
2. H₂O, HCl

PCC
And finally....
Seating is assigned, so each person should be in their assigned seat. Seat Assignments are posted in the glass case outside the top of the room.

Once the exam starts, you will not be allowed to leave until you are done (i.e. use the bathroom before the exam starts).

Write your name and student number on the exam cover, but do not open the exam until the class has been instructed to open them.

No one can leave until 12:20 PM, and no one can enter after 12:20 PM.

Before you begin this exam:  
First: You are allowed to have a simple model set at your seat. Please put away all other materials.  
Second: Place your student identification on your desk. A proctor will come around to check everyone’s ID.  
Third: Read through the entire exam. Your goal, as always, is to score as many points as possible. Do not waste time on problems that you can’t do if there are others that look easy. Fourth: READ EACH QUESTION CAREFULLY. Be sure you answer the question that is asked. Fifth: This exam must be turned in by 12:50 AM SHARP. There will be no extensions, so budget your time carefully.