Synthesis of Ketones and Aldehydes

1. $\text{Ph}-\text{OH} \xrightarrow{\text{PCC}} \text{Ph} \text{CHO}$

2. $\text{Ph} \xrightarrow{\text{H}_2\text{CrO}_4} \text{Ph} \text{CO}$

3. $\text{Ph} \xrightarrow{1. \text{BH}_3\cdot\text{THF}} \text{Ph} \text{OH} \xrightarrow{\text{PCC}} \text{Ph} \text{CO}$

4. $\text{Ph} \xrightarrow{\text{H}_2\text{O}, \text{H}^+} \text{Ph} \xrightarrow{\text{H}_2\text{CrO}_4} \text{Ph} \text{CO}$

5. $\text{Ph} \xrightarrow{1. \text{O}_3} \text{Ph} \xrightarrow{2. \text{Me}_2\text{S}} \text{Ph} \text{CO} + \text{O}_2$

6. $\text{PhCHO} \xrightarrow{1. \text{RMgBr}} \text{PhCOH} \xrightarrow{\text{H}^+} \text{PhCOR}$

7. $\text{PhCOR} \xrightarrow{1. \text{LiAlH}_4} \text{PhCHOH} \xrightarrow{\text{PCC}} \text{PhCHO}$

8. $\text{RBr} \xrightarrow{\text{NaOH}} \text{ROH} \xrightarrow{\text{PCC}} \text{RCHO}$

9. $\text{Br} \xrightarrow{\text{NaOH}} \text{OH} \xrightarrow{\text{H}_2\text{CrO}_4} \text{CO}$

10. $\text{Ph-CC=H} \xrightarrow{\text{Hg}^{2+}, \text{H}_2\text{O}, \text{H}_2\text{SO}_4} \xrightarrow{\text{MECH}} \text{Ph} \xrightarrow{\text{H}^+, \text{H}_2\text{O}} \text{PhCO}$

11. $\text{Ph-CC=H} \xrightarrow{1. (\text{Si})_2\text{BH}} \xrightarrow{2. \text{NaOH}, \text{H}_2\text{O}_2} \text{PhCHO}$
Chem 342 Jasperse Ch. 19 Reactions. Aldehydes and Ketones

12. PhCOOH → 1. 2 RLi → [PhCOOLi] → 2. H+, H2O → [PhCOR] → acid → tetrahedral dianion → tetrahedral "hydrate" → PhCOR → ketone

13. PhCOCl + R2CuLi → PhCOR → ketone

14. H2 + RCOCl + AlCl3 (from the aryl group's perspective)
   RCOCl + Ar-H, AlCl3 (from the acyl group's perspective)


16. PhBr + 1. KCN → PhCN + 2. RMgBr → Nitrile Intermediate (after step 1) → PhCOR
Reactions of Ketones and Aldehydes

19

\[
\begin{align*}
\text{aldehyde or ketone} & \xrightarrow{1. \text{RMgBr}} \text{anion intermediate} \xrightarrow{2. \text{H}^+} \text{Protonate} \xrightarrow{\text{OH}} \\
R' & \quad R
\end{align*}
\]

**Anionic**

19.7
17.5

20

\[
\begin{align*}
\text{aldehyde or ketone} & \xrightarrow{\text{NaBH}_4} \text{anion intermediate} \xrightarrow{\text{Protonate}} \xrightarrow{\text{OH}} \\
R' & \quad R
\end{align*}
\]

**Anionic**

19.7, 17.4

21

\[
\begin{align*}
\text{aldehyde or ketone} & \xrightleftharpoons{\text{KCN, HCN}} \text{anion intermediate} \xrightarrow{\text{Protonate}} \xrightarrow{\text{OH}} \\
R' & \quad R
\end{align*}
\]

**Anionic**

19.6

22

\[
\begin{align*}
\text{aldehyde or ketone} & \xrightleftharpoons{\text{H}_2\text{O, OH}^-} \text{tetrahedral hydrate} \xrightarrow{\text{OH}} \xrightarrow{\text{hydrates} are present only as transient equilibrium species. They never form to 100% and are never isolable. Always in equilibrium their aldehyde or ketone.} \\
R' & \quad R
\end{align*}
\]

**Anionic**

19.5

23

\[
\begin{align*}
\text{aldehyde or ketone} & \xrightleftharpoons{\text{H}_2\text{O, H}^+} \text{tetrahedral hydrate} \xrightarrow{\text{OH}} \xrightarrow{\text{hydrates} are present only as transient equilibrium species. They never form to 100% and are never isolable. Always in equilibrium with their aldehyde or ketone.} \\
R' & \quad R
\end{align*}
\]

**Cationic**
Cationic


Notes:
- Reactions are reversible
- The “hemiacetal” is an intermediate, and can never be isolated
- The acetal can be isolated.
- Equilibrium considerations (LeChatelier’s principle) apply. When water is plentiful, things go to the left. When water is scarce or removed, and alcohol is abundant, things drive to the right.
- Use $\text{H}_2\text{O}/\text{H}^+$ to hydrolyze an acetal back to an aldehyde or ketone
- Use $\text{MeOH}/\text{H}^+$ to convert an aldehyde to an acetal
- Use $\text{HOCH}_2\text{CH}_2\text{OH}/\text{H}^+$ to convert a ketone to an acetal
- Aldehydes or ketones can be temporarily “protected” as their acetals, then later “deprotected” by hydrolysis

Cationic


Notes:
- “Z” can be a carbon, nitrogen, oxygen, or hydrogen atom/group.
- The “aminol” can’t be isolated, it’s only present at equilibrium.
- Equilibrium factors apply. Water drives to the carbonyl side; removal of water drives to the imine side.
No Mech Responsibility

“Tollens test” is a common chemical test for aldehydes. Ag⁺ undergoes redox reaction with aldehydes to produce shiny Ag metal, or a “silver mirror”.

\[
R'\overset{\text{H}_2\text{CrO}_4 \text{ or Ag}^+ \text{ etc.}}{\longrightarrow} R'\overset{\text{OH}^+}{\longrightarrow}
\]
**Ch. 19 Mechanisms**

**Some New Mechanisms Associated with the Syntheses of Aldehydes and Ketones**

10. Enol to Carbonyl, Acid Catalyzed

11. Enol to Carbonyl, Base Catalyzed

12. Acid-catalyzed elimination of a hydrate to a carbonyl

15. Nitrile to Ketone
Review: Several Pertinent Mechanistic Principles

1. **Recognize anionic mechanisms** (when a strong anion is involved)
   - In an anionic mechanism, a strong anion will drive the first step
   - In an anionic mechanism, intermediates should avoid positive charges
   - Recognize anionic species even when they are disguised by a cationic metal counterion.

2. **Recognize cationic mechanisms**
   - Recipes that involve acid will be cationic
   - In a cationic mechanism, the first step will routinely involve protonation
   - In a cationic mechanism, the last step will frequently involve deprotonation to return to neutral
   - Normally the main step or steps are sandwiched in between the protonation and deprotonation events

3. Focus on bonds made and broken
4. Draw in hydrogens on carbons whose bonding changes
5. Keep track of lone pairs on reacting centers (in your head if not on paper)
6. Always draw in formal charges where appropriate
7. Arrows show electron flow, from giver to receiver
8. A good mechanism illustrates not only where electrons go as bonds change, but also the timing of bond changes. Avoid drawing bond changes that occur at different times as if they occur in the same step, i.e. as if they were concerted.
Some Mechanisms Associated with the Reactions of Aldehydes and Ketones

19. \[ R\text{O} \rightarrow \text{RMgBr} \rightarrow R\text{OH} \]
   
   1. RMgBr
   2. $\text{H}_2\text{O}^+$

   Grignard Addition of a Carbanion

20. \[ R\text{O} \rightarrow \text{NaBH}_4, \text{ROH} \]

   Aldehyde or ketone or 1. LiAlH$_4$
   2. $\text{H}^+$

   Hydride addition.

21. \[ R\text{O} \rightarrow \text{HCN} \rightarrow \text{KCN} \rightarrow R\text{CN} \]

   HCN addition, anionic mech.

22. \[ R\text{O} \rightarrow \text{H}_2\text{O}, \text{OH}^- \rightarrow R\text{OH} \rightarrow R\text{O} \]

   Water addition, anionic mech.

22r. \[ \text{tetrahedral "hydrate"} \rightarrow \text{aldehyde or ketone} \rightarrow \text{tetrahedral "hydrate"} \]

   Deprotonate

23. \[ R\text{O} \rightarrow \text{H}_2\text{O}, \text{H}^+ \rightarrow R\text{OH} \rightarrow R\text{O} \]

   Water addition, cationic mech.

23r. \[ \text{tetrahedral "hydrate"} \rightarrow \text{aldehyde or ketone} \rightarrow \text{tetrahedral "hydrate"} \]

   Protonate, eliminate, deprotonate
Acetal formation

\[
\begin{align*}
\text{o} & \quad \text{OR} \\
\text{R'} & \quad \text{R'} \\
\text{R} & \quad \text{H} \\
\end{align*}
\]

Phase 1: Hemiacetal Formation (an addition reaction)

Phase 2: Hemiacetal to Acetal (a substitution reaction)

Acetal hydrolysis.

\[
\begin{align*}
\text{OH} & \quad \text{R'} \\
\text{R'} & \quad \text{OR} \\
\text{R} & \quad \text{OR} \\
\end{align*}
\]

Phase 1: Acetal to Hemiacetal (a substitution reaction)

Phase 2: Hemiacetal Collapse (an elimination reaction)
Imine Formation

\[
\begin{align*}
R' & \quad R \\
\text{aldehyde or ketone} & \quad \xrightarrow{\text{ZnH}_2, H^+} \quad R' \quad R \\
\text{imine} & \quad \xleftarrow{\text{protonate}} \quad \xrightarrow{\text{ADD}} \quad \xleftarrow{\text{deprotonate}} \\
\end{align*}
\]

Phase 1:
Aminol Formation
(an addition reaction)

Phase 2:
Aminol to Imine
(an elimination reaction)

Imine Hydrolysis

\[
\begin{align*}
R' & \quad R \\
\text{imine} & \quad \xrightarrow{\text{H}_2\text{O}, H^+} \quad \xleftarrow{\text{protonate}} \quad \xrightarrow{\text{ADD}} \quad \xleftarrow{\text{deprotonate}} \\
\text{aldehyde or ketone} & \quad \xleftarrow{\text{protonate}} \quad \xrightarrow{\text{eliminate}} \quad \xleftarrow{\text{deprotonate}} \\
\end{align*}
\]

Phase 1:
Aminol Formation
(an addition reaction)

Phase 2:
Aminol to Carbonyl
(an elimination reaction)
Classification of Mechanisms Associated With Ketone/Aldehyde Reactions.
- There may seem to be a dizzying number of mechanisms this chapter. But all of them simplify into some combination of acid- or base-catalyzed addition reaction, elimination reaction and/or substitution reaction.
- To predict what product forms that can be isolated, you will need to know when an addition is all that happens, and when an addition is followed by elimination or substitution.
- Many reactions are reversible, and are controlled by equilibrium principles, so you ought to be able to go in either direction.
- The sequencing of many of the mechanistic steps is dependent on whether you are under acidic (cationic) conditions or basic (anionic) conditions.

ADDICTION REACTIONS.

19
1. MeMgBr
2. H₃O⁺
Grignard Addition of a Carbanion

20
1. LiAlH₄
2. H₃O⁺
Hydride addition.

21
+ HCN
KCN
HCN addition, anionic mech.

22
+ H₂O
Hydrate
Water addition, anionic mech.

23
+ H₂O
Hydrate
Water addition, cationic mech.

24
+ MeOH
H₃O⁺
Alcohol addition, cationic mech.

25
+ MeNH₂
H₃O⁺
Amine addition, cationic mech.

25r
Imine
Water addition to imine, cationic mech.
### Elimination Reactions

<table>
<thead>
<tr>
<th>Reaction</th>
<th>Structure</th>
<th>Conditions</th>
<th>Products</th>
</tr>
</thead>
<tbody>
<tr>
<td>22r</td>
<td><img src="image" alt="22r Structure" /></td>
<td>$\text{H}_2\text{O}, \text{OH}^-$</td>
<td>aldehyde or ketone</td>
</tr>
<tr>
<td>23r</td>
<td><img src="image" alt="23r Structure" /></td>
<td>$\text{H}_2\text{O}, \text{H}^+$</td>
<td>aldehyde or ketone</td>
</tr>
<tr>
<td>24r</td>
<td><img src="image" alt="24r Structure" /></td>
<td>$\text{H}_2\text{O}, \text{H}^+$</td>
<td>aldehyde or ketone</td>
</tr>
<tr>
<td>25r</td>
<td><img src="image" alt="25r Structure" /></td>
<td>$\text{H}_2\text{O}, \text{H}^+$</td>
<td>aldehyde or ketone</td>
</tr>
<tr>
<td>25b</td>
<td><img src="image" alt="25b Structure" /></td>
<td>$\text{H}_2\text{O}, \text{H}^+$</td>
<td>imine</td>
</tr>
</tbody>
</table>

### Substitution Reactions

<table>
<thead>
<tr>
<th>Reaction</th>
<th>Structure</th>
<th>Conditions</th>
<th>Products</th>
</tr>
</thead>
<tbody>
<tr>
<td>24b</td>
<td><img src="image" alt="24b Structure" /></td>
<td>$\text{ROH}, \text{H}^+$</td>
<td>acetal</td>
</tr>
<tr>
<td>24r</td>
<td><img src="image" alt="24r Structure" /></td>
<td>$\text{HOH}, \text{H}^+$</td>
<td>hemiacetal</td>
</tr>
</tbody>
</table>
A. Nomenclature of Aldehydes and Ketones (Section 19.1)

1. Aldehydes:
   a. IUPAC: Alkanal

   ![Aldehyde structures]

   • Note: carbonyl takes precedence over alcohols (hydroxy), aromatics, alkenes, halides.
   • Aldehyde carbon is always #1 (don’t forget to count that carbon!)

   b. Aldehydes are often written as RCHO

   CH₃CHO          PhCHO

c. Common Names: (Memorize)

   ![Common names structures]

2. Ketones:
   a. IUPAC: x-alkanone

   ![Ketone structures]

   Need number, remember to number!!

   b. Common Names: (Memorize)

   ![Ketone structures]

   Acetone
   Acetophenone
   "Acet"
3. Carboxyls as Substituents (needed when there are higher priority functional groups present such as carboxylic acids...): alkanoyl

\[
\text{\begin{center}
\begin{array}{c}
\text{CO}_2\text{H} \\
\text{O} \\
\text{H} \\
\end{array}
\end{center}
\]

Common Names:

formyl

acetyl

B. General Review of Basic Nomenclature Principles

1. **Core name versus Substituents.** Which part of the molecule can be included in the core name, and which parts need to be treated as substituents?

2. **Ranking of Functional Group Priority.**
   - when 2 or more functional groups are present, the priority functional group is included in the core name, and the core numbering is based on the priority group
   - Many common names incorporate two functional groups (benzoic acid, phenol, etc.)

\[
\text{\begin{center}
\begin{array}{ccc}
\text{O} & \text{O} & \text{OH} \\
\text{H} & \text{C} & \text{NH}_2 \\
\end{array}
\end{center}
\]

Families: Acids, Ketones, Esters, Aldehydes

Core Name: Alkanoic acids, Alkanal, x-Alkanol, x-alkanamine, x-Alkenone

Substituent: Alkanoyl, Hydroxy, Amino, Phenyl

3. **Remember Descriptors**
   - Position of functional groups
   - Position of substituents
   - Stereochemical descriptors (cis/trans, E/Z, R/S)

4. **Punctuation**
   - Hyphenate numbers and stereochemical descriptors
   - Parenthesize (R) and (S)
   - Do not put any spaces for molecular-style names
   - Do put spaces for ionic style names

Ionic style:

\[
\begin{array}{c}
\text{NaCl:} \\
\text{PhCO}_2\text{H:} \\
\text{PhCO}_2\text{CH}_3
\end{array}
\]
C. **Properties of Carbonyls**

\[ \text{C} \overset{\delta-}{\overset{\text{O}}{\overset{\delta+}{\text{C}}}} \]

- Strongly polar
- \( \text{Sp}^2 \), flat, \( \sim 120^\circ \) angles
- Can H-bond water (impacting water solubility)
- But cannot H-bond self (impacting boiling point)

For molecules of similar weight:
1. **Boiling Point**: Alcohols (H-bonding) \( \gg \gg \) ketones (polar) > ethers (less polar) > alkanes (nonpolar)
   - Large difference between alcohols and ketones because of H-bonding
2. **Water solubility**: Alcohols > ketones > ethers \( \gg \gg \) alkanes (nonpolar)
   - The difference between alcohols and ketones is much smaller, since both can H-bond to water’s hydrogens

Many Ketones and Aldehydes have Famous, Nice Smells
- Vanilla, almond extract, cinnamon, spearmint, pistachio, butter, camphor, etc.

**Synthesis of Ketones/Aldehydes: Review Routes, Handout Reactions 1-9 (Sections 18.7 and earlier book sections)**

**From Alcohols**

1. \[ \text{HO}-\overset{\text{PCC}}{\overset{\text{C}}{\text{C}}} \]

2. \[ \text{OH} \overset{\text{H}_2\text{CrO}_4}{\rightarrow} \]

**From Alkenes via Alcohols or Oxidative Cleavage**

3. \[ \text{1. BH}_3\cdot\text{THF} \]
   - \[ \text{2. NaOH, H}_2\text{O}_2 \rightarrow \]

4. \[ \rightarrow \]

5. \[ \text{1. O}_3 \]
   - \[ \text{2. Me}_2\text{S} \rightarrow \]
From Carbonyl via Alcohols

6

\[ \text{O} \]

\[ \text{CH}_3 \]

7

\[ \text{O} \]

\[ \text{CH}_3 \]

From Halides via Alcohols

8

\[ \text{Br} \]

9

\[ \text{Br} \]

From Alkynes

10

\[ \text{Ph} \rightleftharpoons \text{C} \rightleftharpoons \text{H} \]

\[ \text{Hg}^{2+}, \text{H}_2\text{O} \]

\[ \text{H}_2\text{SO}_4 \]

Markovnikov Addition

\[ \text{OH} \]

\[ \text{Ph} \]

"enol"

\[ \text{H}^+, \text{H}_2\text{O} \]

MECH Ketone

Two Phases:

1. The first phase is analogous to oxymercuration of an alkene
   a. It involves Hg$^{2+}$ and water
   b. H-OH adds across the π-bond
   c. Markovnikov addition: OH adds to the more substituted end of alkyne
   d. NaBH$_4$ is actually not required

2. Phase 2: The “enol” produced in the first phase is unstable and rapidly converts to the carbonyl
   • Phase 2: Mechanism Responsible.
Mechanism: \((\text{Acid-Catalyzed enol} \rightarrow \text{carbonyl})\)

\[
\begin{align*}
\text{Ph} & \quad \equiv \quad \text{H}^+ \quad \text{H}_2\text{O} \\
\rightarrow & \quad \text{Ph} \\
\text{"enol"} & \quad \rightarrow \\
\text{Ketone} & \quad \text{OH, H}_2\text{O}
\end{align*}
\]

Two Phases:
1. The first phase is analogous to hydroboration of an alkene
   a. H-OH adds across the \( \pi \)-bond
   b. It involves a borane
   c. Anti-Markovnikov addition: OH adds to the less substituted end of alkyne
   d. \((\text{Sia})_2\text{BH} \sim \text{BH}_3\cdot\text{THF}, \) but is much bulkier in order to ensure high anti-
      Markovnikov orientation and to ensure that it stop after one addition and
      leaves the second \( \pi \)-bond untouched. \((\text{BH}_3 \) works but is less selective)

2. Phase 2: The “enol” produced in the first phase is unstable and rapidly converts to the
   carbonyl
   * Phase 2: Mechanism Responsible.

Mechanism: \((\text{Base-Catalyzed enol} \rightarrow \text{carbonyl})\)

\[
\begin{align*}
\text{Ph} & \quad \equiv \quad \text{H}_2\text{O} \\
\rightarrow & \quad \text{Ph} \\
\text{"enol"} & \quad \rightarrow \\
\text{Aldehyde} & \quad \text{OH, H}_2\text{O}
\end{align*}
\]
a. \[ \text{Hg}^{2+}, \text{H}_2\text{O} \quad \text{H}_2\text{SO}_4 \]

b. \[ \text{Hg}^{2+}, \text{H}_2\text{O} \quad \text{H}_2\text{SO}_4 \]

c. 1. (Si)\textsubscript{2}BH  
   2. NaOH, H\textsubscript{2}O\textsubscript{2}

d.  

Remember:
1. Enols quickly convert to carbonyls
2. Remember these two reactions mainly as Markovnikov or anti-Markovnikov addition of H-OH addition to alkyne

From Carboxylic Acids (not in book)

<table>
<thead>
<tr>
<th>Reaction</th>
<th>Structure</th>
<th>Mechanism</th>
<th>Product</th>
</tr>
</thead>
<tbody>
<tr>
<td>12</td>
<td>\text{Ph} \text{C} = \text{O} \quad \text{acid}</td>
<td>1. 2 R\text{Li} \quad 2. \text{H}^+, \text{H}_2\text{O}</td>
<td>\text{Ph} \text{C} = \text{O} \quad \text{carboxylate anion}</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Reaction</th>
<th>Structure</th>
<th>Mechanism</th>
<th>Product</th>
</tr>
</thead>
<tbody>
<tr>
<td>a.</td>
<td>\text{O} \text{C} = \text{O} \quad \text{acid}</td>
<td>1. 2 Me\text{Li} \quad 2. \text{H}^+, \text{H}_2\text{O}</td>
<td></td>
</tr>
<tr>
<td>b.</td>
<td>\text{O} \text{C} = \text{O} \quad \text{acid}</td>
<td>1. 2 Ph\text{Li} \quad 2. \text{H}^+, \text{H}_2\text{O}</td>
<td></td>
</tr>
<tr>
<td>c.</td>
<td>\text{O} \text{C} = \text{O} \quad \text{acid}</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Mechanism: Key new Mechanism Step is the **acid-catalyzed hydrolysis of the tetrahedral hydrate** to the ketone
- Tetrahedral anion is stable until acid/water is added
- Tetrahedral hydrate rapidly “dehydrates” to ketone

\[\text{Ph}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{OH} \rightarrow \text{Ph}_2\text{CH}_2\text{CH}_2\text{C} = \text{O}\]

**From Acid Chlorides**

- Reaction 13, mechanisms from test 1
- R₂CuLi is a special, mild carbanion equivalent. Some special properties enable it to stop at ketone. (RMgBr would not stop at ketone, but would add again to give 3° alcohol)

\[\begin{align*}
\text{PhCl} & \quad \text{R}_2\text{CuLi} \quad \text{Ph} \quad \text{Me}_2\text{CuLi} \\
13 & \quad \text{acid chloride} \quad \text{ketone} \quad \text{Me}_2\text{CuLi} \\
\text{O} & \quad \text{Ph} \quad \text{Cl} & \quad \text{Ph} \quad \text{R} \\
14 & \quad \text{acid chloride} \quad \text{Aromatic ketone} \quad \text{from the aryl group's perspective} \\
\text{H} & \quad \text{O} & \quad \text{O} & \quad \text{O} \\
\quad & \quad \text{AlCl}_3 & \quad \text{Ar-H, AlCl}_3 & \\
\quad & \quad \text{Ph} & \quad \text{R} & \quad \text{R} \\
\end{align*}\]
From Nitriles (Section 20.7)

15. \(\text{PhCN} \xrightarrow{1. \text{RMgBr}} \text{Ph}^+ \xrightarrow{2. \text{H}^+, \text{H}_2\text{O}} \text{Ph}^+ \xrightarrow{\text{MECH}} \text{PhR}\)

16. \(\text{PhBr} \xrightarrow{1. \text{KCN}} \text{PhCN} \xrightarrow{2. \text{RMgBr}} \text{Ph}^+ \xrightarrow{3. \text{H}^+, \text{H}_2\text{O}} \text{PhR}\)

Mechanism: Acid-Catalyzed Hydrolysis of C=NH
Note: Many groups can “hydrolyze” to carbonyls
• A carbon with two heteroatoms attached, single-bonded or double-bonded
• A carbon with one heteroatom and one $\pi$-bond
• Often base or acid or some special acid assistant helps

F. General Reactivity of Ketones and Aldehydes: Addition Reactions (Section 19.4)

Key: Are reaction conditions anionic/basic or cationic/acidic (or perhaps buffered in between?)

1. **Anionic Conditions** (when a strong anion is involved)
   a. General principles review for strongly anionic/basic conditions apply
      1. In an anionic mechanism, a strong anion will drive the first step
      2. In an anionic mechanism, intermediates should avoid positive charges
      3. Recognize anionic species even when they are disguised by a cationic metal counterion.

   b. Anionic additions to ketones
      1. Strong nucleophile required ($R^-$, $H^-$, $HO^-$, …)
         • Intermediates have negative charge
      2. **Addition first, protonation second**
      3. Addition is normally irreversible
         • Addition is often strongly exothermic
         • The proton source is often added in a separate laboratory step, because often the anion and the proton are incompatible
2. **Cationic Conditions** (acid is involved)
   a. **General principles review for strongly anionic/basic conditions apply**
      - Recipes that involve acid will be cationic
      - In a cationic mechanism, the first step will routinely involve protonation
      - In a cationic mechanism, the last step will frequently involve deprotonation to return to neutral
      - Normally the main step or steps are sandwiched in between the protonation and deprotonation events

   ![Cationic Mechanism Diagram]

   b. **Cationic additions to ketones**
      1. Weak, neutral nucleophile involved (ROH, HOH...)
      2. Intermediates have positive charge
      3. **Protonation first, addition second**
         - Weak nucleophile is not strong enough to add to neutral carbonyl
         - Protonation activates the carbonyl as an electrophile
      4. A deprotonation step is routinely required following addition, to get back to neutral
      5. Addition is normally reversible
         - Nucleophile can come back off
         - Nucleophile is normally a reasonable leaving group

3. **Buffer Conditions** (both weak acid and weak base/nucleophile are present at same time)
   - RNH₂/H⁺, KCN/HCN...
   - Reversibility again applies
   - Whether addition comes before protonation, or protonation precedes addition depends on the exact case

4. **Anion Conditions**: Nucleophilic addition versus deprotonation
   - Sometimes an anion will function as a base and remove a proton rather than functioning as a nucleophile and adding to the carbonyl
   - Comparable to S_N2 versus E2 reactions
   - Anion size will again factor, with bulky bases more likely to deprotonate and smaller ones to add
   - Chapters 22+23 will deal with the deprotonation pathway, followed by nucleophilic attack on electrophiles
Addition of R⁻ (RMgBr) and H⁻ (NaBH₄, LiAlH₄) (Review, Section 17.5, 19.9)

1. RMgBr
2. H₃O⁺

Grignard Addition of a Carbanion

Add

Protonate

1º, 2º or 3º?

Hydride addition.

Note: For RMgBr and LiAlH₄, the basicity of the reagent is too strong to permit a proton source to be present at the same time. Thus the proton source must be added in a subsequent laboratory step. The NaBH₄ is weaker, both as a nucleophile but also as a base.

Draw products from the following reactions.

1. PhMgBr
2. H₃O⁺

2. MgBr
1. H₃O⁺

3. LiAlH₄
1. H₃O⁺

4. Br
1. Mg
2. Ph⁺CH₃
3. H₃O⁺

5. Br

6. Draw the mechanism for reaction 1 above.
**Addition of HCN to make “Cyanohydrins” (Section 19.6): Anionic Mechanism**

\[ \text{RC} \text{O} + \text{HCN} \rightarrow \text{RC} \text{N} \text{OH} \]

HCN addition, anionic mech.

**Mechanistic notes**
1. Addition first, protonation second
2. \( \text{CN}^- \) is a good nucleophile, HCN a decent acid
3. KCN/HCN represents a **buffer situation**: weak base/weak acid, not obvious which dominates. But in this case the anion does and it proceeds via anionic mechanism.
4. \( \text{CN}^- \) is actually used as a catalyst: after the HCN donates proton, the \( \text{CN}^- \) is regenerated
5. In reality, KCN/HCl or KCN/H\(_2\)SO\(_4\) is often used
   - Easier to put together and handle
6. Reaction is reversible
   - Strongly favors product cyanohydrin, unless a strongly hindered ketone is used

**Draw products**

a. [Chemical structure]

b. [Chemical structure]

**Key Application (Not test responsible)**

\[ \text{R'}\text{R}^+ \text{CN} \rightarrow \text{R'}\text{R}^+ \text{CO}_2\text{H} \]

- No Mech Responsibility
- Unique access to 2-hydroxyacids
- Indirect provides the equivalent (“Synthon”) for a \( \text{CO}_2\text{H} \) anion

**Draw Products**

1. KCN, HCN
2. \( \text{H}_2\text{O}, \text{H}^+ \)
Reversible Addition of H₂O (H-OH) to Make Hydrates: Addition (and elimination) under Acidic or Basic Conditions (Section 19.5).

- Know mechanism under either base or acid
- Know mechanism for the reverse direction (hydrate to carbonyl) as well

\[
\text{Aldehyde or ketone} \stackrel{\text{H₂O, } \text{H}^+ \text{ or } \text{OH}^-}{\rightleftharpoons} \text{"Hydrate"}
\]

**Anionic**

**Cationic**

**Notes:**
1. True equilibrium.
2. Super unfavorable for ketones, moderately unfavorable for aldehydes
   - Ketone is stabilized more by the two alkyl donors
   - Ketone hydrate is destabilized more by steric effects

<table>
<thead>
<tr>
<th>Reaction</th>
<th>K</th>
<th>Reaction</th>
<th>K</th>
<th>Reaction</th>
<th>K</th>
</tr>
</thead>
<tbody>
<tr>
<td>( \text{CH₃CHO} + \text{H₂O} \quad \rightleftharpoons \quad \text{CH₃COH} )</td>
<td>0.002</td>
<td>( \text{CH₃COH} + \text{H₂O} \quad \rightleftharpoons \quad \text{CH₃COO}^- )</td>
<td>0.7</td>
<td>( \text{i-PrCHO} + \text{H₂O} \quad \rightleftharpoons \quad \text{i-PrCOH} )</td>
<td>0.1</td>
</tr>
</tbody>
</table>

3. Hydrates can never be isolated, because as soon as you try to take them out of water, the drives back to the carbonyl side (LeChatelier’s Principle)
4. While the hydrate is not present in high concentration, it is often a crucial intermediate in a variety of biological processes
   - We’ve also seen its importance in the oxidation of 1º alcohols to carboxylic acids using \( \text{H₂CrO₄} \) in water.

Draw the **ANIONIC addition** mechanism

\[
\text{H₂O, } \text{H}^+ \quad \rightleftharpoons \quad \text{OH}^- \quad \rightleftharpoons \quad \text{OH}
\]

Draw the **CATIONIC addition** mechanism

\[
\text{H₂O, } \text{H}^+ \quad \rightleftharpoons \quad \text{OH}^- \quad \rightleftharpoons \quad \text{OH}
\]
Hydrate Hydrolysis (Elimination of Water from Hydrate to Generate Carbonyl)

Draw the **ANIONIC elimination** mechanism

- Deprotonation precedes elimination
- E2-like

\[
\begin{align*}
\text{OH} & \xrightarrow{\ \text{H}_2\text{O}, \text{OH}^-\ } \text{O} \\
\text{OH} & \quad \quad \text{O} \\
\text{H}_2\text{O} & \quad \quad \text{OH}
\end{align*}
\]

Draw the **CATIONIC elimination** mechanism

- Elimination precedes deprotonation
- E1-like

\[
\begin{align*}
\text{OH} & \xrightarrow{\ \text{H}_2\text{O}, \text{H}^+\ } \text{O} \\
\text{OH} & \quad \quad \text{O} \\
\text{H}_2\text{O} & \quad \quad \text{OH}
\end{align*}
\]


Also know the reverses process, substitution/elimination under acid conditions

\[
\begin{align*}
\text{R'} & \quad \quad \text{R} & \xrightarrow{\ \text{ROH}, \text{H}^+\ } \text{H}_2\text{O}, \text{H}^+ & \xrightarrow{\ \text{ROH}, \text{H}^+\ } \text{H}_2\text{O}, \text{H}^+ & \xrightarrow{\ \text{ROH}, \text{H}^+\ } \text{H}_2\text{O}, \text{H}^+ & \xrightarrow{\ \text{ROH}, \text{H}^+\ } \text{H}_2\text{O}, \text{H}^+
\end{align*}
\]

Cationic

**Mech Forward:** Protonation-Addition-deprotonation (hemiacetal) Protonation-elimination-addition-deprotonation (acetal). Weak nucleophile, cationic mechanism. Reversible.

**Mech Reverse:** Protonation-Elimination-Addition-deprotonation. (hemiacetal) protonation-elimination-deprotonation (aldehyde or ketone). Reversible.

Notes:
- Reactions are reversible
- The “hemiacetal” is an intermediate, and can never be isolated
- The acetal can be isolated. (It is stable in absence of water)
- Equilibrium considerations (LeChatelier’s principle) apply. When water is plentiful, things go to the left. When water is scarce or removed, and alcohol is abundant, things drive to the right.
- Use H₂O/H⁺ to hydrolyze an acetal back to an aldehyde or ketone
- Use MeOH/H⁺ to convert an aldehyde to an acetal
- Use HOCH₂CH₂OH/H⁺ to convert a ketone to an acetal
- Aldehydes or ketones can be temporarily “protected” as their acetals, then later “deprotected” by hydrolysis
Notes:
1. While the acetal can be isolated, the hemiacetal cannot
2. Four reactions, each with their own mechanism:
   a. Carbonyl to hemiacetal = acid-catalyzed addition reaction.
   b. Hemiacetal to acetal = acid-catalyzed substitution reaction (S\textsubscript{N}1-type)
   c. Acetal back to hemiacetal = acid-catalyzed substitution reaction (S\textsubscript{N}1-type)
   d. Hemiacetal back to carbonyl = acid-catalyzed elimination (E1-type)

Draw the mechanism

\[
\begin{array}{c}
  \text{MeOH, } H^+ \\
  \text{H} & \text{O} & \text{Me} \\
  \text{H} & \text{O} & \text{Me} \\
  \text{H} & \text{O} & \text{Me}
\end{array}
\]

Draw the mechanism

\[
\begin{array}{c}
  \text{HOH, } H^+ \\
  \text{H} & \text{O} & \text{Me} \\
  \text{H} & \text{O} & \text{Me} \\
  \text{H} & \text{O} & \text{Me}
\end{array}
\]

We have now seen three major acid-catalyzed reaction types in this chapter
1. Additions (protonate-\texttt{add}-deprotonate)
2. Eliminations (protonate-\texttt{eliminate}-deprotonate)
3. Substitutions (protonate-\texttt{eliminate-add}-deprotonate)

Notice that a protonation/deprotonation sandwiches the key step(s) in each of them
Draw the products for the following reactions

1. \[
\text{H}_2\text{O} \quad \text{MeOH, H}^+ \quad \text{Cyclic Acetal}
\]

2. \[
\text{HO\text{-}OH} \quad \text{H}^+ \quad \text{Cyclic Acetal}
\]

**Key Synthetic Notes:**

1. **Ethylene glycol** works well for making acetals from aldehydes or ketones. Use *ethylene glycol for KETONES.*
   a. Once the first oxygen adds, the second oxygen is always close by and ready to add
   b. The cyclic acetal is more stable; even if one oxygen comes off, it can come right back on.
   c. The cyclic acetal formation is actually more favorable energetically (enthalpy)
   d. The cyclic acetal also has entropy advantages (entropy)

2. Methanol is simpler for making acetals from aldehydes, but often has problems for ketones. Use *methanol for KETONES*

3. **Selective protection:**
   a. Methanol can be used to protect an aldehyde, while a ketone or ester will go untouched.
   b. Ethylene glycol can be used to protect a ketone, while an ester will be untouched.

**Equilibrium and Acetals**

1. Normally favors the carbonyl, especially for ketones
2. Push to the acetal side by using excess alcohol
3. Push to carbonyl side by using excess water
4. **Equilibrium improves greatly for cyclic acetals.**
5. **Hemiacetals have a favorable equilibrium if and only if a 5- or 6-ring hemiacetal can form.** (This is central to carbohydrate/sugar chemistry.)
Hemiacetals, mixed acetals, and Sugar/Carbohydrate Chemistry (interest, not test)
**Acetals as Protecting Groups in Synthesis**

1. Reactivity: Aldehydes > Ketones >> Esters
   a. Aldehydes versus Ketones Why:
      - Sterics, ketones are more cluttered and additions make things worse
      - Electronics, ketones are more stable with two electron-donating groups
   b. Ketones versus Esters Why:
      - Electronics, the conjugation stabilizes esters

2. **Selective protection:**
   a. Methanol can be used to protect an aldehyde, while a ketone or ester will go untouched.
   b. Ethylene glycol can be used to protect a ketone, while an ester will be untouched.

![Chem 342 Jasperse Ch. 19 Reactions. Aldehydes and Ketones](image)

**Addition of H₂N-Z Reagents (Sections 19.8)**

Cationic


Notes:
- “Z” can be a carbon, nitrogen, oxygen, or hydrogen atom/group.
- The “aminol” can’t be isolated, it’s only present at equilibrium.
- Equilibrium factors apply. Water drives to the carbonyl side; removal of water drives to the imine side.
**Chem 342 Jasperse Ch. 19 Reactions. Aldehydes and Ketones**

1. \( \text{PhCHO} + \text{MeNH}_2 \xrightarrow{\text{H}^+} \) \text{“Imine”}  
   \( (Z = \text{alkyl}) \)

2. \( \text{PhCHO} + \text{H}_2\text{NNH}_2 \xrightarrow{\text{H}^+} \) Hydrazone  
   \( (Z = \text{Nitrogen}) \)

3. \( \text{PhCHO} + \text{H}_2\text{NOH} \xrightarrow{\text{H}^+} \) Oxime  
   \( (Z = \text{Oxygen}) \)

4. \( \text{PhCHO} + \text{2,4-}
dinitrophenylhydrazine (2,4-DNPH) \xrightarrow{\text{H}^+} \) hydrazine  
   2,4-DNP derivative

**Notes:**
1. C=N species can sometimes be hydrolyzed back to carbonyls by \( \text{H}_2\text{O/}H^+ \)
2. “Imines” are frequent biology intermediates
3. 2,4-DNP derivatives are easily made and usually crystalline
   a. reaction of an unknown with DNPH to make a solid DNP-derivative is proof of aldehyde or ketone
   b. The melting point of DNP-derivatives permits identification
Draw the mechanism for the following:

\[
\begin{align*}
\text{Ph} & \quad \text{H} \\
\text{O} & \quad \text{H}_2\text{NMe}, \text{H}^+ & \quad \text{OH} & \quad \text{-H}_2\text{O}, \text{H}^+ \\
\text{Ph} & \quad \text{NHMe} & \quad \text{Ph} & \quad \text{NMe} \\
\text{H} & \quad \text{aminol} & \quad & \text{H} \\
& \quad \text{Phase 1: Aminol Formation (an addition reaction)} & \quad & \text{Phase 2: Aminol to Imine (an elimination reaction)}
\end{align*}
\]

Notes:
1. All steps are reversible, under equilibrium control
2. I’m writing these as cationic, acid-catalyzed steps
   a. Conditions are actually buffered;
   b. \(1 \text{RNH}_2 + 0.5 \text{H}^+ \rightarrow 0.5 \text{RNH}_2 + 0.5 \text{RNH}_3^+ \rightarrow \) a buffer system.
   c. In some cases, nucleophilic addition addition by the neutral but reactive amines (to give oxyanions) may actually precede protonation.
Oxidation of Aldehydes (Section 19.3)

\[
\begin{align*}
    R'\text{CH}_2\text{O} &\xrightleftharpoons[R']\text{H}_2\text{CrO}_4 \text{ or } \text{Ag}^+ \text{ etc.} \xrightarrow[\text{H}^+, \text{H}_2\text{O}]{26} R'\text{COH} \\
\end{align*}
\]

No Mech Responsibility

“Tollens test” is a common chemical test for aldehydes. \(\text{Ag}^+\) undergoes redox reaction with aldehydes to produce shiny \(\text{Ag}\) metal, or a “silver mirror”.

Review: Chromic Acid Oxidation proceeds in water via hydrate

\[
\begin{align*}
    \text{PhCHO} &\xrightarrow[H_2\text{CrO}_4, \text{H}^+, \text{H}_2\text{O}]{\text{PhCHO}} \xrightarrow[H_2\text{CrO}_4, \text{H}^+, \text{H}_2\text{O}]{\text{PhCOOH}} \\
\end{align*}
\]

New: \(\text{Ag}^+\) salts oxidize aldehydes in presence of alcohols, ketones

**Tollens reagent:** \(\text{Ag(NH}_3)_2^+\) Chemical test for **aldehydes**
- A silver mirror forms

---

Chemical Tests

<table>
<thead>
<tr>
<th>Class</th>
<th>DNP</th>
<th>Tollens</th>
<th>(\text{H}_2\text{CrO}_4)</th>
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</thead>
<tbody>
<tr>
<td>Aldehydes</td>
<td>![O]</td>
<td>![Tollens]</td>
<td>![H2CrO4]</td>
</tr>
<tr>
<td>Ketones</td>
<td>![Keto]</td>
<td>![Tollens]</td>
<td>![H2CrO4]</td>
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<tr>
<td>Alcohols</td>
<td>![Alcohol]</td>
<td>![Tollens]</td>
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