Aldehydes & Ketones

Chapter 16
In this and several following chapters, we study the physical and chemical properties of classes of compounds containing the carbonyl group, C=O

- aldehydes and ketones (Chapter 16)
- carboxylic acids (Chapter 17)
- acid halides, acid anhydrides, esters, amides (Chapter 18)
- enolate anions (Chapter 19)
The Carbonyl Group

- the carbonyl group consists of one sigma bond formed by the overlap of $sp^2$ hybrid orbitals and one pi bond formed by the overlap of parallel $2p$ orbitals
- pi bonding and pi antibonding MOs for formaldehyde
Structure

- the functional group of an aldehyde is a carbonyl group bonded to a H atom and a carbon atom
- the functional group of a ketone is a carbonyl group bonded to two carbon atoms

\[
\begin{align*}
\text{Methanal (Formaldehyde)} & : \quad \text{O} \quad \text{HCH} \\
\text{Ethanal (Acetaldehyde)} & : \quad \text{O} \quad \text{CH}_3 \text{CH} \\
\text{Propanone (Acetone)} & : \quad \text{O} \quad \text{CH}_3 \text{CCH}_3
\end{align*}
\]
Nomenclature

◆ IUPAC names:
  • the parent chain is the longest chain that contains the functional group
  • for an aldehyde, change the suffix from \(-e\) to \(-al\)
  • for an unsaturated aldehyde, change the infix from \(-an-\) to \(-en-\); the location of the suffix determines the numbering pattern
  • for a cyclic molecule in which \(-CHO\) is bonded to the ring, add the suffix \(-carbaldehyde\)
Nomenclature: Aldehydes

- 3-Methylbutanal
- 2-Propenal (Acrolein)
- (2E)-3,7-Dimethyl-2,6-octadienal (Geranial)
- Cyclopentane-carbaldehyde
- trans-4-Hydroxycyclohexanecarbaldehyde
- Benzaldehyde
- trans-3-Phenyl-2-propenal (Cinnamaldehyde)

- the IUPAC retains the common names benzaldehyde and cinnamaldehyde, as well formaldehyde and acetaldehyde
Nomenclature: Ketones

- **IUPAC names**
  - the parent alkane is the longest chain that contains the carbonyl group
  - indicate the ketone by changing the suffix -e to -one
  - number the chain to give C=O the smaller number
  - the IUPAC retains the common names acetone, acetophenone, and benzophenone

```
\begin{align*}
\text{Acetone} & \quad \text{Acetophenone} & \quad \text{Benzophenone} & \quad \text{1-Phenyl-1-pentanone} \\
\text{Propanone} & \quad \text{(Acetone)} & \quad & \\
\end{align*}
```
# Order of Precedence

- For compounds that contain more than one functional group indicated by a suffix

<table>
<thead>
<tr>
<th>Functional Group</th>
<th>Suffix if higher priority</th>
<th>Prefix if lower priority</th>
<th>Example when the functional group has a lower priority</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carboxyl</td>
<td>-oic acid</td>
<td></td>
<td><a href="#">Chemical structure</a> 3-Oxo propanoic acid</td>
</tr>
<tr>
<td>Aldehyde</td>
<td>-al</td>
<td>oxo-</td>
<td>3-Oxo propanoic acid</td>
</tr>
<tr>
<td>Ketone</td>
<td>-one</td>
<td>oxo-</td>
<td>3-Oxo butanoic acid</td>
</tr>
<tr>
<td>Alcohol</td>
<td>-ol</td>
<td>hydroxy-</td>
<td>4-Hydroxy butanoic acid</td>
</tr>
<tr>
<td>Amino</td>
<td>-amine</td>
<td>amino-</td>
<td>3-Amino butanoic acid</td>
</tr>
<tr>
<td>Sulfhydryl</td>
<td>-thiol</td>
<td>mercapto</td>
<td>2-Mercapto ethanol</td>
</tr>
</tbody>
</table>
Common Names

- for an aldehyde, the common name is derived from the common name of the corresponding carboxylic acid
- for a ketone, name the two alkyl or aryl groups bonded to the carbonyl carbon and add the word ketone
Physical Properties

- Oxygen is more electronegative than carbon (3.5 vs 2.5) and, therefore, a C=O group is polar

  ![Polarity of a carbonyl group](image)

  ![More important contributing structure](image)

- Aldehydes and ketones are polar compounds and interact in the pure state by dipole-dipole interaction
- They have higher boiling points and are more soluble in water than nonpolar compounds of comparable molecular weight
One of the most common reaction themes of a carbonyl group is **addition of a nucleophile** to form a tetrahedral carbonyl addition compound.
A second common theme is reaction with a proton or other Lewis acid to form a resonance-stabilized cation.

- Protonation increases the electron deficiency of the carbonyl carbon and makes it more reactive toward nucleophiles.

\[
\begin{align*}
\text{R-} & \text{C=O:} + \text{H-B} \xrightarrow{\text{fast}} \text{B}^{-} + \text{R-} \text{C=O-H} \\
\text{B}^{-} + \text{H-Nu} + & \xrightarrow{\text{slow}} \text{Nu-C-O-H} + \text{H-B}
\end{align*}
\]

Tetrahedral carbonyl addition compound.
Reaction Themes

- often the tetrahedral product of addition to a carbonyl is a new chiral center
- if none of the starting materials is chiral and the reaction takes place in an achiral environment, then enantiomers will be formed as a racemic mixture
Addition of carbon nucleophiles is one of the most important types of nucleophilic additions to a C=O group

- a new carbon-carbon bond is formed in the process
- we study addition of these carbon nucleophiles

\[ RMgX \quad RLi \quad RC\equiv C:\quad \text{Cyanide ion} \]

A Grignard reagent
An organolithium reagent
An alkyne anion
Grignard Reagents

- Given the difference in electronegativity between carbon and magnesium (2.5 - 1.3), the C-Mg bond is polar covalent, with Cδ- and Mgδ+
  - in its reactions, a Grignard reagent behaves as a carbanion

- **Carbanion**: an anion in which carbon has an unshared pair of electrons and bears a negative charge
  - a carbanion is a good nucleophile and adds to the carbonyl group of aldehydes and ketones
Grignard Reagents

- addition of a Grignard reagent to formaldehyde followed by $\text{H}_3\text{O}^+$ gives a $1^\circ$ alcohol

$$\text{CH}_3\text{CH}_2\cdot\text{MgBr} + \text{H-C-H} \rightarrow \text{ether} \rightarrow \text{Formaldehyde}$$

$$\begin{align*}
\text{CH}_3\text{CH}_2\cdot\text{MgBr} & \rightarrow \text{CH}_3\text{CH}_2\cdot\text{Mg}^+ \\
\text{[MgBr]}^- & \rightarrow \text{HCl} \rightarrow \text{CH}_3\text{CH}_2\cdot\text{CH}_2\cdot\text{OH} \\
\text{A magnesium alkoxide} & \rightarrow \text{H}_2\text{O} \rightarrow \text{1-Propanol (a 1$^\circ$ alcohol)} \\
\text{Mg}^2+ &
\end{align*}$$
Grignard Reagents

- addition to any other RCHO gives a 2° alcohol

\[ \text{MgBr} + \text{RCHO} \rightarrow \text{ether} \]

Acetaldehyde (an aldehyde)

\[ \text{A magnesiu} \text{m alkoxide} \quad \overset{\text{HCl}}{\rightarrow} \quad \overset{\text{H}_2\text{O}}{\rightarrow} \quad \text{1-Cyclohexylethanol} \]

(a 2° alcohol; racemic)

+ Mg\(^{2+}\)
Grignard Reagents

- addition to a ketone gives a 3° alcohol

Ph-MgBr + Acetone (a ketone) → ether

Ph-[MgBr]⁺ + H₂O → 2-Phenyl-2-propanol (a 3° alcohol) + Mg²⁺
Problem: 2-phenyl-2-butanol can be synthesized by three different combinations of a Grignard reagent and a ketone. Show each combination.

Problem 1
Organolithium compounds are generally more reactive in C=O addition reactions than RMgX, and typically give higher yields.
Salts of Terminal Alkynes

Addition of an alkyne anion followed by H$_3$O$^+$ gives an $\alpha$-acetylenic alcohol

\[
\text{HC≡C}^- \text{Na}^+ + \text{Cyclohexanone} \rightarrow \text{HC≡C}_2\text{O}^- \text{Na}^+ + \text{HCl} \rightarrow \text{HC≡C}_2\text{OH}
\]

Sodium acetylide + Cyclohexanone → A sodium alkoxide → 1-Ethynylocyclohexanol
Salts of Terminal Alkynes

1. (sia)$_2$ BH
2. $\text{H}_2\text{O}_2$, NaOH

$\xrightarrow{\text{H}_2\text{O}}$

$\text{H}_2\text{SO}_4$, HgSO$_4$

An $\alpha$-hydroxyketone

A $\beta$-hydroxyaldehyde
HCN adds to the C=O group of an aldehyde or ketone to give a cyanohydrin

**Cyanohydrin:** a molecule containing an -OH group and a -CN group bonded to the same carbon

\[
\begin{align*}
\text{CH}_3\text{CH} & + \text{HC}≡\text{N} \\
\rightarrow & \text{CH}_3\text{C}-\text{C}≡\text{N} \\
\text{OH} & \text{H}
\end{align*}
\]

2-Hydroxypropanenitrile
(Acetaldehyde cyanohydrin)
**Addition of HCN**

- **Mechanism of cyanohydrin formation**
  - **Step 1:** nucleophilic addition of cyanide to the carbonyl carbon

\[
\begin{array}{c}
\text{H}_3\text{C} \\
\text{C} = \text{O} \\
\text{H}_3\text{C}
\end{array}
+ \begin{array}{c}
\text{H}_3\text{C} \\
\text{C} = \text{N}^-
\end{array}
\xrightarrow{\text{step 1}}
\begin{array}{c}
\text{H}_3\text{C} \\
\text{C} = \text{O}^- \\
\text{H}_3\text{C}
\end{array}
\]

- **Step 2:** proton transfer from HCN gives the cyanohydrin and regenerates cyanide ion

\[
\begin{array}{c}
\text{H}_3\text{C} \\
\text{C} = \text{O}^- \\
\text{H}_3\text{C}
\end{array} + \begin{array}{c}
\text{H}^- \\
\text{C} = \text{N}^-
\end{array}
\xrightarrow{\text{step 2}}
\begin{array}{c}
\text{H}_3\text{C} \\
\text{C} = \text{O}^- - \text{H} \\
\text{H}_3\text{C}
\end{array}
+ \begin{array}{c}
\text{H}_3\text{C} \\
\text{C} = \text{N}^-
\end{array}
\]
Cyanohydrins

The value of cyanohydrins

- acid-catalyzed dehydration of alcohol gives an alkene

\[
\text{OH} \quad \begin{array}{c}
\text{CH}_3 \text{CHC}≡\text{N} \\
\text{catalyst}
\end{array} \rightarrow \text{CH}_2=\text{CHC}≡\text{N} + \text{H}_2\text{O}
\]

2-Hydroxypropanenitrile
(Acetaldehyde cyanohydrin)

Propenenitrile
(Acrylonitrile)

- catalytic reduction of the cyano group gives a 1° amine

\[
\begin{array}{c}
\text{OH} \\
\text{CHC}≡\text{N} + 2\text{H}_2 \quad \text{Ni}
\end{array} \rightarrow \begin{array}{c}
\text{OH} \\
\text{CHCH}_2\text{NH}_2
\end{array}
\]

Benzaldehyde cyanohydrin
(racemic)

2-Amino-1-phenylethanol
(racemic)
The Wittig reaction is a very versatile synthetic method for the synthesis of alkenes from aldehydes and ketones.
Phosphonium Ylides

Phosphonium ylides are formed in two steps:

- **Step 1:** nucleophilic displacement of iodine by triphenylphosphine
  
  \[
  \text{Ph}_3\text{P}^- + \text{CH}_3\text{I} \xrightarrow{\text{SN2}} \text{Ph}_3\text{P-CH}_3^+ \text{I}^- \\
  \text{Triphenylphosphine} \quad \text{Methyltriphenylphosphonium iodide} \\
  \text{(an alkyltriphenylphosphine salt)}
  \]

- **Step 2:** treatment of the phosphonium salt with a very strong base, most commonly BuLi, NaH, or NaNH$_2$
  
  \[
  \text{CH}_3\text{CH}_2\text{CH}_2\text{CH}_2^- \text{Li}^+ + \text{H-CH}_2^-\text{PPh}_3^+ \text{I}^- \xrightarrow{} \text{CH}_3\text{CH}_2\text{CH}_2\text{CH}_3 + \text{H-CH}_2^-\text{PPh}_3^- + \text{LiI} \\
  \text{Butyllithium} \quad \text{Butane} \quad \text{A phosphonium ylide}
  \]
Phosphonium ylides react with the C=O group of an aldehyde or ketone to give an alkene

- **Step 1:** nucleophilic addition of the ylide to the electrophilic carbonyl carbon

\[
\begin{align*}
\text{Ph}_3\text{P} = \text{CH}_2 & \quad \text{Ph}_3\text{P} = \text{CH}_2 \\
\end{align*}
\]

- **Step 2:** decomposition of the oxaphosphatane

\[
\begin{align*}
\text{Ph}_3\text{P} = \text{CH}_2 & \quad \text{Ph}_3\text{P} = \text{CH}_2 \\
\end{align*}
\]
Wittig Reaction

• Examples:

\[
\text{Acetone} + \text{Ph}_3\text{P} \rightarrow \text{2-Methyl-2-heptene} + \text{Ph}_3\text{P}=\text{O}
\]

\[
\text{Ph}_{\text{H}}\text{Ph} + \text{Ph}_3\text{P} \rightarrow \text{(Z)-1-Phenyl-2-butene} (87\%) + \text{(E)-1-Phenyl-2-butene} (13\%) + \text{Ph}_3\text{P}=\text{O}
\]

\[
\text{Ph}_{\text{H}}\text{Ph} + \text{Ph}_3\text{P} \rightarrow \text{Ethyl (E)-4-phenyl-2-butenoate} \text{ (only the E isomer is formed)} + \text{Ph}_3\text{P}=\text{O}
\]
• some Wittig reactions are $Z$ selective, others are $E$ selective

• Wittig reagents with an anion-stabilizing group, such as a carbonyl group, adjacent to the negative charge are generally $E$ selective

$\text{Resonance contributing structures for an ylide stabilized by an adjacent carbonyl group}$

• Wittig reagents without an anion-stabilizing group are generally $Z$ selective
Wittig Reaction

- Horner-Emmons-Wadsworth modification
  - uses a phosphonoester

\[
\begin{align*}
\text{(MeO)}_3\text{P} : & \quad \text{Trimethylphosphite} \\
\text{Br-CH}_2\text{-C-OEt} & \quad \text{an } \alpha\text{-bromoester} \\
\text{Br-CH}_2\text{-C-R} & \quad \text{an } \alpha\text{-bromoketone} \\
\rightarrow & \quad \text{(MeO)}_2\text{P-CH}_2\text{-C-OEt} + \text{MeBr} \\
& \quad \text{An } \alpha\text{-phosphonoester} \\
\rightarrow & \quad \text{(MeO)}_2\text{P-CH}_2\text{-C-R} + \text{MeBr} \\
& \quad \text{An } \alpha\text{-phosphonoketone}
\end{align*}
\]
Wittig Reaction

- phosphonoesters are prepared by successive $S_N 2$ reactions

\[
\begin{align*}
(\text{MeO})_3\text{P}^+ &+ \text{CH}_2\text{-C-OEt} \xrightarrow{S_N 2} \\
\text{MeBr} &+ \text{CH}_3\text{-O-P-CH}_2\text{-C-OEt} \xrightarrow{S_N 2} (\text{MeO})_2\text{P-CH}_2\text{-C-OEt} + \text{MeBr}
\end{align*}
\]

An $\alpha$-phosphonoester
Wittig Reaction

- treatment of a phosphonoester with a strong base followed by an aldehyde or ketone gives an alkene
- a particular value of using a phosphonoester-stabilized anion is that they are almost exclusively \( E \) selective

Problem 3