Chapter 18
Ketones and Aldehydes

Carbonyl Compounds

<table>
<thead>
<tr>
<th>Class</th>
<th>General Formula</th>
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<th>General Formula</th>
</tr>
</thead>
<tbody>
<tr>
<td>ketones</td>
<td>R—C—R’</td>
<td>aldehydes</td>
<td>R—C—H</td>
</tr>
<tr>
<td>carboxylic acids</td>
<td>R—C—OH</td>
<td>acid chlorides</td>
<td>R—C—Cl</td>
</tr>
<tr>
<td>esters</td>
<td>R—C—O—R’</td>
<td>amides</td>
<td>R—C—NH₂</td>
</tr>
</tbody>
</table>

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Carbonyl Structure

- Carbon is $sp^2$ hybridized.
- C=O bond is shorter, stronger, and more polar than C=C bond in alkenes.

<table>
<thead>
<tr>
<th>Bond Type</th>
<th>Length</th>
<th>Energy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ketone C=O bond</td>
<td>1.23 Å</td>
<td>745 kJ/mol (178 kcal/mol)</td>
</tr>
<tr>
<td>Alkene C=C bond</td>
<td>1.34 Å</td>
<td>611 kJ/mol (146 kcal/mol)</td>
</tr>
</tbody>
</table>

IUPAC Names for Ketones

- Replace -e with -one. Indicate the position of the carbonyl with a number.
- Number the chain so that carbonyl carbon has the lowest number.
- For cyclic ketones the carbonyl carbon is assigned the number 1.
Examples

\[
\begin{align*}
\text{CH}_3\text{C}\text{H}_2\text{CH} & \text{CH}_3 \\
\text{CH}_3 & \\
\text{3-methyl-2-butanone} & \\
\text{3-methylbutan-2-one} & \\
\text{CH}_3\text{C}\text{H}_2\text{CH} & \text{CH}_2\text{OH} \\
\text{CH}_3 & \\
\text{4-hydroxy-3-methyl-2-butanone} & \\
\text{4-hydroxy-3-methylbutan-2-one} \\
\end{align*}
\]

3-bromocyclohexanone

Naming Aldehydes

- IUPAC: Replace \(-e\) with \(-al\).
- The aldehyde carbon is number 1.
- If \(-CHO\) is attached to a ring, use the suffix \(-carbaldehyde\).

=>
Examples

\[
\begin{align*}
\text{CH}_3 & \quad \text{O} \\
\text{CH}_3-\text{CH}_2-\text{CH}-\text{CH}_2-\text{C}=\text{H} \\
\text{3-methylpentanal}
\end{align*}
\]

2-cyclopentene-carbaldehyde

cyclopent-2-en-1-carbaldehyde

Name as Substituent

- On a molecule with a higher priority functional group, C=O is oxo- and -CHO is formyl.
- Aldehyde priority is higher than ketone.

\[
\begin{align*}
\text{CH}_3 & \quad \text{O} & \text{CH}_3 & \quad \text{O} \\
\text{CH}_3-\text{C}-\text{CH}-\text{CH}_2-\text{C}=\text{H} & & \text{COOH} & \text{CHO} \\
\text{3-methyl-4-oxopentanal} & & \text{3-formylbenzoic acid}
\end{align*}
\]
Common Names for Ketones

- Named as alkyl attachments to -C=O.
- Use Greek letters instead of numbers.

\[
\begin{align*}
\text{CH}_3\text{C} \equiv \text{CH}\text{CH}_3 &\quad \text{CH}_3\text{CH}_2\text{O} \equiv \text{CH}\text{CH}_3 \\
\text{methyl isopropyl ketone} &\quad \alpha\text{-bromoethyl isopropyl ketone}
\end{align*}
\]

Historical Common Names

- \text{CH}_3\text{C} \equiv \text{CH}\text{CH}_3 \quad \text{CH}_2=\text{CH}\text{CH}_3\text{O} \equiv \text{CH}_3 \\
\text{acetone} \quad \text{acetophenone}

\[
\begin{align*}
\text{CH}_3\text{C} \equiv \text{CH}\text{CH}_3 &\quad \text{CH}_2=\text{CH}\text{CH}_3\text{O} \equiv \text{CH}_3 \\
\text{benzophenone}
\end{align*}
\]
Aldehyde Common Names

- Use the common name of the acid.
- Drop -ic acid and add -aldehyde.
  - 1 C: formic acid, formaldehyde
  - 2 C’s: acetic acid, acetaldehyde
  - 3 C’s: propionic acid, propionaldehyde
  - 4 C’s: butyric acid, butyraldehyde.

Boiling Points

- More polar, so higher boiling point than comparable alkane or ether.
- Cannot H-bond to each other, so lower boiling point than comparable alcohol.
Solubility

- Good solvent for alcohols.
- Lone pair of electrons on oxygen of carbonyl can accept a hydrogen bond from O-H or N-H.
- Acetone and acetaldehyde are miscible in water.

IR Spectroscopy

- Very strong C=O stretch around 1710 cm\(^{-1}\).
- Conjugation lowers frequency.
- Ring strain raises frequency.
- Additional C-H stretch for aldehyde: two absorptions at 2710 cm\(^{-1}\) and 2810 cm\(^{-1}\).
Chapter 18: Aldehydes and Ketones

\[ \text{\(^1H NMR Spectroscopy}\]

\[ \text{\(^13C NMR Spectroscopy}\]

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Chapter 18: Aldehydes and Ketones

### MS for 2-Butanone

- **Radical Cation**: $m/z$ 72
- **Acylum Ion**: $m/z$ 43 (base peak)
- **Ethyl Radical**: loss of 29

### MS for Butyraldehyde

- **Radical Cation**: $m/z$ 72
- **Acylum Ion**: $m/z$ 57
- **Methyl Radical**: loss of 15

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For more information, refer to Slide 18-17

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For more information, refer to Slide 18-18
McLafferty Rearrangement

- Loss of alkene (even mass number)
- Must have $\gamma$-hydrogen

![McLafferty rearrangement of butyraldehyde](image)

UV Spectra, $\pi \rightarrow \pi^*$

- C=O conjugated with another double bond.
- Large molar absorptivities (> 5000)

![UV spectra examples](image)
UV Spectra, \( n \rightarrow \pi^* \)

- Small molar absorptivity.
- “Forbidden” transition occurs less frequently.

```
\begin{align*}
\pi^* & \quad \text{allowed} \\
\pi & \quad \text{nonbonding orbital}
\end{align*}
```

```
\begin{align*}
\text{"allowed" transition} & \quad \varepsilon \equiv 5000 - 200,000 \\
\text{"forbidden" transition} & \quad \varepsilon \equiv 10 - 200
\end{align*}
```

Synthesis Review

- Oxidation
  - \( 2^\circ \) alcohol + \( \text{Na}_2\text{Cr}_2\text{O}_7 \) → ketone
  - \( 1^\circ \) alcohol + PCC → aldehyde
- Ozonolysis of alkenes.

```
\begin{align*}
\text{R} & \quad \text{C} & \quad \text{C} & \quad \text{R}\,^\prime \\
\text{H} & \quad \text{C} & \quad \text{O} & \quad \text{R}\,^\prime \\
\text{H} & \quad \text{C} & \quad \text{O} & \quad \text{R}\,^\prime \\
\text{H} & \quad \text{C} & \quad \text{O} & \quad \text{R}\,^\prime
\end{align*}
```

\[ \begin{align*} \text{(1) O}_3 & \quad \text{R} \quad \text{C} \quad \text{O} \\
\text{(2) (CH}_3\text{)}_2\text{S} & \quad \text{R} \quad \text{C} \quad \text{O} \quad \text{R}\,^\prime \quad \text{O} \quad \text{C} \quad \text{R}\,^\prime \\
\text{R} & \quad \text{C} \quad \text{O} \quad \text{R}\,^\prime \quad \text{O} \quad \text{C} \quad \text{R}\,^\prime \\
\text{R} & \quad \text{C} \quad \text{O} \quad \text{R}\,^\prime \quad \text{O} \quad \text{C} \quad \text{R}\,^\prime
\end{align*} \]
Synthesis Review (2)

- Friedel-Crafts acylation
  - Acid chloride/AlCl₃ + benzene → ketone
  - CO + HCl + AlCl₃/CuCl + benzene → benzaldehyde (Gatterman-Koch)
- Hydration of terminal alkyne
  - Use HgSO₄, H₂SO₄, H₂O for methyl ketone
  - Use Sia₂BH followed by H₂O₂ in NaOH for aldehyde.

Synthesis Using 1,3-Dithiane

- Remove H⁺ with n-butyllithium.

\[
\begin{align*}
\text{1,3-dithiane, } pK_a = 32 & \quad \text{C}_6\text{H}_5\text{Li} \quad \text{dithiane anion} \quad \text{C}_4\text{H}_{10}^+ \\
\text{alkylating agent (primary alkyl halide)} & \quad \text{thioacetal} \quad \text{aldehyde}
\end{align*}
\]

- Alkylate with primary alkyl halide, then hydrolyze.
Ketones from 1,3-Dithiane

After the first alkylation, remove the second H⁺, react with another primary alkyl halide, then hydrolyze.

Ketones from Carboxylates

- Organolithium compounds attack the carbonyl and form a dianion.
- Neutralization with aqueous acid produces an unstable hydrate that loses water to form a ketone.
**Ketones from Nitriles**

- A Grignard or organolithium reagent attacks the nitrile carbon.
- The imine salt is then hydrolyzed to form a ketone.

```
CH₃CH₂MgBr + \left[ \begin{array}{c} \text{C} \\ \text{≡N} \end{array} \right] \rightarrow \left[ \begin{array}{c} \text{C} \\ \text{N} \end{array} \right] \xrightarrow{\text{ether}} \left[ \begin{array}{c} \text{C} \\ \text{N} \end{array} \right] \xrightarrow{\text{H₂O}⁺} \left[ \begin{array}{c} \text{O} \\ \text{C} \\ \text{CH}_₂\text{CH}_₃ \end{array} \right]
```

**Aldehydes from Acid Chlorides**

Use a mild reducing agent to prevent reduction to primary alcohol. Bulk of reagent helps also.

```
\text{CH₃CH₂CH₂COCl} \xrightarrow{\text{LiAlH(O-O-t-Bu)₃}} \text{CH₃CH₂CH₂CHO}
```

=>
Ketones from Acid Chlorides

Use lithium dialkylcuprate (R₂CuLi), formed by the reaction of 2 moles of R-Li with cuprous iodide.

\[
2 \text{CH}_3\text{CH}_2\text{CH}_2\text{Li} \xrightarrow{\text{CuI}} (\text{CH}_3\text{CH}_2\text{CH}_2)_2\text{CuLi}
\]

\[
(\text{CH}_3\text{CH}_2\text{CH}_2)_2\text{CuLi} + \text{CH}_3\text{CH}_2\text{C}=\text{OCl} \rightarrow \text{CH}_3\text{CH}_2\text{C}=\text{OCH}_2\text{CH}_2\text{CH}_3
\]

Nucleophilic Addition

- A strong nucleophile attacks the carbonyl carbon, forming an alkoxide ion that is then protonated.
- A weak nucleophile will attack a carbonyl if it has been protonated, thus increasing its reactivity.
- Aldehydes are more reactive than ketones.
Wittig Reaction

- Nucleophilic addition of phosphorus ylides.
- Product is alkene. C=O becomes C=C.

**The Wittig reaction**

\[
\begin{align*}
R' & \quad \text{R'} \quad \text{ketone or aldehyde} \\
\text{C=O} & \quad \text{R} \quad \text{R} \quad \text{Ph} \\
\text{H} & \quad \text{H} \quad \text{Ph} \\
\text{phosphorus ylide} & \quad \text{phosphorus ylide}
\end{align*}
\]

\[
\text{alkene} \quad \text{C=C} \quad \text{Ph}_3\text{P}=\text{O} \quad \Rightarrow
\]

Phosphorus Ylides

- Prepared from triphenylphosphine and an unhindered alkyl halide.
- Butyllithium then abstracts a hydrogen from the carbon attached to phosphorus.

\[
\begin{align*}
\text{Ph}_3\text{P;} & \quad + \quad \text{CH}_3\text{CH}_2\text{Br} \quad \Rightarrow \quad \text{Ph}_3\text{P}--\text{CH}_2\text{CH}_3 \quad \text{Br}^- \\
+ & \quad \text{Ph}_3\text{P}--\text{CH}_2\text{CH}_3 \quad \text{BuLi} \quad \Rightarrow \quad + \quad \text{Ph}_3\text{P}--\text{CHCH}_3 \quad \text{ylide} \quad \Rightarrow
\end{align*}
\]
Mechanism for Wittig

- The negative C on ylide attacks the positive C of carbonyl to form a betaine.
- Oxygen combines with phosphine to form the phosphine oxide.

Phosphonate Modification
Addition of Water

- In acid, water is the nucleophile.
- In base, hydroxide is the nucleophile.
- Aldehydes are more electrophilic since they have fewer e\textsuperscript{-}-donating alkyl groups.

\[
\begin{align*}
\text{HCHO} + \text{H}_2\text{O} & \rightleftharpoons \text{CH}_3\text{CHOH} \\
\text{CH}_3\text{C(OH)}\text{CH}_3 + \text{H}_2\text{O} & \rightleftharpoons \text{CH}_3\text{CH(OH)}\text{CH}_3
\end{align*}
\]

\[K = 2000 \quad \text{and} \quad K = 0.002\]

Addition of HCN (Cyanohydrins)

- HCN is highly toxic.
- Use NaCN or KCN in base to add cyanide, then protonate to add H.
- Reactivity formaldehyde > aldehydes > ketones >> bulky ketones.

\[
\begin{align*}
\text{CH}_3\text{CH}_2\text{C(OH)}\text{CH}_3 + \text{HCN} & \rightleftharpoons \text{CH}_3\text{CH}_2\text{C(OH)}\text{CN} \\
\end{align*}
\]

=>
Formation of Imines

- Nucleophilic addition of ammonia or primary amine, followed by elimination of water molecule.
- C=O becomes C=N-R

\[
\text{RNH}_2 + \text{H}_3\text{C} + \text{C}=\text{O} \rightarrow \text{R} + \text{N} + \text{C} = \text{N} + \text{CH}_3
\]

pH Dependence

- Loss of water is acid catalyzed, but acid destroys nucleophiles.
- \( \text{NH}_3 + \text{H}^+ \rightarrow \text{NH}_4^+ \) (not nucleophilic).
- Optimum pH is around 4.5.
Other Condensations

\[ \text{C} = \text{O} + \text{H}_2\text{N} \rightarrow \text{Z} \xrightarrow{\text{H}^+} \text{C} = \text{N} \rightarrow \text{Z} + \text{H}_2\text{O} \]

<table>
<thead>
<tr>
<th>Z in (Z \rightarrow \text{NH}_2)</th>
<th>Reagent</th>
<th>Product</th>
</tr>
</thead>
<tbody>
<tr>
<td>(\text{H})</td>
<td>(\text{H}_2\text{N} \rightarrow \text{H}) ammonia</td>
<td>(\text{C} = \text{N} \rightarrow \text{H}) an imine</td>
</tr>
<tr>
<td>(\text{R})</td>
<td>(\text{H}_2\text{N} \rightarrow \text{R}) primary amine</td>
<td>(\text{C} = \text{N} \rightarrow \text{R}) an imine (Schiff base)</td>
</tr>
<tr>
<td>(\text{OH})</td>
<td>(\text{H}_2\text{N} \rightarrow \text{OH}) hydroxylamine</td>
<td>(\text{C} = \text{N} \rightarrow \text{OH}) an oxime</td>
</tr>
<tr>
<td>(\text{NH}_2)</td>
<td>(\text{H}_2\text{N} \rightarrow \text{NH}_2) hydrazine</td>
<td>(\text{C} = \text{N} \rightarrow \text{NH}_2) a hydrazone</td>
</tr>
<tr>
<td>(\text{NHPH})</td>
<td>(\text{H}_2\text{N} \rightarrow \text{NHPH}) phenylhydrazine</td>
<td>(\text{C} = \text{N} \rightarrow \text{NHPH}) a phenylhydrazine</td>
</tr>
<tr>
<td>(\text{O})</td>
<td>(\text{H}_2\text{N} \rightarrow \text{HN} \rightarrow \text{C} \rightarrow \text{NH}_2) semicarbazide</td>
<td>(\text{C} = \text{N} \rightarrow \text{HN} \rightarrow \text{C} \rightarrow \text{NH}_2) a semicarbazide</td>
</tr>
</tbody>
</table>

Addition of Alcohol

\[ \text{RCH}_2\text{H} + 2 \text{R'} \rightarrow \text{OH} \xrightarrow{\text{H}^+} \text{R'OCH}_2\text{R'} + \text{H}_2\text{O} \]

\[ \text{RCR'} + 2 \text{R''} \rightarrow \text{OH} \xrightarrow{\text{H}^+} \text{R'OCH}_2\text{R''} + \text{H}_2\text{O} \]

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Mechanism

- Must be acid-catalyzed.
- Adding $\text{H}^+$ to carbonyl makes it more reactive with weak nucleophile, ROH.
- Hemiacetal forms first, then acid-catalyzed loss of water, then addition of second molecule of ROH forms acetal.
- All steps are reversible.

Mechanism for Hemiacetal

- Oxygen is protonated.
- Alcohol is the nucleophile.
- $\text{H}^+$ is removed.
Hemiacetal to Acetal

Cyclic Acetals

- Addition of a diol produces a cyclic acetal.
- Sugars commonly exist as acetals or hemiacetals.
Acetals as Protecting Groups

- Hydrolyze easily in acid, stable in base.
- Aldehydes more reactive than ketones.

\[
\begin{align*}
    \text{CH}_2\text{--CH}_2
\end{align*}
\]

Selectiv Reaction of Ketone

- React with strong nucleophile (base).
- Remove protective group.

\[
\begin{align*}
    \text{CH}_3\text{MgBr} & \rightarrow \text{CH}_3 \text{MgBr}^+ \rightarrow \text{CH}_3 \text{MgBr}^+ \\
    \text{MgBr} & \rightarrow \text{MgBr}^+ \rightarrow \text{MgBr}^+ \\
    \text{H}_3\text{O}^+ & \rightarrow \text{H}_3\text{O}^+ \rightarrow \text{H}_3\text{O}^+
\end{align*}
\]
Oxidation of Aldehydes

Easily oxidized to carboxylic acids.

\[
\begin{align*}
\text{R} - \text{C} = \text{H} & \quad \xrightarrow{\text{[O]}} \quad \text{R} - \text{C} \quad \text{(oxidizing agent)} \quad \text{O} \\
\text{CH}_3 - \text{CH} = \text{C} - \text{H} & \xrightarrow{\text{Na}_2\text{Cr}_2\text{O}_7, \text{dil } \text{H}_2\text{SO}_4} \quad \text{CH}_3 - \text{CH} = \text{C} - \text{OH} \\
\text{isobutyraldehyde} & \quad \text{isobutyric acid (90\%)}
\end{align*}
\]

\[
\begin{align*}
\text{R} - \text{C} = \text{H} & \quad \xrightarrow{\text{Ag}_2\text{O, THF/H}_2\text{O}} \quad \text{R} - \text{C} \quad \text{O} \\
\text{R} - \text{C} = \text{H} \quad & \quad \text{(97\%)}
\end{align*}
\]

Tollens Test

- Add ammonia solution to AgNO₃ solution until precipitate dissolves.
- Aldehyde reaction forms a silver mirror.
- Mild, basic way to make carboxylic acids.

\[
\begin{align*}
\text{R} - \text{C} = \text{H} + 2 \text{Ag(NH}_3)_2^+ + 3 \text{OH}^- & \xrightarrow{\text{H}_2\text{O}} \quad 2 \text{Ag} + \text{R} - \text{C} \quad \text{O}^- \\
& \quad + 4 \text{NH}_3 + 2 \text{H}_2\text{O}
\end{align*}
\]

=>
Reduction Reagents

- Sodium borohydride, NaBH₄, reduces C=O, but not C=C.
- Lithium aluminum hydride, LiAlH₄, much stronger, difficult to handle.
- Hydrogen gas with catalyst also reduces the C=C bond.

Catalytic Hydrogenation

- Widely used in industry.
- Raney nickel, finely divided Ni powder saturated with hydrogen gas.
- Pt and Rh also used as catalysts.
Deoxygenation

- Reduction of C=O to CH₂
- Two methods:
  - Clemmensen reduction if molecule is stable in hot acid.
  - Wolff-Kishner reduction if molecule is stable in very strong base.
Wolff-Kishler Reduction

- Form hydrazone, then heat with strong base like KOH or potassium t-butoxide.
- Use a high-boiling solvent: ethylene glycol, diethylene glycol, or DMSO.

\[
\begin{align*}
\text{CH}_2\text{C}=\text{H} & \xrightarrow{\text{H}_2\text{N}-\text{NH}_2} \text{CH}_2\text{C}=\text{H} \\
\text{KOH} \quad \text{heat} & \xrightarrow{} \text{CH}_2\text{CH}_3
\end{align*}
\]

End of Chapter 18

Homework: 40, 46, 47, 49, 51, 52, 56, 61, 62, 66, 68, 70, 74, 75