Organic Chemistry

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In this and several following chapters we study the physical and chemical properties of classes of compounds containing the carbonyl group, $\text{C}=\text{O}$

- aldehydes and ketones (Chapter 15)
- carboxylic acids (Chapter 16)
- acid halides, acid anhydrides, esters, amides (Chapter 17)
- enolate anions (Chapter 18)
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
The functional group of an aldehyde is a carbonyl group bonded to a H atom
- in methanal, it is bonded to two H atoms
- in all other aldehydes it is bonded to one H and one carbon atom

Methanal (formaldehyde)

Ethanal (acetaldehyde)
The functional group of a ketone is a carbonyl group bonded to two carbon atoms.

**CH₃-C-CH₃**  
Propanone (Acetone)

**Cyclohexanone**  

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Nomenclature-Aldehydes

- IUPAC names: select as the parent alkane the longest chain of carbon atoms that contains the carbonyl group
  - because the carbonyl group of the aldehyde must be on carbon 1, there is no need to give it a number

- For unsaturated aldehydes, show the presence of the C=C by changing the infix -an- to -en-
  - the location of the suffix determines the numbering pattern
15 Nomenclature-Aldehydes

Pentanal

3-Methylbutanal

2-Propenal (Acrolein)

(2E)-3,7-Dimethyl-2,6-octadienal (Geranial)
For cyclic molecules in which the -CHO group is attached to the ring, the name is derived by adding the suffix \textit{-carbaldehyde} to the name of the ring.

- 2,2-Dimethylcyclohexanecarbaldehyde
- 2-Cyclopentene-carbaldehyde
Nomenclature-Ketones

IUPAC names:

- select as the parent alkane the longest chain that contains the carbonyl group,
- indicate its presence by changing the suffix -e to -one, and
- number to give C=O the smaller number

<table>
<thead>
<tr>
<th>Structure</th>
<th>Name</th>
</tr>
</thead>
<tbody>
<tr>
<td>CH₃CCH₃</td>
<td>Propanone (Acetone)</td>
</tr>
<tr>
<td>CH₃CH₂CCH₂CHCH₃</td>
<td>5-Methyl-3-hexanone</td>
</tr>
<tr>
<td>CH₃</td>
<td>Bicyclo[2.2.1]-2-heptanone</td>
</tr>
</tbody>
</table>

5-Methyl-3-hexanone
The IUPAC system retains the names acetone, acetophenone, and benzophenone.
## 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 in Precedence</th>
<th>Prefix if Lower in Precedence</th>
</tr>
</thead>
<tbody>
<tr>
<td>-CO₂H</td>
<td>-oic acid</td>
<td></td>
</tr>
<tr>
<td>-CHO</td>
<td>-al</td>
<td>oxo-</td>
</tr>
<tr>
<td>C=O</td>
<td>-one</td>
<td>oxo-</td>
</tr>
<tr>
<td>-OH</td>
<td>-ol</td>
<td>hydroxy-</td>
</tr>
<tr>
<td>-NH₂</td>
<td>-amine</td>
<td>amino-</td>
</tr>
<tr>
<td>-SH</td>
<td>-thiol</td>
<td>mercapto-</td>
</tr>
</tbody>
</table>

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15 Physical Properties

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

\[ \delta^+ \delta^- \]

\[ \text{C} \equiv \text{O} : \]

- 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
15 Mass Spectrometry

A characteristic fragmentation pattern of aliphatic aldehydes and ketones is cleavage of one of the bonds to the carbonyl group (α-cleavage)

\[ \text{CH}_3\text{C}^+ \quad \xrightarrow{m/z\ 43} \quad \text{CH}_3\text{C}^+ \]

\[ \text{O} \quad \xrightarrow{m/z\ 113} \quad \text{CCH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_3 \]

\[ \text{m/z}\ 114 \]

\[ \text{O} \]

\[ \text{CCH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_3 \]
Aldehydes and ketones with sufficiently long carbon chains undergo McLafferty rearrangement, which involves a cyclic flow of electrons in a six-membered ring transition state.

Molecular ion

\[ \begin{array}{cccc}
    \text{C}_2\text{H}_5 & \text{CH} & \text{H} & \text{O} \\
    \text{H}_2\text{C} & \text{C} & \text{CH}_2 & \text{CH}_3 \\
\end{array} \]  

\[ + \]  

\[ \begin{array}{cccc}
    \text{C}_2\text{H}_5 & \text{CH} & \text{CH}_2 \\
    \text{H}_2\text{C} & \equiv & \text{C} & \text{CH}_3 \\
\end{array} \]  

m/z 58
NMR Spectroscopy

\(^1\)H-NMR

- The pi system of the C=O group causes a large downfield shift in the signal of the aldehyde hydrogen, typically to \(\delta \ 9.5-10.1\)
- Hydrogens on the \(\alpha\)-carbon of aldehydes and ketones typically appear at \(\delta \ 2.2-2.6\)

\(^{13}\)C-NMR

- The carbonyl carbon of aldehydes and ketones is readily identifiable by the position of its signal between \(\delta \ 180 \text{ and } 210\)
Aldehydes and ketones show strong IR absorption between 1630 and 1810 cm\(^{-1}\) associated with the C=O stretching vibration. The position of this vibration is quite sensitive to the molecular environment of the C=O group.

- Cyclohexanone: 1715 cm\(^{-1}\)
- Pentanone: 1745 cm\(^{-1}\)
- Diamond: 1780 cm\(^{-1}\)
- Cyclic ketone: 1850 cm\(^{-1}\)
The presence of a carbon-carbon double bond or a benzene ring in conjugation with the carbonyl group causes a shift in the C=O absorption to a lower wavenumber.

\[ \text{H}_3\text{C} - \text{CH-CH}_2\text{-C-CH}_3 \quad \text{H}_3\text{C} - \text{C}=\text{CH-C-CH}_3 \quad \text{H}_3\text{C} - \text{CH-CH}_2\text{-C-CH}_3 \]

1717 cm\(^{-1}\) \quad 1690 cm\(^{-1}\) \quad 1700 cm\(^{-1}\)
Simple aldehydes and ketones show only weak UV absorption due to an n to $\pi^*$ transition.

If, however, the carbonyl group is conjugated with one or more carbon-carbon double bonds, intense $\pi$ to $\pi^*$ absorption occurs.

3-Pentanone

\[ \text{CH}_3 \text{CH}_2 \text{CH}_2 \text{CCH}_3 \]

$\lambda_{\text{max}}$ 180 nm ($\epsilon$ 900)

3-Penten-2-one

\[ \text{CH}_3 \text{CH}=\text{CHCCH}_3 \]

$\lambda_{\text{max}}$ 224 nm ($\epsilon$ 12,590)
One of the most common reaction themes of a carbonyl group is addition of a nucleophile to form a tetrahedral carbonyl addition compound.

\[
\text{Nu}^- + \text{C} = \text{O} \rightarrow \text{NuC} = \text{O}^- \quad \text{Tetrahedral carbonyl addition compound}
\]
A second common theme is reaction with a proton or Lewis acid to form a resonance-stabilized cation.

\[
\text{C}=\text{O}^+ + \text{H}^- \rightarrow \text{C}=\text{O}^- + \text{H}^+
\]

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

- $\text{RMgX}$: A Grignard reagent
- $\text{RLi}$: An organolithium reagent
- $\text{RC≡C}^{-}$: An anion of a terminal alkyne
- $\text{CN}^{-}$: Cyanide ion
Given the difference in electronegativity between carbon and magnesium (2.5 - 1.3), the C-Mg bond is polar covalent, with C\(\delta^-\) and Mg\(\delta^+\)

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

$$\begin{align*}
\delta^- \quad \text{CH}_3\text{CH}_2\text{-MgBr} \quad + \quad \text{H}-\text{C}-\text{H} \\
\delta^+ \\
\text{Formaldehyde} \\
\delta^- \\
\delta^- \\
\text{ether} \\
\delta^- \\
\text{CH}_3\text{CH}_2\text{-CH}_2\text{OH}
\end{align*}$$

A magnesium alkoxide

$\text{CH}_3\text{CH}_2\text{-CH}_2\text{OH}$ (a primary alcohol)
Grignard Reagents

Addition to any other RCHO gives a 2° alcohol

\[ \text{Acetaldehyde (an aldehyde)} \xrightarrow{\text{ether}} \text{A magnesium alkoxide} \]

\[ \text{1-Cyclohexylethanol (a secondary alcohol)} \]
Grignard Reagents

Addition to a ketone gives a 3° alcohol

\[
\begin{align*}
C_6H_5\text{MgBr} & \rightarrow [\text{MgBr}]^- + \text{O}^- \\
\text{Acetone} & \rightarrow \text{ether}
\end{align*}
\]

\[
\begin{align*}
\text{C}_6\text{H}_5\text{C}-\text{CH}_3 & \rightarrow \text{HCl} \\
\text{H}_2\text{O} & \rightarrow \text{C}_6\text{H}_5\text{C}-\text{CH}_3 + \text{Mg}^{2+}
\end{align*}
\]

A magnesium alkoxide

2-Phenyl-2-propanol (a tertiary alcohol)
Grignard Reagents

Addition to CO₂ gives a carboxylic acid

\[
\text{MgBr} + \text{CO}_2 \rightarrow \text{ether} \rightarrow \text{Mg}^{2+} \text{[MgBr]} + \text{carbon dioxide}
\]

\[
\text{Cyclopentane-carboxylic acid}
\]

\[
\text{HCl} \quad \text{H}_2\text{O} \quad \text{COH} + \text{Mg}^{2+}
\]
Problem: 2-phenyl-2-butanol can be synthesized by three different combinations of a Grignard reagent and a ketone. Show each combination.
Organolithium compounds are generally more reactive in C=O addition reactions than RMgX, and typically give higher yields.

\[
\text{Catalyst} + \text{Organolithium compound} \rightarrow \text{Organometallic compound} \\
\text{Organometallic compound} + \text{Acid} \rightarrow \text{Organic product}
\]
Addition of an acetylide anion followed by $\text{H}_3\text{O}^+$ gives an $\alpha$-acetylenic alcohol.

\[
\text{HC}≡\text{C}^-\text{Na}^+ + \text{Cyclohexanol} \rightarrow \text{HC}≡\text{C}^-\text{Na}^+ \text{Cyclohexanol}
\]

\[
\text{HC}≡\text{C}^-\text{Na}^+ \text{Cyclohexanol} + \text{HCl} \xrightarrow{\text{H}_2\text{O}} \text{HC}≡\text{C}^-\text{Na}^+ \text{Cyclohexanol}
\]

\[
\text{A sodium alkoxide} \rightarrow \text{HC}≡\text{C}^-\text{Na}^+ \text{Cyclohexanol} \rightarrow \text{HC}≡\text{C}^-\text{Na}^+ \text{Cyclohexanol}
\]
Salts of Terminal Alkynes

1. Reaction with H$_2$O:
   - Product: An $\alpha$-hydroxyketone

2. Reaction with H$_2$SO$_4$, HgSO$_4$:
   - Product: $\beta$-hydroxyaldehyde

3. Reduction with (sia) BH:
   - Product: An $\alpha$-hydroxyketone

4. Oxidation with H$_2$O$_2$, NaOH:
   - Product: A $\beta$-hydroxyaldehyde
Addition of HCN

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.

\[
\text{CH}_3\text{CH} + \text{HC≡N} \rightleftharpoons \text{CH}_3\text{C-C≡N} \quad \text{2-Hydroxypropanenitrile (Acetaldehyde cyanohydrin)}
\]
Mechanism of cyanohydrin formation

\[
\begin{align*}
\text{H}_3\text{C} & + \text{C} & \text{C} & \text{N} \\
\text{H}_3\text{C} & \text{C} & \text{O} & \text{H} \\
\text{C} & \text{C} & \text{N} & \\
\text{C} & \text{C} & \text{C} & \text{N} \\
\text{H}_3\text{C} & \text{C} & \text{C} & \text{N} & \\
\end{align*}
\]

2-Hydroxy-2-methylpropanenitrile (Acetone cyanohydrin)
The value of cyanohydrins is for the new functional groups into which they can be converted

- acid-catalyzed dehydration of the 2° or 3° alcohol

\[
\text{OH} \quad \begin{array}{c}
\text{acid} \\
\text{catalyst}
\end{array} \quad \begin{array}{c}
\text{CH}_3\text{CHC}≡\text{N} \\
\text{2-Hydroxypropanenitrile} \\
\text{(Acetaldehyde cyanohydrin)}
\end{array} \quad \begin{array}{c}
\rightarrow \\
\text{CH}_2≡\text{CHC}≡\text{N} \quad + \quad \text{H}_2\text{O}
\end{array} \\
\text{Propenenitrile} \\
\text{(Acrylonitrile)}
\]
Cyanohydrins

• acid-catalyzed hydrolysis of the cyano group gives a carboxylic acid

Benzaldehyde cyanohydrin (Mandelonitrile)

\[
\text{CHC} = \text{N} + \text{H}_2\text{O} \xrightarrow{\text{acid catalyst}} \text{CHCOH} \quad \text{HO}^\circ\text{O}^\circ
\]

2-Hydroxy-2-phenyl-ethanoic acid (Mandelic acid)
15 Cyanohydrins

- catalytic reduction of the carbon-nitrogen triple bond converts the cyano group gives a 1° amine

\[
\text{Benzaldehyde cyanohydrin} + 2 \text{H}_2 \xrightarrow{\text{Ni}} \text{2-Amino-1-phenylethanol}
\]
The Wittig reaction is a very versatile synthetic method for the synthesis of alkenes from aldehydes and ketones.

\[
\text{Triphenylphosphine oxide} + \text{Methylene-cyclohexane} \rightarrow \text{Ph}_3\text{P-CH}_2\text{O} + \text{Ph}_3\text{P-O}^-
\]

A phosphonium ylide
Phosphonium Ylides

Ylide: a molecule which, when written in a Lewis structure showing all atoms with complete valence shells, has positive and negative charges on adjacent atoms

Phosphonium ylides are formed in two steps:
1. treatment of triphenylphosphine with a 1° or 2° alkyl halide to form a phosphonium salt followed by
2. treatment of the phosphonium salt with strong base, typically butyllithium
15 Phosphonium Ylides

\[ \text{Ph}_3\text{P: } + \text{CH}_3\text{I} \xrightarrow{\text{S}_{\text{N}2}} \text{Ph}_3\text{P-CH}_3\text{I}^- \]

Triphenylphosphine

An alkyltriphenylphosphonium iodide

\[ \text{CH}_3\text{CH}_2\text{CH}_2\text{CH}_2\text{Li}^+ + \text{H-CH}_2\text{-PPh}_3\text{I}^- \rightarrow \]

Butyllithium

\[ \text{CH}_2\text{-PPh}_3^- + \text{CH}_3\text{CH}_2\text{CH}_2\text{CH}_3 + \text{Li}^+ \text{I}^- \]

A phosphonium ylide

Butane
Wittig Reaction

Phosphonium ylides react with the C=O group of an aldehyde or ketone to give an alkene

\[
\begin{align*}
\text{Ph}_3\text{P} \& \text{CH}_2 + \text{O} \& \text{CR}_2 & \rightarrow \text{Ph}_3\text{P} \& \text{CH}_2 + \text{O} \& \text{CR}_2 \\
\text{An oxaphosphetane} & \\
\text{Ph}_3\text{P}^+ \quad \text{CR}_2 & \rightarrow \text{Ph}_3\text{P}^+ \quad \text{CR}_2 \\
\text{Triphenylphosphine oxide} & \\
\end{align*}
\]

An alkene
Wittig Reaction

Examples:

\[
\text{CH}_3\text{C}=\text{CH}\left(\text{CH}_2\right)_3\text{CH}_3 + \text{Ph}_3\text{P}-\text{CH}\left(\text{CH}_2\right)_3\text{CH}_3 \rightarrow
\]

\[
\text{CH}_3 \text{C}=\text{CH}\left(\text{CH}_2\right)_3\text{CH}_3 + \text{Ph}_3\text{P}^+\text{O}^- \rightarrow 2\text{-Methyl-2-heptene}
\]
15 Wittig Reaction

Examples (contd.)

\[
\text{PhCH}_2\text{CH} + \text{Ph}_3\text{P-CHCH}_3 \rightarrow \\
\text{PhCH}_2\text{CH}=\text{CHCH}_3 + \text{Ph}_3\text{P-O}^-
\]

1-Phenyl-2-butene
(87% Z isomer; 13% E isomer)
**Wittig Reaction**

**Examples (contd.)**

\[
\text{PhCH}_2\text{CH} + \text{Ph}_3\text{P-CHCOCH}_2\text{CH}_3 \rightarrow \text{PhCH}_2\text{H} + \text{Ph}_3\text{P-O}^{-}
\]

**Ethyl (E)-4-phenyl-2-butenoate**

*(only the E isomer is formed)*
Addition of water (hydration) of a carbonyl group of an aldehyde or ketone forms a 1,1-diol, commonly referred to as a hydrate.

- When formaldehyde is dissolved in water at 20°C, the carbonyl group is more than 99% hydrated.

Formaldehyde + H₂O → Formaldehyde hydrate (>99%)
Addition of $\text{H}_2\text{O}$

- The equilibrium concentration of hydrated ketone is considerably smaller.

\[
\text{H}_3\text{C} \quad \text{C}=\text{O} \quad + \quad \text{H}_2\text{O} \quad \xrightleftharpoons{} \quad \text{H}_3\text{C} \quad \text{C} \quad \text{OH} \quad \text{C} \quad \text{OH} \\
\text{H}_3\text{C} \quad \text{Acetone} \quad (99.9\%) \quad \text{H}_3\text{C} \quad \text{2,2-Propanediol} \quad (0.1\%)
\]
Addition of Alcohols

Addition of one molecule of alcohol to the C=O group of an aldehyde or ketone gives a hemiacetal.

Hemiacetal: a molecule containing an -OH and an -OR or -OAr bonded to the same carbon.

```
CH₃CCH₃ + OCH₂CH₃ ⇌ CH₃COCH₂CH₃
```

A hemiacetal
Hemiacetals are only minor components of an equilibrium mixture, except where a five- or six-membered ring can form (the trans isomer is shown here).

\[
\begin{align*}
\text{CH}_3\text{CHCH}_2\text{CH}_2\text{CH} & \quad \text{CH}_3\text{C}\
\text{OH} & \quad \text{OH}
\end{align*}
\]

4-Hydroxypentanal

\[
\begin{align*}
\text{H}_3\text{C} & \quad \text{OH}
\end{align*}
\]

A cyclic hemiacetal (major form present at equilibrium)
Addition of Alcohols

Formation of a hemiacetal is acid-catalyzed

Step 1: proton transfer from the acid, HA, to the carbonyl oxygen

\[
\text{CH}_3\text{-C-CH}_3 + \text{H-A} \rightleftharpoons \text{CH}_3\text{-C-CH}_3 + \text{A}^-\text{O}^+\text{-H}
\]
Step 2: attack of ROH on the carbonyl carbon followed by proton transfer to $A^-$ to regenerate the acid catalyst.

\[
\begin{align*}
\text{CH}_3&-\text{C}-\text{CH}_3 + \text{H}\cdot\text{O}\cdot\text{R} \\
\leftrightarrow & \\
\text{CH}_3&-\text{C}-\text{CH}_3 + \text{H-A} + \text{O-R}
\end{align*}
\]
Addition of Alcohols

- Hemiacetals react with alcohols to form acetals.

- Acetal: A molecule containing two -OR or -OAr groups bonded to the same carbon.

\[
\begin{align*}
&\text{CH}_3\text{COCH}_2\text{CH}_3 + \text{CH}_3\text{CH}_2\text{OH} \xrightleftharpoons{H^+} \\
&\text{CH}_3\text{COCH}_2\text{CH}_3 + \text{H}_2\text{O} \\
&\text{A hemiacetal} \\
&\text{A diethyl acetal}
\end{align*}
\]
Addition of Alcohols

Steps 1 and 2: proton transfer from HA to the carbonyl oxygen followed by loss of H₂O

\[
\begin{align*}
\text{HO} & \quad \text{H} \\
\text{R-C-OCH}_3 & \quad \text{R-C-OCH}_3
\end{align*}
\]

An oxonium ion

\[
\begin{align*}
\text{R-C} & \quad \text{OCH}_3 \\
\text{H} & + \text{H}_2\text{O}^- + \text{A}^-
\end{align*}
\]
15 Addition of Alcohols

Steps 3 and 4: reaction of the oxonium ion with ROH followed by proton transfer to A⁻.

An acetal
Addition of Alcohols

With a glycol, such as ethylene glycol, the product is a five-membered cyclic acetal

\[
\text{A cyclic acetal}
\]

\[\text{HOCH}_2\text{CH}_2\text{OH} + \text{H}_2\text{O} \rightarrow \text{A cyclic acetal}\]
Suppose you wish to bring about a Grignard reaction between these compounds:

\[
\text{Benzaldehyde} + \text{3-Bromopropanal} \rightarrow \text{4-Hydroxy-4-phenylbutanone}
\]

15 Acetals as Protecting Grps
If the Grignard reagent were prepared from 3-bromopropanal, it would self-destruct!

First protect the -CHO group as an acetal:

\[
\text{BrCH}_2\text{CH}_2\text{CH} + \text{HOCH}_2\text{CH}_2\text{OH} \xrightarrow{\text{H}^+} \text{BrCH}_2\text{CH}_2\text{CH} + \text{H}_2\text{O}
\]

A cyclic acetal
Then do the Grignard reaction

\[
\begin{align*}
\text{BrCH}_2\text{CH}_2\text{CH} & \quad \text{1. Mg, ether} \\
\text{O} & \quad \text{O} \\
\text{O} & \quad \text{CH}_2 \\
\text{CH}_2 & \quad 2. \text{C}_6\text{H}_5\text{CHO}
\end{align*}
\]
Hydrolysis gives the alcohol and regenerates the -CHO group

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

\[
\begin{align*}
\text{O}^- \text{[MgBr]}^+ & \quad \text{CHCH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{O} \quad \text{CH}_2 \quad \text{HCl, H}_2\text{O} \\
\end{align*}
\]

\[
\begin{align*}
\text{OH} & \quad \text{O} \quad \text{HOCH}_2\text{CH}_2\text{OH} \\
\end{align*}
\]
Thiols, like alcohols, add to the C=O of aldehydes and ketones to give tetrahedral carbonyl addition products.

The sulfur atom of a thiol is a better nucleophile than the oxygen atom of an alcohol.

A common sulfur nucleophile used for this purpose is 1,3-propanedithiol.
The product is a 1,3-dithiane

\[ \text{RCH} + \text{HSCH}_2\text{CH}_2\text{CH}_2\text{SH} \xrightleftharpoons{H^+} \text{RCH} + \text{H}_2\text{O} \]

An aldehyde

A 1,3-dithiane
(a cyclic thioacetal)
The hydrogen on carbon 2 of the 1,3-dithiane ring is weakly acidic, $pK_a$ approximately 31.

Stronger acid

$\text{pK}_a$ 31

Weaker base

$\text{pK}_a$ 50
A 1,3-dithiane anion is a good nucleophile and undergoes $S_N2$ reactions with $1^\circ$ alkyl and benzylic halides. Hydrolysis gives a ketone.
Treatment of the 1,3-dithiane anion with an aldehyde or ketone gives an \( \alpha \)-hydroxyketone.

Lithium salt of a 1,3-dithiane

\[
\text{S} \quad \text{O}^{-} \quad \text{Li}^{+} \\
\text{C} \quad \text{Li}^{+} \quad + \quad \text{H-C-R'} \\
\text{S} \quad \text{S} \quad \text{Li}^{+} \quad \text{OH} \\
\text{R} \quad \text{H-C-R'} \\
\text{H}_2\text{O, HgCl}_2 \quad \text{R-C-CH-R'} \quad \text{an } \alpha\text{-hydroxyketone}
\]
Ammonia, 1° aliphatic amines, and 1° aromatic amines react with the C=O group of aldehydes and ketones to give imines (Schiff bases).

\[
\text{Ethanal} + \text{H}_2\text{N}\text{C}_6\text{H}_4\text{CH}_3 \xrightleftharpoons[H^+]\text{H}_2\text{O} \rightarrow \text{CH}_3\text{CH}=\text{N}\text{C}_6\text{H}_4\text{CH}_3 + \text{H}_2\text{O}
\]

\[
\text{Cyclopentanone} + \text{H}_2\text{NCH}_3 \xrightleftharpoons[H^+]\text{H}_2\text{O} \rightarrow \text{NCH}_3\text{C}_6\text{H}_4\text{CH}_3 + \text{H}_2\text{O}
\]
Addn of N Nucleophiles

Formation of an imine occurs in two steps:

Step 1: addition of the nitrogen nucleophile to the carbonyl carbon followed by proton transfer.

\[ \text{C} + \text{H}_2\text{N-R} \rightarrow \text{C-N}^+\text{R} \rightarrow \text{C=N-R} \]

A tetrahedral carbonyl addition compound.
Addn of N Nucleophiles

Step 2: protonation of the -OH followed by loss of H₂O and proton transfer to solvent

\[ \text{An imine} \]
A value of imines is that the carbon-nitrogen double bond can be reduced to a carbon-nitrogen single bond.

\[
\text{Cyclohexanone} + \text{H}_2\text{N-N-Cyclohexylamine} \overset{\text{H}^+}{\longrightarrow} \text{H}_2\text{O}
\]

\[
\text{(An imine)} \overset{\text{H}_2/\text{Ni}}{\longrightarrow} \text{Dicyclohexylamine}
\]
Addn of N Nucleophiles

Rhodopsin (visual purple) is the imine formed between 11-cis retinal (vitamin A aldehyde) and the protein opsin.
Addn of N Nucleophiles

Secondary amines react with the C=O group of aldehydes and ketones to form enamines.

\[ \text{Piperidine} + \text{aldehyde or ketone} \rightarrow \text{enamine} + \text{water} \]

Piperidine
(a secondary amine)

An enamine
The mechanism of enamine formation involves:
- formation of a tetrahedral carbonyl addition compound followed by
- its acid-catalyzed dehydration

We discuss the chemistry of enamines in more detail in Chapter 18.
The carbonyl group of aldehydes and ketones reacts with hydrazine and its derivatives in a manner similar to its reactions with 1° amines.

\[
\text{Hydrazine} \quad \text{H}_2\text{NNH}_2 \quad \text{A hydrazone} \quad \text{H}_2\text{NNH}_2 \quad \text{H}_2\text{O}
\]

- Hydrazine derivatives include
  - Hydroxylamine: \( \text{H}_2\text{N-OH} \)
  - Phenylhydrazine: \( \text{H}_2\text{N-NH} \)
Hydrogens alpha to a carbonyl group are more acidic than hydrogens of alkanes, alkenes, and alkynes but less acidic than the hydroxyl hydrogen of alcohols.

<table>
<thead>
<tr>
<th>Type of Bond</th>
<th>pK$_a$</th>
</tr>
</thead>
<tbody>
<tr>
<td>CH$_3$CH$_2$O-H</td>
<td>16</td>
</tr>
<tr>
<td>CH$_3$C=CH$_2$-H</td>
<td>20</td>
</tr>
<tr>
<td>CH$_3$C≡C-H</td>
<td>25</td>
</tr>
<tr>
<td>CH$_2$=CH-H</td>
<td>44</td>
</tr>
<tr>
<td>CH$_3$CH$_2$-H</td>
<td>51</td>
</tr>
</tbody>
</table>
15 Acidity of $\alpha$-Hydrogens

$\alpha$-Hydrogens are more acidic because of

1. the electron-withdrawing inductive effect of the adjacent carbonyl group weakens the C-H bond and
2. delocalization of the negative charge stabilizes the resulting enolate anion

\[
\begin{align*}
\text{CH}_3\text{-C-CH}_2\text{-CH}_2\text{-H} + \text{A}^- & \rightarrow \text{CH}_3\text{-C-CH}_2\text{-CH}_2\text{-H}^- + \text{A}^+ \\
\text{Resonance-stabilized enolate anion} & \quad 15-72
\end{align*}
\]
Keto-Enol Tautomerism

Protonation of the enolate anion on oxygen gives the enol form; protonation on carbon gives the keto form.

\[
\begin{align*}
&\text{Enolate anion} \\
&\text{A}^- + \text{CH}_3\text{C}=\text{CH}_2 \\
&\text{Keto form} \\
&\text{Enol form}
\end{align*}
\]
Acid-catalyzed equilibration of keto and enol tautomers occurs in two steps:

Step 1: proton transfer to the carbonyl oxygen

\[ \text{CH}_3\text{-C-CH}_3 + \text{H-A} \xleftrightarrow{\text{fast}} \text{CH}_3\text{-C-CH}_3 + \text{A}^- \]

keto form
Keto-Enol Tautomerism

Step 2: proton transfer to A⁻ to give the enol

\[
\text{CH}_3\text{-C-C=CH}_2 + \cdot\cdot\cdot\text{H} \rightarrow \text{CH}_3\text{-C-CH}_2\text{-H} + \cdot\cdot\cdot\text{A}^- \overset{\text{slow}}{\rightleftharpoons} \text{CH}_3\text{-C-CH}_2 \text{OH} + \text{H-A}
\]

Enol form
### 15 Keto-Enol Tautomerism

Keto-enol equilibria for simple aldehydes and ketones lie far toward the keto form.

<table>
<thead>
<tr>
<th>Keto form</th>
<th>Enol form</th>
<th>% Enol at Equilibrium</th>
</tr>
</thead>
<tbody>
<tr>
<td>( CH_3CH )</td>
<td>( OH )</td>
<td>( CH_2=CH )</td>
</tr>
<tr>
<td>( CH_3CCH_3 )</td>
<td>( OH )</td>
<td>( CH_3C=CH_2 )</td>
</tr>
<tr>
<td>( )</td>
<td>( OH )</td>
<td>( )</td>
</tr>
</tbody>
</table>

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For certain types of molecules, however, the enol is the major form present at equilibrium.

- For β-diketones, the enol is stabilized by conjugation of the pi system of the carbon-carbon double bond and the carbonyl group.

\[
\text{1,3-Cyclohexanedione}
\]

![Diagram of 1,3-Cyclohexanedione enol tautomerism]
Open-chain $\beta$-diketones are further stabilized by intramolecular hydrogen bonding.

\[ \text{2,4-Pentanenedione (Acetylacetone)} \]

\[ \text{80\%} \]

\[ \text{20\%} \]
Racemization at an $\alpha$-carbon may be catalyzed by either acid or base.

(R)-3-Phenyl-2-butanone

An achiral enol

(S)-3-Phenyl-2-butanone
Deuterium exchange at an $\alpha$-carbon may be catalyzed by either acid or base

\[
\begin{align*}
\text{Acetone} & \quad + \quad 6 \text{D}_2\text{O} & \quad \xrightarrow{\text{D}^+ \text{ or OD}^-} & \quad \text{Acetone-d}_6 \\
\text{CD}_3\text{C} = \text{CD}_3 & \quad + \quad 6 \text{HOD}
\end{align*}
\]
α-Halogenation

α-Halogenation: aldehydes and ketones with at least one α-hydrogen react at an α-carbon with Br₂ and Cl₂

Acetophenone

CH₃CO₂H

• reaction is catalyzed by both acid and base
15 $\alpha$-Halogenation

- Acid-catalyzed $\alpha$-halogenation
  
  **Step 1:** acid-catalyzed enolization
  
  $\text{R'-C-C-R} \xleftrightarrow{\text{slow}} \text{R'-C=C-R}$

  **Step 2:** Nucleophilic attack of the enol on halogen
  
  $\text{H-O : C=C} \rightarrow \text{R} \xrightarrow{\text{fast}} \text{Br-Br}$

  $\text{C=C} \rightarrow \text{R} \rightarrow \text{Br} \rightarrow \text{C-C-R} + \text{H-Br}$
15 α-Halogenation

Base-promoted α-halogenation

Step 1: formation of an enolate anion

Resonance-stabilized enolate anion

\[ \text{R'}-\text{C} \equiv \text{C}-\text{R} + \text{OH}^- \xrightarrow{\text{slow}} \text{R'}-\overset{\text{O}^-}{\text{C} \equiv \text{C}}-\text{R} + \text{H}_2\text{O} \]
Base-promoted $\alpha$-halogenation (contd.)

Step 2: nucleophilic attack of the enolate anion on halogen

$$\text{O}^- \quad C \equiv C \quad + \quad Br-Br \quad \xrightarrow{\text{fast}} \quad R'-C-C-R \quad + \quad Br^-$$
There is a major difference between acid-catalyzed and base-promoted $\alpha$-halogenation.

The rate of acid-catalyzed introduction of a second halogen is slower than the first.

- Introduction of the electronegative halogen on the $\alpha$-carbon decreases the basicity of the carbonyl oxygen toward protonation.
For base-promoted $\alpha$-halogenation, each successive halogenation is more rapid than the previous one

- the introduction of the electronegative halogen on the $\alpha$-carbon increases the acidity of the remaining $\alpha$-hydrogens and, thus, each successive $\alpha$-hydrogen is removed more rapidly than the previous one
Haloform Reaction

In the presence of base, a methyl ketone reacts with three equivalents of halogen to form a 1,1,1-trihaloketone, which then reacts with an additional mol of hydroxide ion to form a carboxylic salt and a trihalomethane.

\[
\begin{align*}
\text{RCCH}_3 & \quad \xrightarrow{3 \text{ Br}_2, 3 \text{ NaOH}} \quad \text{RCCBr}_3 \\
\text{O} & \quad \text{O} & \quad \text{NaOH} \\
\text{RCO}^- \text{Na}^+ & \quad + \quad \text{CHBr}_3 \\
\text{Tribromomethane (Bromoform)}
\end{align*}
\]
Haloform Reaction

The final stage is divided into two steps:

Step 1: addition of $\text{OH}^-$ to the carbonyl group to form a tetrahedral carbonyl addition intermediate, followed by its collapse.

\[
\text{RC-CBr}_3 + \text{OH}^- \rightleftharpoons \text{RC-Br} + \text{OH}_2^- \\
\text{RC-CBr}_3 + \text{OH}^- \rightarrow \text{RC} + \text{Br}^- + \text{OH}_2^- 
\]
Haloform Reaction

Step 2: proton transfer from the carbonyl group to the haloform anion

\[
RC-\text{O-H} + \text{CBr}_3^- \rightarrow RC-\text{O}^- + \text{H-CBr}_3
\]

Example:

\[
\begin{align*}
\text{CH}_3 & \quad \text{CHCH=CHCCH}_3 \quad \text{1. Cl}_2/\text{NaOH} \\
\text{5-Methyl-3-hexen-2-one} & \quad \rightarrow \text{CH}_3 \quad \text{CHCH=CHCOH} \quad \text{4-Methyl-2-pentenoic acid}
\end{align*}
\]
Aldehydes are oxidized to carboxylic acids by a variety of oxidizing agents, including $\text{H}_2\text{CrO}_4$.

$$\text{CH}_3(\text{CH}_2)_4\text{CH} \xrightarrow{\text{H}_2\text{CrO}_4} \text{CH}_3(\text{CH}_2)_4\text{COH}$$

Hexanal  \[\rightarrow\] Hexanoic acid
15 Oxidation of Aldehydes

Aldehydes are oxidized by $O_2$ in a radical chain reaction

- liquid aldehydes are so sensitive to air that they must be stored under $N_2$

$$\text{2 Benzaldehyde} + \text{O}_2 \rightarrow \text{2 Benzoic acid}$$
Aldehydes are also oxidized by Ag(I) in one method, a solution of the aldehyde in aqueous ethanol or THF is shaken with a slurry of silver oxide.

\[
\text{Vanillin} + \text{Ag}_2\text{O} \xrightarrow{\text{THF, H}_2\text{O}} \text{Vanillic acid}
\]

+ Ag
Ketones are oxidized using peroxyacids

\[
\text{CCH}_3 + \text{CF}_3\text{COOH} \rightarrow \text{OCCH}_3 + \text{CF}_3\text{COH}
\]

Peroxytrifluoroacetic acid
Trifluoroacetic acid

\[
\text{O} + \text{CH}_3\text{COOH} \rightarrow \text{O} + \text{CH}_3\text{COH}
\]

Peroxyacetic acid
Acetic acid
B-V oxidation involves formation and collapse of a tetrahedral carbonyl addition intermediate.
With symmetrical ketones, there is no ambiguity about which group migrates.

With unsymmetrical ketones, the following migratory aptitudes are observed:

$$3^\circ \text{ alkyl} > 2^\circ \text{ alkyl, aryl} > 1^\circ \text{ alkyl} > \text{methyl}$$
Aldehydes can be reduced to 1° alcohols and ketones to 2° alcohols. In addition, the C=O group can be reduced to a -CH₂- group.

<table>
<thead>
<tr>
<th>Aldehydes</th>
<th>Can be Reduced to</th>
<th>Ketones</th>
<th>Can be Reduced to</th>
</tr>
</thead>
<tbody>
<tr>
<td>RCH₂OH</td>
<td>RCH₃</td>
<td>RCHR'</td>
<td>RCH₂R'</td>
</tr>
</tbody>
</table>

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Catalytic reductions are generally carried out from 25° to 100°C and from 1 to 5 atm H₂.

\[
\text{Cyclohexanone} + \text{H}_2 \xrightarrow{\text{Pt, 25°C, 2 atm}} \text{Cyclohexanol}
\]
A carbon-carbon double bond may also be reduced under these conditions.

\[ \text{trans-2-Butenyal} \rightarrow \text{1-Butanol} \]

- by careful choice of experimental conditions, it is often possible to selectively reduce a carbon-carbon double in the presence of an aldehyde or ketone.
The most common laboratory reagents for the reduction of aldehydes and ketones are NaBH₄ and LiAlH₄.

- Both reagents are sources of hydride ion, H⁻, a very powerful nucleophile.

\[
\begin{align*}
\text{Na}^+ & \quad \text{H-B-H} \\
\text{H} & \quad \text{H} \\
\text{Sodium borohydride} & \\
\text{Li}^+ & \quad \text{H-Al-H} \\
\text{H} & \quad \text{H} \\
\text{Lithium aluminum hydride (LAH)} & \\
\text{H} & \quad \text{H} \\
\text{Hydride ion} &
\end{align*}
\]
Reductions with NaBH₄ are most commonly carried out in aqueous methanol, in pure methanol, or in ethanol. One mol of NaBH₄ reduces four mol of aldehyde or ketone:

\[
4 \text{RCH}_2\text{O} + \text{NaBH}_4 \xrightarrow{\text{methanol}} \text{(RCH}_2\text{O)}_4\text{B}^- + \text{Na}^+ + \text{H}_2\text{O} \rightarrow 4 \text{RCH}_2\text{OH} + \text{borate salts}
\]

A tetraalkyl borate
The key step in metal hydride reduction is transfer of a hydride ion to the C=O group to form a tetrahedral carbonyl addition compound.
Unlike NaBH$_4$, LiAlH$_4$ reacts violently with water, methanol, and other protic solvents. Reductions using it are carried out in diethyl ether or tetrahydrofuran (THF):

$$\text{4 RCR} + \text{LiAlH}_4 \xrightarrow{\text{ether}} \left(\text{R}_2\text{CHO}\right)_4\text{Al}^- \text{Li}^{+} \xrightarrow{\text{H}_2\text{O}} \text{4 RCHR} + \text{aluminum salts}$$

A tetraalkyl aluminate
Metal hydride reducing agents do not normally reduce carbon-carbon double bonds, and selective reduction of C=O or C=C is often possible.

\[
\begin{align*}
RCH=CHCR' & \xrightarrow{1. \text{NaBH}_4} RCH=CHCHR' \\
RCH=CHCR' & \xrightarrow{2. \text{H}_2 \text{O}} RCH=CHCHR' \\
RCH=CHCR' + \text{H}_2 & \xrightarrow{\text{Rh}} RCH_2 CH_2 CR'
\end{align*}
\]
Refluxing an aldehyde or ketone with amalgamated zinc in concentrated HCl converts the carbonyl group to a methylene group.

\[
\text{Zn(Hg), HCl}
\]

Before:

\[
\text{C}(\text{CH}_2)_5\text{CH}_3
\]

After:

\[
\text{CH}_2(\text{CH}_2)_5\text{CH}_3
\]
In the original procedure, the aldehyde or ketone and hydrazine are refluxed with KOH in a high-boiling solvent. The same reaction can be brought about using hydrazine and potassium tert-butoxide in DMSO.

\[
\text{CCH}_3 + \text{H}_2 \text{NNH}_2 \xrightarrow{\text{KOH}} \text{Hydrazine} \rightarrow \text{CH}_2 \text{CH}_3 + \text{N}_2 + \text{H}_2 \text{O}
\]
15 Aldehydes & Ketones

End Chapter 15