Chapter 17: Aldehydes and Ketones: Nucleophilic Addition to the Carbonyl Group

17.1: Nomenclature (please read)
17.2: Structure and Bonding: Carbonyl groups have a significant dipole moment

Carbonyl carbons are electrophilic sites and can be attacked by nucleophiles. The carbonyl oxygen is a basic site.

17.3: Physical Properties (please read)
17.4: Sources of Aldehydes and Ketones (Table 17.1, p. 708)
   1a. Oxidation of 1° and 2° alcohols (15.10)

   1b. From carboxylic acids

   1c. Ketones from aldehydes
2. Ozonolysis of alkenes (6.20)

3. Hydration of alkynes (9.12)

4. Friedel-Craft Acylation (12.7) - aryl ketones

5. Hydroformylation of alkenes (please read)

17.5: Reactions of Aldehydes and Ketones: A Review and a Preview

Reactions of aldehydes and ketones: Review:
1. Reduction to hydrocarbons
   a. Clemmenson reduction (Zn-Hg, HCl)
   b. Wolff-Kishner (H₂NNH₂, KOH, Δ)
2. Reduction to $1^\circ$ and $2^\circ$ alcohols (15.2)

3. Addition of Grignard Reagents (14.6-14.7)

17.6: Principles of Nucleophilic Addition: Hydration of Aldehydes and Ketones

Water can reversibly add to the carbonyl carbon of aldehydes and ketones to give 1,1-diols (geminal or gem-diols)

\[
\begin{align*}
\text{R= H, H} & \quad 99.9 \% \text{ hydrate} \\
\text{R= CH}_3, \text{ H} & \quad 50 \% \\
\text{R= (H}_3\text{C)}_2\text{C, H} & \quad 17 \% \\
\text{R= CH}_3, \text{ CH}_3 & \quad 0.14 \% \\
\text{R= CF}_3, \text{ CF}_3 & \quad > 99 \%
\end{align*}
\]

The hydration reaction is base and acid catalyzed

Base-catalyzed mechanism (Fig. 17.1): hydroxide is a better nucleophile than water
Acid-catalyzed mechanism (Fig. 17.2): protonated carbonyl is a better electrophile

The hydration is reversible

Does adding acid or base change the amount of hydrate?
Does a catalysts affect $\Delta G^o$, $\Delta G^\dagger$, both, or neither

17.7: Cyanohydrin Formation
Addition of H-CN adds to the aldehydes and unhindered ketones. (related to the hydration reaction)
The equilibrium favors cyanohydrin formation
Mechanism of cyanohydron fromation (Fig. 17.3)
17.8: Acetal Formation
Acetals are geminal diethers- structurally related to hydrates, which are geminal diols.

Mechanism of acetal (ketal) formation is acid-catalyzed (Fig 17.4)

The mechanism for acetal/ketal formation is reversible
How is the direction of the reaction controlled?
Dioxolanes and dioxanes: cyclic acetal (ketals) from 1,2- and 1,3-diols

17.9: Acetals (Ketals) as Protecting Groups

Protecting group: Temporarily convert a functional group that is incompatible with a set of reaction conditions into a new functional group (with the protecting group) that is compatible with the reaction. The protecting group is then removed giving the original functional group (deprotection).
The reaction cannot be done directly, as shown. Why?

17.10: Reaction with Primary Amines: Imines (Schiff base)

Mechanism of imine formation (Fig. 17.5):

See Table 17.4 for the related carbonyl derivative, oximes, hydrazones and semicarbazides (please read)
17.11: Reaction with Secondary Amines: Enamines

1° amine: \[
\text{R}^1\text{C}=\text{O} \quad \overset{\text{R}^2\text{NH}_2}{\longrightarrow} \quad \text{R}_2\text{C}=\text{C}^+\text{NHR}^1 \quad \overset{-\text{H}_2\text{O}}{\longrightarrow} \quad \text{R}_2\text{C}=\text{C}^+\text{NHR}^1 \quad \text{Imine}
\]

2° amine: \[
\text{R}^1\text{C}=\text{O} \quad \overset{\text{R}^2\text{NHR}^1}{\longrightarrow} \quad \text{R}_2\text{C}=\text{C}^+\text{NHR}^1 \quad \overset{-\text{HO}^-}{\longrightarrow} \quad \text{R}_2\text{C}=\text{C}^+\text{NHR}^1 \quad \text{Iminium ion}
\]

ketone with \(\alpha\)-protons

Mechanism of enamine formation (Fig. 17.6)

17.12: The Wittig Reaction

1979 Nobel Prize in Chemistry: Georg Wittig (Wittig Reaction) and H.C. Brown (Hydroboration)

The synthesis of an alkene from the reaction of an aldehyde or ketone and a phosphorus ylide (Wittig reagent), a dipolar intermediate with formal opposite charges on adjacent atoms (overall charge neutral).

\[
\text{R}_1\text{C}=\text{O} \quad \overset{+\text{Ph}_3\text{P}=\text{C}^-\text{R}_3}{\longrightarrow} \quad \text{R}_2\text{C}=\text{C}^-\text{R}_3 \quad \overset{+\text{Ph}_3\text{P}=\text{O}}{\longrightarrow} \quad \text{R}_1\text{C}=\text{O} \quad \text{Ph}_3\text{P}=\text{C}^-\text{R}_3 \quad \text{Ph}_3\text{P}=\text{O}
\]

aldehyde or ketone triphenylphosphonium ylide (Wittig reagent) alkene triphenylphosphine oxide

Accepted mechanism (Fig. 17.7) (please read)
The Wittig reaction gives C=C in a defined location, based on the location of the carbonyl group (C=O)

\[
\text{CH}_2 + \text{CH}_3 \xrightarrow{1) \text{CH}_3\text{MgBr, THF}} \xrightarrow{2) \text{POCl}_3} \text{CH}_2 \tag{1: 9}
\]

The Wittig reaction is highly selective for ketones and aldehydes; esters, lactones, nitriles and amides will not react but are tolerated in the substrate. Acidic groups (alcohols, amine and carboxylic acids) are not tolerated.

Predicting the geometry (E/Z) of the alkene product is complex and is dependent upon the nature of the ylide.

17.13: Planning an Alkene Synthesis via the Wittig Reaction

A Wittig reagent is prepared from the reaction of an alkyl halide with triphenylphosphine (\(\text{Ph}_3\text{P}\)) to give a phosphonium salt. The protons on the carbon adjacent to phosphorous are acidic.

\[
\text{Ph}_3\text{P} \xrightarrow{\text{H}_3\text{C-Br}} \text{Ph}_3\text{P}^+\text{CH}_3 \xrightarrow{\text{H}_2\text{ClI}} \text{Ph}_3\text{P}^+\text{CH}_2\text{Br} \xrightarrow{\text{THF}} \left[ \begin{array}{c} \text{Ph}_3\text{P}^+\text{CH}_3 \text{ (ylide)} \\ \text{Ph}_3\text{P}^+\text{CH}_2 \text{ (phosphorane)} \end{array} \right]
\]

Deprotonation of the phosphonium salt with a strong base gives the ylide. A phosphorane is a neutral resonance structure of the ylide.
• There will be two possible Wittig routes to an alkene.
• Analyze the structure \textit{retrosynthetically}, i.e., work the synthesis out backworks
• \textit{Disconnect} (break the bond of the target that can be formed by a known reaction) the doubly bonded carbons. One becomes the aldehyde or ketone, the other the ylide

\[ \text{Disconnect this bond} \]

\[ \begin{array}{c}
\text{R}_2 \\
\text{R}_1 \\
\text{C}=\text{O} \\
\text{R}_3
\end{array} + \begin{array}{c}
\text{Ph}_3\text{P} \text{= C} \\
\text{R}_4
\end{array} \rightarrow \begin{array}{c}
\text{R}_2 \\
\text{R}_1 \\
\text{R}_3 \text{OR} \\
\text{R}_4
\end{array} + \begin{array}{c}
\text{O}=\text{C} \\
\text{R}_3
\end{array} \]

\[
\begin{array}{c}
\text{CH}_3\text{CH}_2\text{CH}_2 \\
\text{CH}_3
\end{array} \quad \begin{array}{c}
\text{C}=\text{C} \\
\text{H} \quad \text{H}
\end{array}
\]

17.14: Stereoselective Addition to Carbonyl Groups (please read)
17.15: Oxidation of Aldehydes

Increasing oxidation state
Aldehydes are oxidized by Cr(VI) reagents to carboxylic acids in aqueous acid. The reactions proceed through the hydrate.

17.16: Baeyer-Villiger Oxidation of Ketones. Oxidation of ketones with a peroxoacid (mCPBA) to give as esters

Oxygen insertion occurs between carbonyl carbon and more the substituted \( \alpha \)-carbon.
**19.17: Spectroscopic Analysis of Aldehydes and Ketones**

*Infrared Spectroscopy:* highly diagnostic for carbonyl groups

Carbonyls have a strong C=O absorption peak between 1660 - 1770 cm\(^{-1}\)

Aldehydes also have two characteristic C–H absorptions around 2720 - 2820 cm\(^{-1}\)

---

**Butanal**

![Butanal IR spectrum](image)

**2-Butanone**

![2-Butanone IR spectrum](image)

---

C=O stretches of aliphatic, conjugated, aryl and cyclic carbonyls:

- **Aliphatic aldehyde**: 1730 cm\(^{-1}\)
- **Conjugated aldehyde**: 1705 cm\(^{-1}\)
- **Aromatic aldehyde**: 1705 cm\(^{-1}\)
- **Aliphatic ketone**: 1715 cm\(^{-1}\)
- **Conjugated ketone**: 1690 cm\(^{-1}\)
- **Aromatic ketone**: 1690 cm\(^{-1}\)

*Conjugation moves the C=O stretch to lower energy (right, lower cm\(^{-1}\))*

*Ring (angle) strain moves the C=O stretch to higher energy (left, higher cm\(^{-1}\))*
$^1$H NMR Spectra of Aldehydes and Ketones: The $^1$H chemical shift range for the aldehyde proton is $\delta$ 9-10 ppm. The aldehyde proton will couple to the protons on the $\alpha$-carbon with a typical coupling constant of $J \approx 2$ Hz. A carbonyl will slightly deshield the protons on the $\alpha$-carbon; typical chemical shift range is $\delta$ 2.0 - 2.5 ppm.

$\delta = 9.8, \text{t, } J = 1.8, 1\text{H}$

$\delta = 2.5, \text{q, } J = 7.3$
$2.1, \text{3H, s}$
$1.1, \text{3H, t, } J = 7.3$

$\delta = 6.8, \text{dq, } J = 15, 7.0$
$6.1, \text{1H, d, } J = 15$
$2.6, \text{2H, q, } J = 7.4$
$1.9, \text{3H, d, } J = 7.0$
$1.1, \text{3H, t, } J = 7.4$
$^{13}$C NMR:
The intensity of the carbonyl resonance in the $^{13}$C spectrum usually weak and sometimes not observed. The chemical shift range is diagnostic for the type of carbonyl ketones & aldehydes: $\delta = \sim 190 - 220$ ppm
carboxylic acids, esters, and amides: $\delta = \sim 165 - 185$ ppm

\[
\begin{align*}
\text{carbonyl} & \quad \delta = 220, 38, 23 \\
\text{carbonyl} & \quad \delta = 174, 60, 27, 14, 9
\end{align*}
\]

C$_9$H$_{10}$O$_2$
IR: 1695 cm$^{-1}$  
$^{13}$C NMR: 191 163 130 128 115 65 15

C$_{10}$H$_{12}$O
IR: 1710 cm$^{-1}$  
$^{13}$C NMR: 207 134 130 128 126 52 37 10
$C_9H_{10}O$

9.8 (1H, t, $J = 1.5$)

7.3 (2H, m)

7.2 (3H, m)

2.9 (2H, t, $J = 7.7$)

2.7 (2H, dt, $J = 7.7, 1.5$)

129, 128, 125

28

45

CDCl$_3$

140

201

125