16.6 Nucleophilic Addition to the Carbon-Oxygen Double Bond
The most characteristic reaction of aldehydes and ketones is **nucleophilic addition** to the carbon-oxygen double bond.

\[
\text{C}=\text{O} + \text{H}^-\text{Nu} : \rightleftharpoons \text{C} - \text{OH} \quad \text{Nu}
\]

Nucleophilic addition to the carbon-oxygen double bond occurs in either of two general ways.
1. Addition of a Strong Nucleophile to an Aldehyde or Ketone

The important aspect of this step is the ability of the carbonyl oxygen atom to accommodate the electron pair of the carbon-oxygen double bond.
2. Acid-Catalyzed Nucleophilic Addition to an Aldehyde or Ketone
16.6A Reversibility of Nucleophilic Addition to the Carbon-Oxygen Double Bond

- Many nucleophilic additions to carbon-oxygen double bonds are reversible,
- The overall results of these reactions depend on the position of an equilibrium.

$$
\begin{align*}
RCH_2C=O + NaHSO_3 & \rightleftharpoons RCH(OH)(SO_3Na)
\end{align*}
$$
16.6B Relative Reactivity: Aldehydes versus Ketones

In general, aldehydes are more reactive in nucleophilic addition than are ketones.

- Aldehyde: Carbonyl carbon is more positive.
- Ketone: Carbonyl carbon is less positive.
16.6C Subsequent Reactions of Addition Products

- Nucleophilic Addition a C=O may lead to a product that is stable under the reaction conditions that we employ.
- In other reactions the products formed initially may be unstable and may spontaneously undergo subsequent reactions. (elimination reactions)
16.7 The Addition of Alcohols: Hemiacetals and Acetals
Most open-chain hemiacetals are not sufficiently stable to allow their isolation.

Cyclic hemiacetals with five- or six-membered rings, however, are usually much more stable:

$$\text{HCl (g)}$$, TsOH / C₆H₆, HCl / Et₂O
Acetals are stable when isolated and purified

Acetal formation is reversible

- An excess of water in the presence of an acid catalyst will hydrolyze an acetal to the corresponding aldehyde (or ketone)

\[
\text{Acetal} \quad \overset{\text{H}_2\text{O}}{\underset{\text{H}^+}{\rightleftharpoons}} \quad \text{Aldehyde}
\]

Hydrolysis of Acetals
Aldehyde Hydrates: *Gem*-Diols

Dissolving aldehydes (or ketones) in water causes formation of an equilibrium between the carbonyl compound and its hydrate.

The equilibrium favors a ketone over its hydrate because the tetrahedral ketone hydrate is sterically crowded.

\[
\text{RCH} = \text{O} + \text{H}_2\text{O} \rightleftharpoons \text{RCH(OH)}_2
\]

Aldehyde

Hydrate (a *gem*-dial)

\[
\text{Cl}_3\text{CCH(OH)}_2
\]

Chloral hydrate

a stable *gem*-dial
Protecting Groups

- Acetal protecting groups are stable to most reagents except aqueous acid.

- Example: An ester can be reduced in the presence of a ketone protected as an acetal.

\[
\begin{align*}
R & \quad \text{C}=\text{O} & \quad \text{HOCH}_2\text{R'} \quad \text{H}^+ \\
\quad \text{HOCH}_2 & \quad \text{HOCH}_2 \quad \text{R'} \quad \text{C} \quad \text{O} \quad \text{O} \quad \text{CH}_2 & \quad \text{H}_2\text{O}
\end{align*}
\]
Thioacetals can be formed by reaction of an aldehyde or ketone with a thiol.

Thioacetals can be converted to CH₂ groups by hydrogenation using a catalyst such as Raney nickel.

This sequence provides a way to remove an aldehyde or ketone carbonyl oxygen:

\[
\begin{align*}
R\text{C}=O + \text{HSCH}_2\text{HSCH}_2 & \xrightleftharpoons{\text{BF}_3} R\text{C}\text{S}−\text{CH}_2 + \text{HSCH}_2 \\
R\text{S}−\text{CH}_2 + \text{H}_2 & \xrightarrow{\text{Raney Ni}} \text{CH}_2 + \text{CH}_3\text{CH}_3 + \text{NiS}
\end{align*}
\]
16.8 The Addition of Derivatives of Ammonia
The Addition of Ammonia or Amines

\[
\begin{align*}
\text{CH}_3\text{CHO} & \xrightarrow{\text{NH}_3, \text{H}^+} \text{CH}_3\text{CH}^-\text{NH} \xrightarrow{\text{H}_2\text{O}} \text{CH}_3\text{CH}=\text{NH} & \text{Imines} \\
\text{CH}_3\text{CHO} & \xrightarrow{\text{RNH}_2, \text{H}^+} \text{CH}_3\text{CH}^-\text{NR} \xrightarrow{\text{H}_2\text{O}} \text{CH}_3\text{CH}=\text{NR} & \text{Schiff's base} \\
\text{CH}_3\text{CHO} & \xrightarrow{\text{R}_2\text{NH}, \text{H}^+} \text{CH}_2\text{CH}^-\text{NR}_2 \xrightarrow{\text{H}_2\text{O}} \text{CH}_2=\text{CH}^-\text{NR}_2 & \text{Enamine}
\end{align*}
\]
Mechanism

\[ \overset{\text{C}=\text{O}}{+} \overset{\text{H}_2\text{NR}}{\rightarrow} \overset{\text{C}}{+} \overset{\text{O}^-}{\overset{\text{NH}_2\text{R}}{\rightarrow}} \overset{\text{C}}{+} \overset{\text{OH}}{\overset{\text{H}_2\text{O}}{\rightarrow}} \overset{\text{C}}{+} \overset{\text{NHR}}{\rightarrow} \overset{\text{C}=\text{NR}}{\rightarrow} \]
The Addition Derivatives of Ammonia

\[
\text{C}=\text{O} \quad + \quad \text{H}_2\text{N}-\text{G} \quad \leftrightarrow \quad \text{C}=\text{N}-\text{G}
\]

\( G = \text{OH} , \ \text{NH}_2 , \ \text{NHAr} , \ \text{NHCONH}_2 \)

\((\text{CH}_3)_2\text{C}=\text{O} \quad + \quad \text{H}_2\text{N}--\text{OH} \quad \rightarrow \quad (\text{CH}_3)_2\text{C}=\text{N}--\text{OH} \)

\( \) (Oxime)

\( \) (Hydroxylamine)

\((\text{CH}_3)_2\text{C}=\text{O} \quad + \quad \text{H}_2\text{N}--\text{NH}_2 \quad \rightarrow \quad (\text{CH}_3)_2\text{C}=\text{N}--\text{NH}_2 \)

\( \) (Hydrazine)
(CH$_3$)$_2$C=O + H$_2$N−NH−C$_6$H$_5$ → (CH$_3$)$_2$C=NN−NH−C$_6$H$_5$

Phenylhydrazine → Phenylhydrazone


2,4-Dinitrophenylhydrazine

2,4-Dinitrophenylhydrazone

Orange
CH₃C=O + H₂N−NH₂−C−NH₂ → □ □ □ (Semicarbazide)

CH₃C=N−NH₂−C−NH₂ → □ □ □ (Semicarbazone)
**Wolff-Kishner Reduction**

\[
\text{C-CH}_2\text{CH}_3 + \text{H}_2\text{NNH}_2, \text{NaOH} \rightarrow \text{CH}_2\text{-CH}_2\text{CH}_3 + \text{N}_2
\]

**Beckmann Rearrangement**

\[
\begin{array}{c}
\text{C-} \quad \text{OH} \\
\text{NHR'}
\end{array} \quad \text{H}^+ \rightarrow \quad \begin{array}{c}
\text{R-} \quad \text{C} \quad \text{NHR'} \\
\text{O}
\end{array}
\]

Catalysts: \( \text{H}_2\text{SO}_4, \text{HCl (g)}, \text{PCl}_3, \text{PCl}_5, \text{POCl}_3, \text{HOAc-Ac}_2\text{O} \)