Hydration of Aldehydes and Ketones

• Treatment of a carbonyl compound with H₂O in the presence of an acid or base catalyst adds the elements of H and OH across the C–O π bond, forming a gem-diol or hydrate.

![Nucleophilic addition of H₂O](image)

• Gem-diol product yields are good only when unhindered aldehydes or aldehydes with nearby electron withdrawing groups are used.

Examples

- Formaldehyde
  - Reaction with H₂O
  - Product: Formaldehyde hydrate

- Chloral
  - Reaction with H₂O
  - Product: Chloral hydrate

• Mechanism of acid-catalyzed & base-catalyzed hydration
Hydration Level vs. Carbonyl Stability

Increasing stability of the carbonyl compound

![Chemical structures of formaldehyde, acetaldehyde, and acetone showing hydration levels and stability.]

- Formaldehyde: 99.9% product
- Acetaldehyde: 58% product
- Acetone: 0.2% product

Increasing amount of hydrate present at equilibrium

Having two similar charges (δ⁺) on adjacent atoms destabilizes the carbonyl group.

A less stable carbonyl compound means more hydrate at equilibrium.

Chloral

Cl δ⁺ C δ⁺ Cl
Cl H
Addition of Alcohols—Acetal Formation

- Aldehydes and ketones react with two equivalents of alcohol to form acetals.
- Acetal formation is catalyzed by acids, such as TsOH.
- Acetals are NOT formed under basic conditions.
- Note that acetals are not ethers.
- Like gem-diol formation, the synthesis of acetals is reversible, and often, the equilibrium favors the reactants.
- In acetal synthesis, since water is formed as a by-product, the equilibrium can be driven to the right by removing H₂O as it is formed using distillation or other techniques.

$$\text{Acetal formation}$$

$$\begin{align*}
\text{R}^' \text{C} \text{R}^' + \text{R}''\text{OH} & \xrightleftharpoons{H^+} \xrightarrow{} \text{R}''\text{C} \text{R}' + \text{H}_2\text{O} \\
\text{R}' = \text{H or alkyl} & \quad \text{(2 equiv)} & \text{acetal}
\end{align*}$$

**Example**

$$\begin{align*}
\text{CH}_3\text{CH}_2\text{CHO} + \text{CH}_3\text{OH} & \xrightleftharpoons{T\text{SOH}} \xrightarrow{} \text{CH}_3\text{CH}_2\text{CCH} + \text{H}_2\text{O} \\
\text{(2 equiv)} & \quad \text{acetal}
\end{align*}$$

$$\text{two new } \sigma \text{ bonds}$$
Addition of Alcohols—Acetal Formation

• When a diol such as ethylene glycol is used in place of two equivalents of ROH, a cyclic acetal is formed.

Chemical reaction:

\[
\text{Ketone} + \text{HOCH}_2\text{CH}_2\text{OH} \xrightleftharpoons{\text{TsOH}} \text{a cyclic acetal} + \text{H}_2\text{O}
\]

ethylene glycol

• Mechanism of acid-catalyzed acetal formation

• The mechanism for acetal formation is similar to the formation of a hydrate.

• The mechanism for acetal formation can be divided into two parts, the first of which is addition of one equivalent of alcohol to form the hemiacetal.

• The second part of the mechanism involves conversion of the hemiacetal into the acetal.
Hydrolysis of Acetals

- Because conversion of an aldehyde or ketone to an acetal is a reversible reaction, an acetal can be hydrolyzed to an aldehyde or ketone by treatment with aqueous acid.
- Since the reaction is also an equilibrium process, it is driven to the right by using a large excess of water for hydrolysis.
- Acetals are **not** hydrolyzed under basic conditions.

\[
\text{Acetals} \quad \overset{\text{Acetal hydrolysis}}{\underset{\text{H}^+}{\xrightarrow{\text{large excess}}} \overset{\text{H}^+}{\xrightarrow{\text{H}_2\text{O}}} \overset{\text{R'}R''}{\xrightarrow{\text{R'}R''}} \overset{\text{R'}R''}{\xrightarrow{\text{R'}R''}}} \]

\[
\text{Example} \quad \overset{\text{Cyclopentane acetal}}{\underset{\text{Ethylene glycol}}{\xrightarrow{\text{H}^+}}} \overset{\text{Cyclohexanone}}{\xrightarrow{\text{H}^+}} \overset{\text{HOCH}_2\text{CH}_2\text{OH}}{\xrightarrow{\text{HOCH}_2\text{CH}_2\text{OH}}} \]

Acetals are valuable protecting groups for aldehydes and ketones.

Suppose we wish to selectively reduce the ester to an alcohol in compound A, leaving the ketone untouched.

Because ketones are more readily reduced, methyl-5-hydroxyhexanoate is formed instead.

To solve this problem, we can use a protecting group to block the more reactive ketone carbonyl.
Protection–Deprotection Process

- The overall process requires three steps.

[1] Protect the interfering functional group—the ketone carbonyl.
[2] Carry out the desired reaction.

![Chemical Diagram]

desired product + HOCH₂CH₂OH
Cyclic Hemiacetals

- Cyclic hemiacetals containing five- and six-membered rings are stable compounds that are readily isolated.

A hemiacetal—
General structure

\[
\begin{align*}
\text{HO} & \text{OR} \\
\text{One C is bonded to:} & \\
\bullet \text{an OH group} & \\
\bullet \text{an OR group} \\
\end{align*}
\]

Cyclic hemiacetals

\[
\begin{align*}
\text{OH} & \text{O} \\
\text{Each indicated C is bonded to:} & \\
\bullet \text{an OH group} & \\
\bullet \text{an OR group that is part of a ring} \\
\end{align*}
\]
Formation of Cyclic Hemiacetals

- Cyclic hemiacetals are formed by intramolecular cyclization of hydroxy aldehydes.

- Such intramolecular reactions to form five- and six-membered rings are faster than the corresponding intermolecular reactions.

- The two reacting functional groups (OH and C=O), are held in close proximity, increasing the probability of reaction.
Acid-Catalyzed Hemiacetal Formation

- Hemiacetal formation is catalyzed by both acid and base.

**Mechanism 21.11 Acid-Catalyzed Cyclic Hemiacetal Formation**

Intramolecular Hemiacetal Formation

- Intramolecular cyclization of a hydroxy aldehyde forms a hemiacetal with a new stereogenic center, so that an equal amount of two enantiomers results.

- Re-drawing the starting material and products in a 3-dimensional representation results in the following:

[* denotes a stereogenic center.]
Cyclic hemiacetals can be converted to acetals by treatment with an alcohol and acid. This converts the OH of the hemiacetal into the OR group of an acetal.

**Cyclical Hemiacetal-Acetal Formation**

**Steps [1]–[2]** Protonation and loss of the leaving group

**Steps [3]–[4]** Nucleophilic attack and deprotonation

This O atom comes from CH₃OH.
Cyclical Hemiacetal-Acetal Formation

• In the conversion of hemiacetals to acetics, the overall result is the replacement of the hemiacetal OH group by an OCH$_3$ group.

• This reaction occurs readily because the carbocation formed in step 2 is stabilized by resonance, making the hemiacetal OH group different from the hydroxy group in other alcohols.

• Thus, when a compound with both an alcohol OH and a hemiacetal OH is treated with an alcohol and acid, only the hemiacetal OH reacts to form the acetal.
Introduction to Carbohydrates

- **Carbohydrates**, commonly referred to as sugars and starches, are polyhydroxy aldehydes and ketones, or compounds that can be hydrolyzed to them.
- Many carbohydrates contain cyclic acetals or hemiacetals.
- Examples include **glucose** and **lactose**.
Introduction to Carbohydrates

- Hemiacetals in sugars are formed by cyclization of hydroxy aldehydes.
- The hemiacetal in glucose is formed by cyclization of an acyclic polyhydroxy aldehyde (A), as shown.

- When the OH group on C5 is the nucleophile, cyclization yields a six-membered ring, and this ring size is preferred.
- Cyclization forms a new stereogenic center - the new OH group of the hemiacetal can occupy the equatorial or axial position.