

# Aldehydes and Ketones

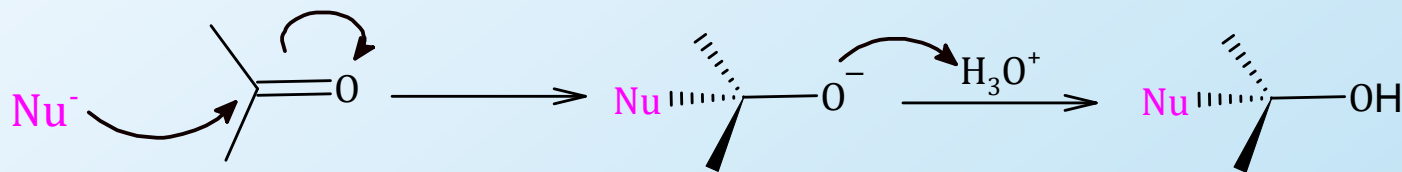
## 3 - Oxygen Nucleophilic Reactions

*Dr. Sapna Gupta*

# Reactions of Aldehydes and Ketones

Aldehyde and ketones will undergo nucleophilic addition reactions.

- A strong nucleophile attacks the carbonyl carbon, forming an alkoxide ion which is then protonated to form an alcohol.
- A weak nucleophile will attack a carbonyl if it has been protonated, thus increasing its (the carbonyl's) reactivity.
- Aldehydes are more reactive than ketones. (*WHY?*)
- Also note that after the addition reaction, a  $sp^2$  carbon is converted to  $sp^3$ , a tetrahedral geometry. This can lead to formation of a chiral center depending on the groups around carbonyl.



# Reactions of Aldehydes and Ketones

Different nucleophiles can be used for addition reactions. We will cover them as different types of nucleophiles.

## 1) Nucleophilic addition

### a) Oxygen nucleophile

- i. Addition of water
- ii. Addition of alcohol

### b) Carbon nucleophile

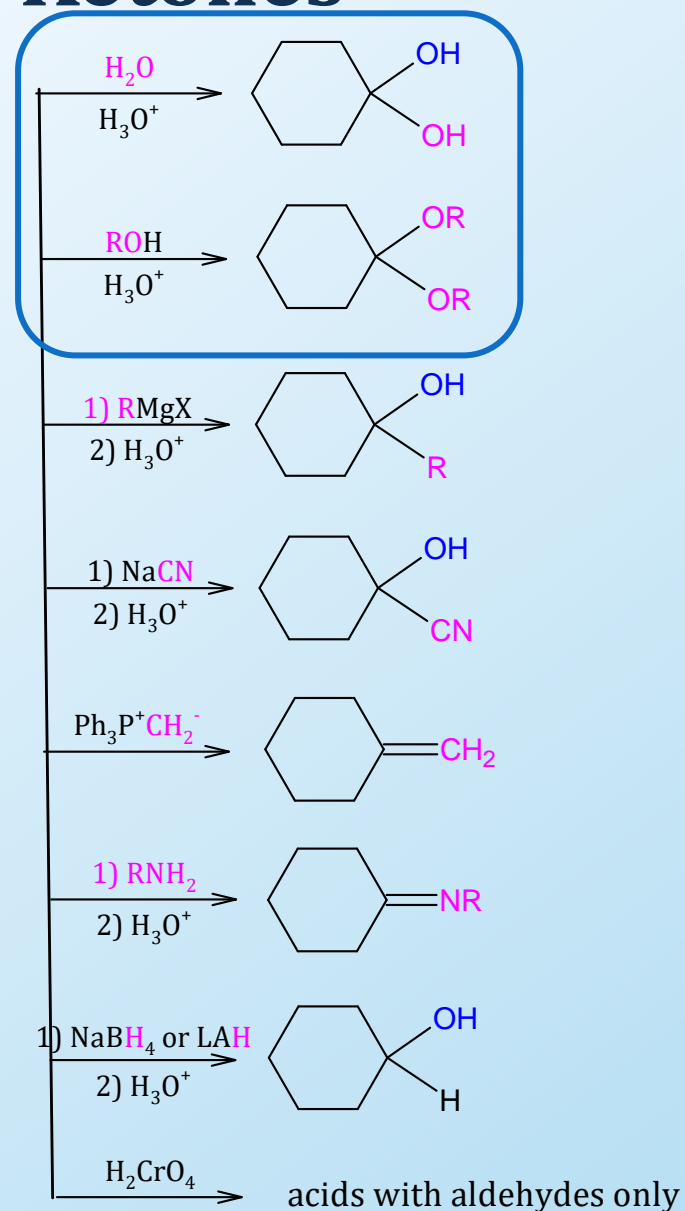
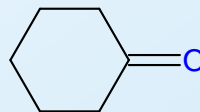
- i. Grignard reaction
- ii. Addition of HCN
- iii. Wittig reaction

### c) Nitrogen nucleophile

## 2) Hydrogen nucleophile - Reduction

## 3) Oxidation

***Only oxygen nucleophiles are covered in this power point.***

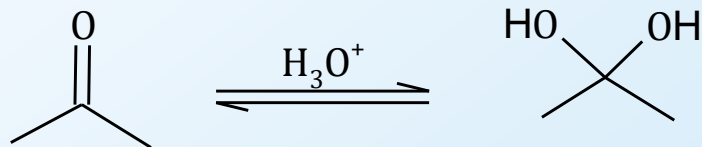


# (O-Nu) - Addition of Water - Hydrates

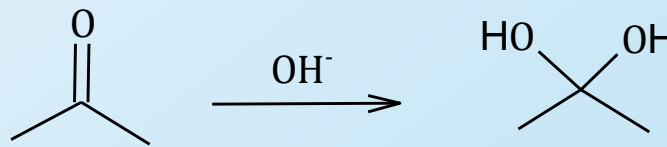
Addition of water to carbonyl forms a geminal diol – a hydrate. There are two ways to make the hydrate – in basic and acidic medium. We will cover the acidic medium. In acid medium, the first nucleophile is the aldehyde/ketone followed by the water as the nucleophile. Note that the mechanism is in equilibrium.

- In base, hydroxide is the nucleophile, and mechanism would be straightforward nucleophilic addition.
- Hydrates are not stable thus synthetically not useful.

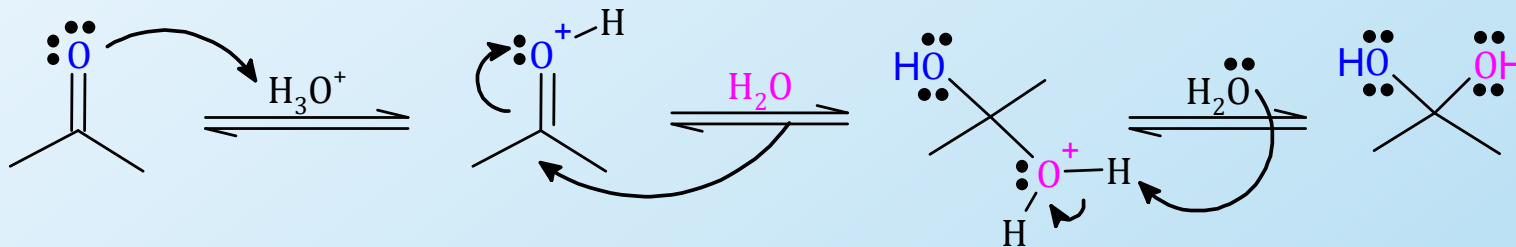
## Acid Reaction



## Base Reaction

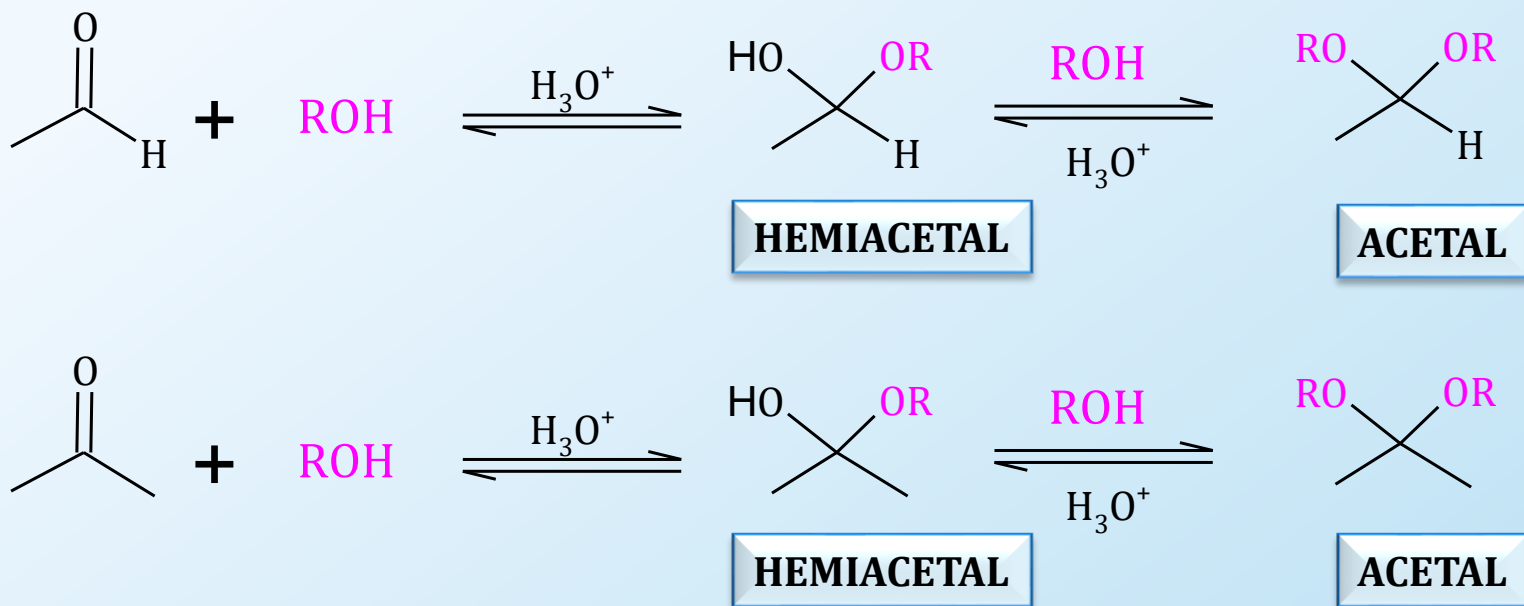


## Acid Mechanism

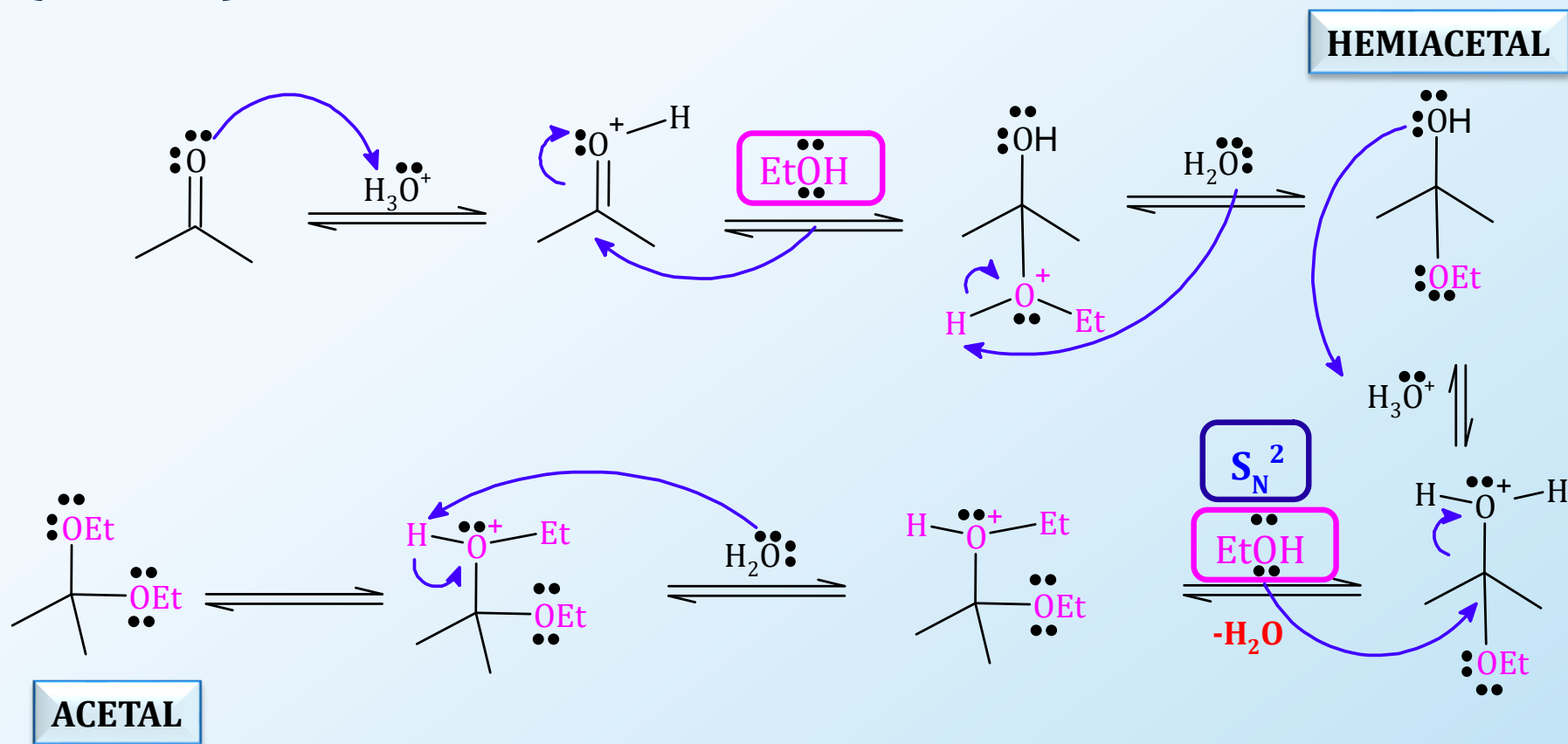


# (O-Nu) - Addition of Alcohol - Acetals

Reaction of alcohol with aldehyde and ketones give acetals, via hemiacetals. Acetals require two moles of alcohols. Since alcohols are weak nucleophiles, this reaction is done in an acidic medium.



# (O-Nu) - Mechanism of Acetal Formation



Note that the entire mechanism is acidic, there are only hydronium ions, no ethoxide or hydroxides. Also note that in the step where 2<sup>nd</sup> ethanol is attacking is  $\text{S}_\text{N}2$  mechanism. It is not  $\text{S}_\text{N}1$  so no carbocation will be formed. Most of the steps involve protonation and deprotonation. There is one molecule of water lost in the process.

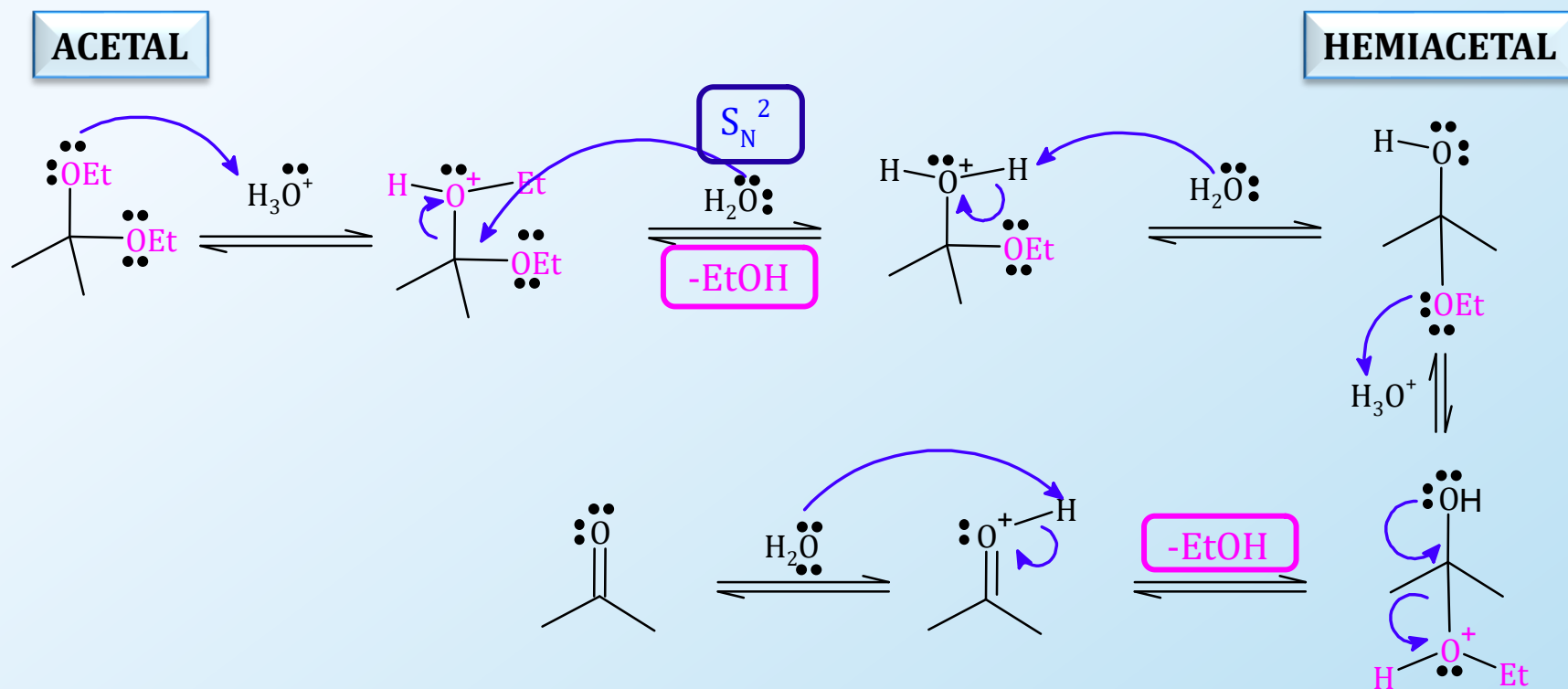
# (O-Nu) - Mechanism of Acetal Formation

Keep a few things in mind as you write the mechanism.

- It is acid-catalyzed. There will be absolutely no negatively charged intermediate in the mechanism.
- The first step will be adding  $\text{H}_3\text{O}^+$  causes the carbonyl oxygen to be the nucleophile.
- Adding  $\text{H}^+$  to carbonyl makes the C of the carbonyl to be more reactive with weak nucleophile, ROH.
- Hemiacetal forms first, then acid-catalyzed loss of water, then addition of second molecule of ROH forms acetal.
- Depending on the substrate, hemiacetals can also be the final product.
- All steps are reversible so the it can be shifted forward by adding more alcohol and reverse by adding more water.

# (O-Nu) - Hydrolysis of the Acetal

Since all acetal formations are reversible; they can be converted back to aldehyde or ketone using water, acidic hydrolysis. Below is the mechanism for acidic hydrolysis. If you look at the mechanism for forming acetal, it is completely reverse of that, since it is all in equilibrium.

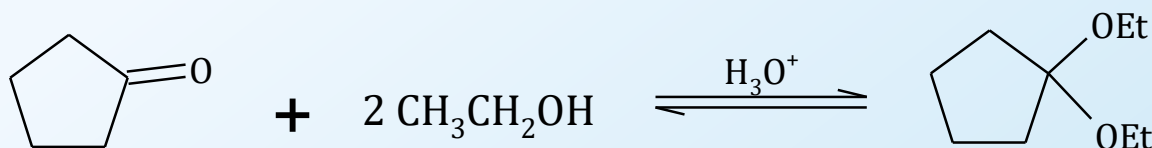




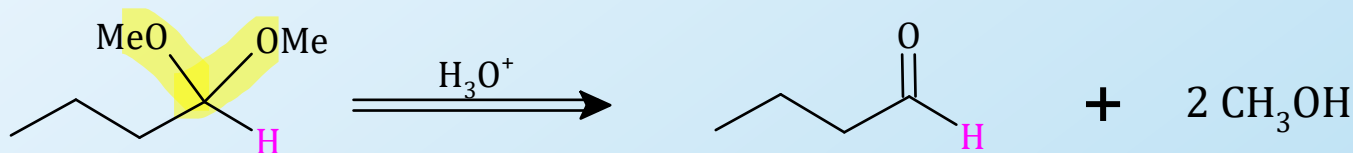
# (O-Nu) - Acetal Formation

It is important to recognize acetals in order to know what carbonyl and alcohol can be used to make them; and then also be able to look at the acetal or hemiacetal and find out which carbonyl and alcohol will result from acidic hydrolysis. Below are some examples of this.

The two alcohol groups will be attached on the carbonyl carbon.

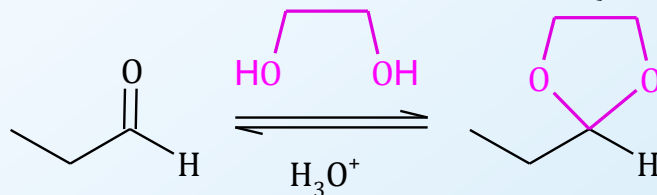


In acidic hydrolysis example below, focus on the two -OMe attached to the same carbon. That is the carbonyl carbon. The H on the carbonyl carbon indicates that the starting carbonyl is an aldehyde. (*More examples are given in a later slide*).

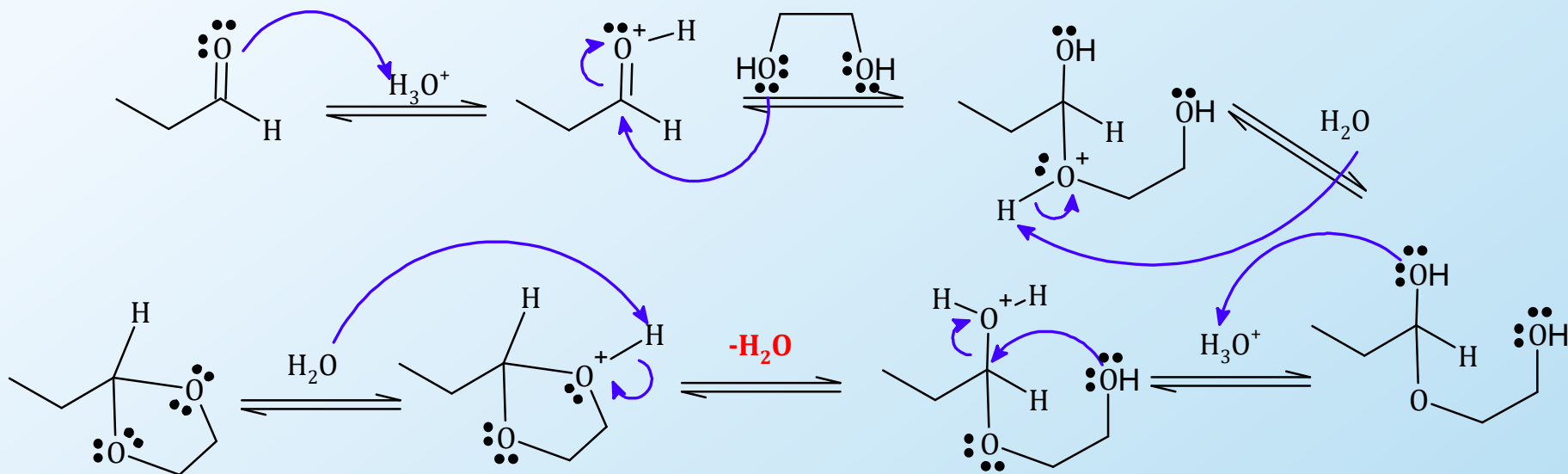


# (O-Nu) - Cyclic Acetals

Two mols of alcohol are needed for each carbonyl to make an acetal, so if we use a diol, it provides both the alcohol groups, and a cyclic acetal is formed as a result. Sugars commonly exist as acetals or hemiacetals (shown in the next slide).

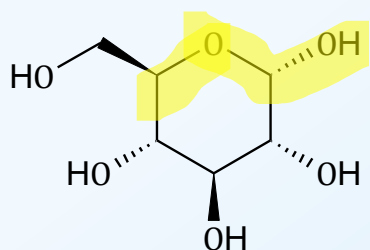


Here is the mechanism.

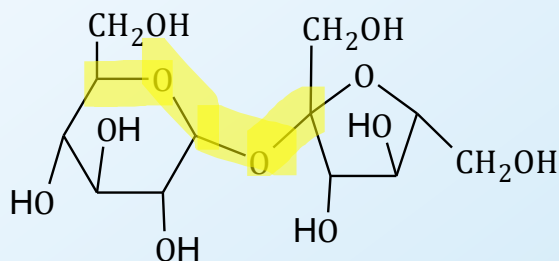


# (O-Nu) - Acetals in Sugars

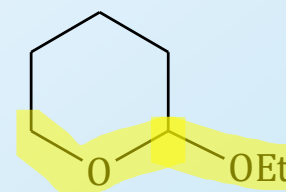
Cyclic hemiacetals and acetals are formed by internal cyclization due to presence of carbonyl and alcohol on the same molecule. This is an intramolecular cyclization. They are commonly formed in sugars. I have highlighted the hemiacetal and acetal.



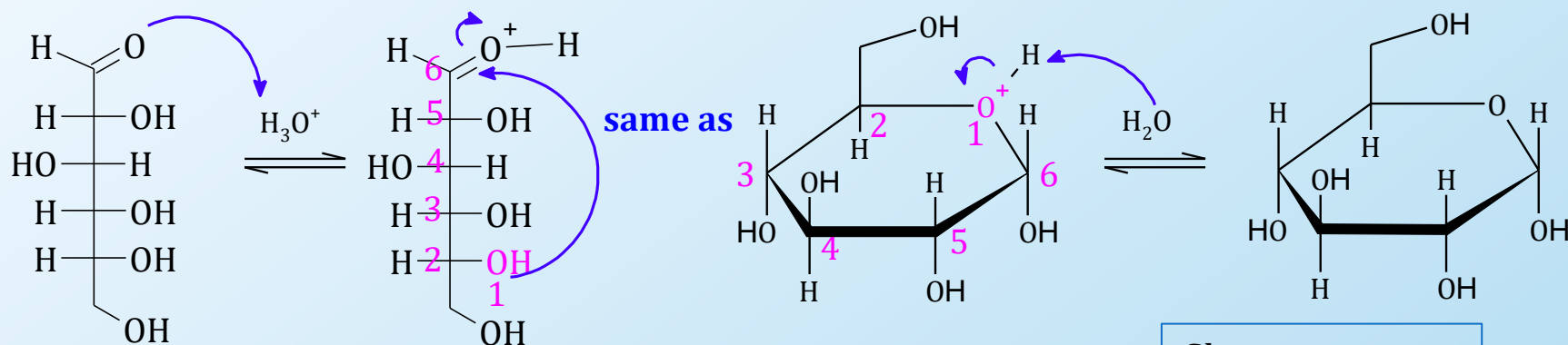
Glucopyranose -  
hemiacetal



Sucrose -  
acetal



acetal

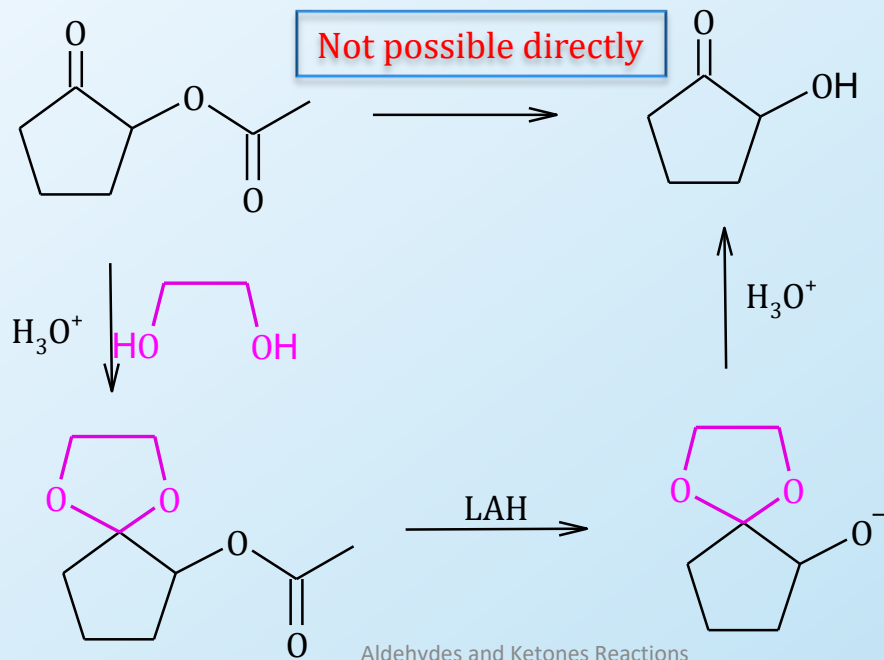


Glucopyranose -  
hemiacetal

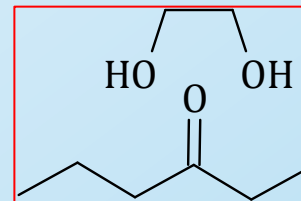
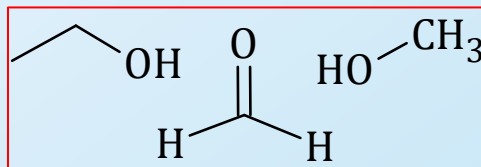
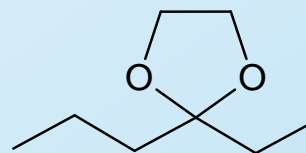
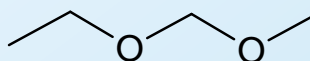
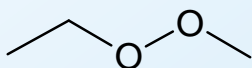
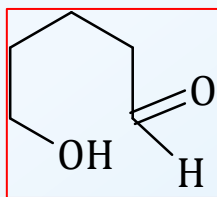
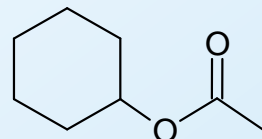
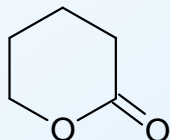
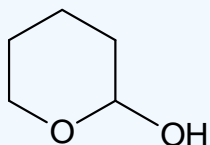
# (O-Nu) - Acetals as Protecting Groups

Acetals are used as protecting groups when there are functional groups that could react with the same reagent. Acetals are stable to most reagents except aqueous acid.

- Aldehydes more reactive than ketones so if there is an aldehyde and ketone to protect then aldehyde will be protected first.
- Example: An ester can be reduced in the presence of a ketone by protecting the ketone as an acetal first.



**Worked Example:** Identify the acetals or hemiacetals in the compounds given below. In case of the acetals and hemiacetals, identify the carbonyl and alcohol needed to synthesize it.



# Key Concepts

## Nucleophilic addition

- a) Oxygen nucleophile
  - i. Addition of water
  - ii. Addition of alcohol