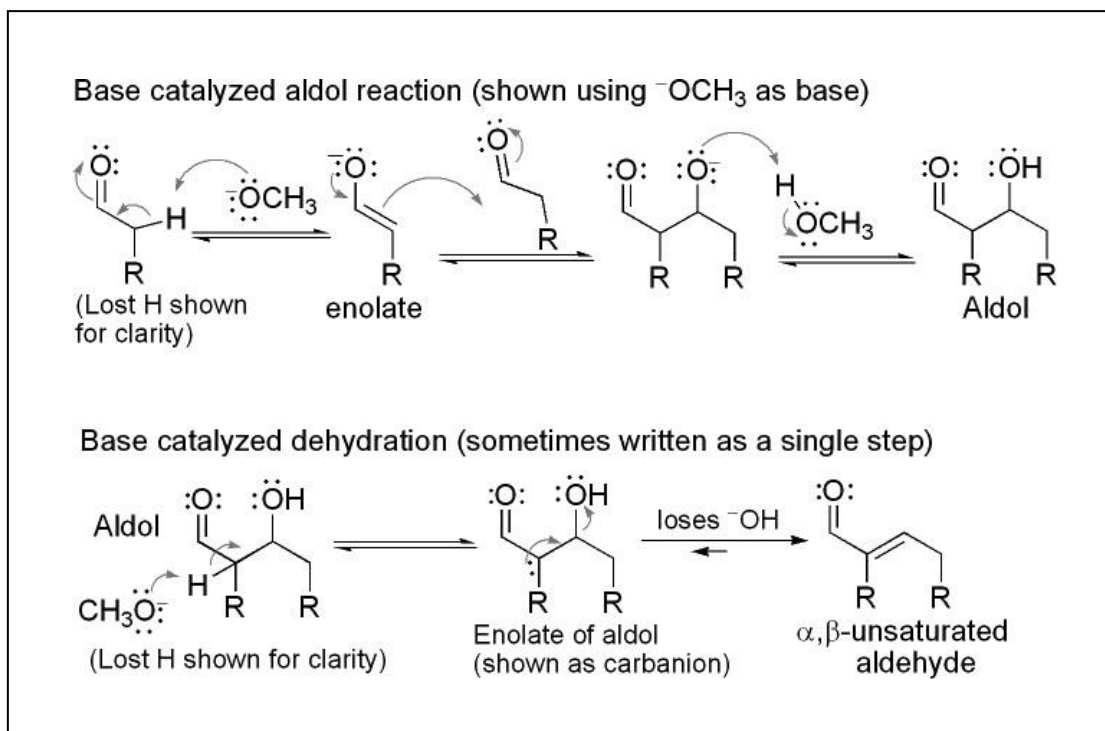
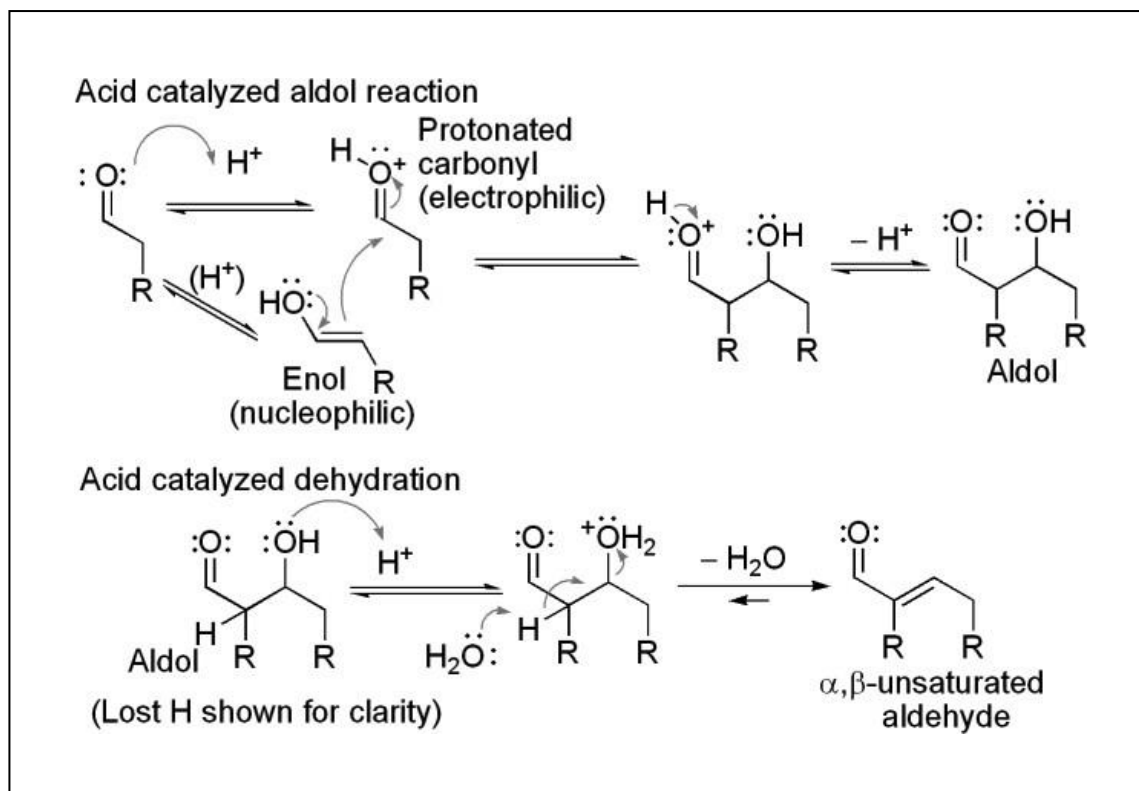


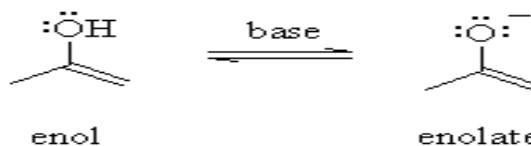




## - The mechanism of aldol condensation reaction of a ALDEHYDE

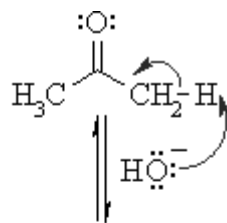

**Note By:**

- ✓ **Enolates** are the conjugate bases or anions of **enols** (like **alkoxides** are the **anions of alcohols**) and can be prepared using a base.

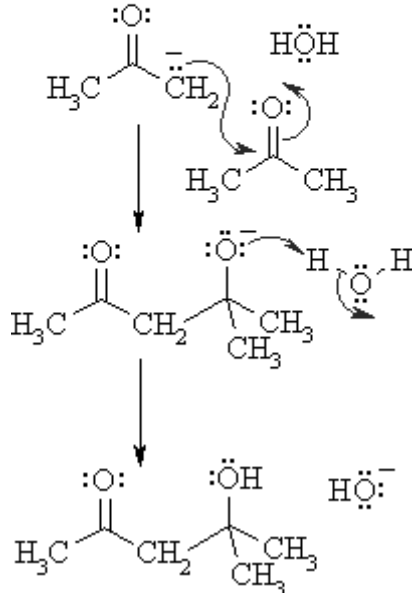


**- The mechanism of aldol condensation reaction of a KETONE**
**Step 1:**

First, an acid-base reaction. Hydroxide functions as a base and removes the acidic  $\alpha$ -hydrogen giving the reactive enolate.


**Step 2:**

The nucleophilic enolate attacks the ketone at the electrophilic carbonyl C in a nucleophilic addition type process giving an intermediate alkoxide.


**Step 3:**

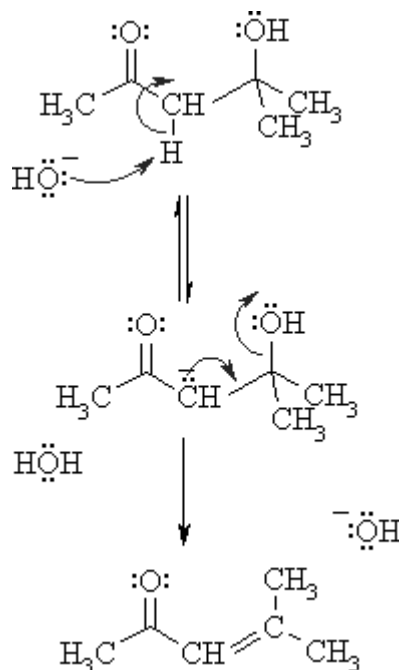
An acid-base reaction. The alkoxide deprotonates a water molecule creating hydroxide and the  $\beta$ -hydroxyketone, the **aldol** product.

**MECHANISM OF THE DEHYDRATION OF THE ALDOL PRODUCT**
**Step 1:**

First, an acid-base reaction. Hydroxide functions as a base and removes an acidic  $\alpha$ -hydrogen giving the reactive enolate.

**Step 2:**

The electrons associated with the negative charge of the enolate are used to form the  $C=C$  and displace the leaving group, regenerating hydroxide giving the conjugated ketone.



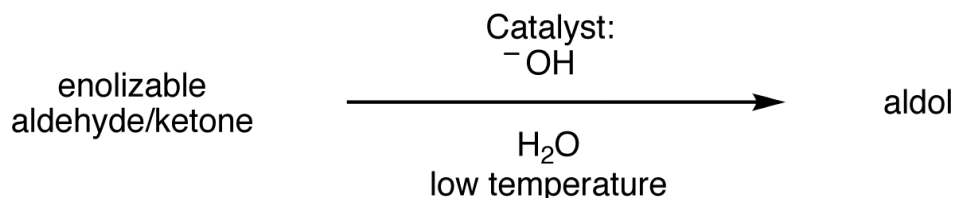
• **Why formal aldehyde does not give aldol reaction in alkaline medium?**

- For a carbonyl compound to undergo aldol condensation, the necessary condition is that it MUST possess at-least 1 "alpha-hydrogen" (an alpha-hydrogen is a hydrogen attached to an alpha-carbon, while an alpha carbon is the carbon attached DIRECTLY to the functional group) since formaldehyde(i-e HCHO) has only 1 carbon which is the carbonyl carbon (i-e the functional group) and there is no alpha-carbon present and hence no alpha-hydrogen, so formaldehyde doesn't undergo aldol condensation. e.g Acetaldehyde can undergo aldol condensation since it has alpha-hydrogens.
- The 2 hydrogens present in the formaldehyde molecule are not alpha-hydrogens; they are simply the hydrogens attached to the functional group.

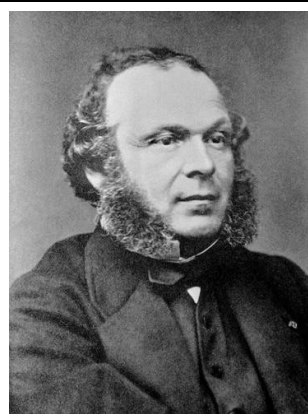
• **What is an alpha hydrogen atom needed for aldol condensation reaction to occur?**

- Due to the acidic nature of  $\alpha$ -hydrogen of aldehydes and ketones, they undergo a number of reactions. This acidity is because of the strong electron withdrawing nature of the carbonyl groups and resonance stabilization of the conjugate base.
- Because, the C-H proton is not acidic enough. Further, carbonyl group of aldehyde is highly electrophilic (hard electrophile) hence the base (hard nucleophile) prefers to attack the carbonyl carbon leading to alcohol & acid.
- So, in-order to get the aldol product, the presence of alpha hydrogens is necessary. These hydrogens are more acidic than the hydrogen attached to the carbonyl group.

• **General representation of Aldol reaction:**



Sir Alexander Porfirievich Borodin (Russian Composer and chemist: 12 November 1833 – 27 February 1887) was a Russian Romantic composer of Georgian origin, as well as a doctor and chemist. He was one of the prominent 19th-century composers

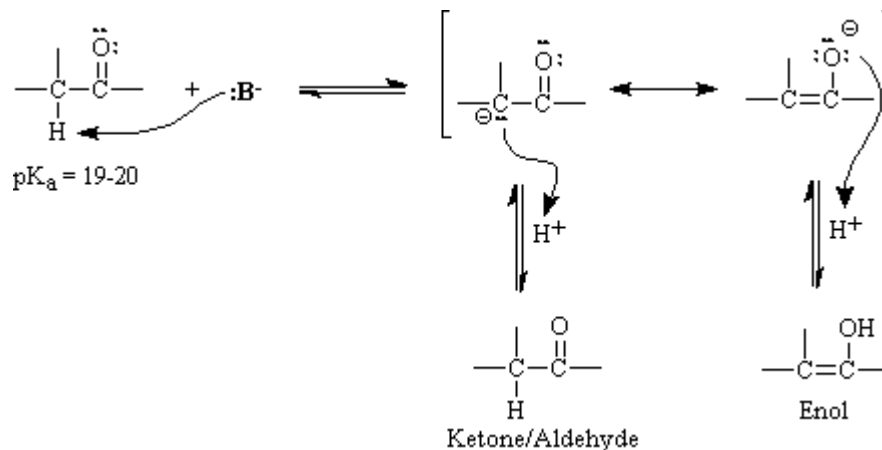


- Sir Charles Adolphe Wurtz (26 November 1817– 10 May 1884) was an Alsatian French chemist.  
 - Known for Wurtz reaction  
 - Awards: Faraday Lectureship Prize (1879) Copley Medal (1881)

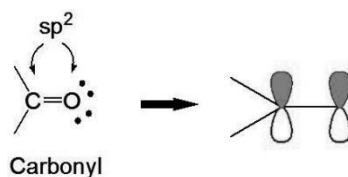
known as The Mighty Handful, a group dedicated to producing a uniquely Russian kind of classical music, rather than imitating earlier Western European models.

### • Acidity of Alpha Hydrogens & Keto-enol Tautomerism

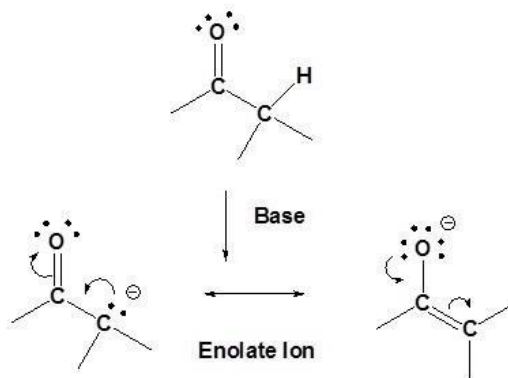
- Alkyl hydrogen atoms bonded to a carbon atom in a (alpha) position relative to a carbonyl group display unusual acidity. While the  $pK_a$  values for alkyl C-H bonds is typically on the order of 40-50,  $pK_a$  values for these alpha hydrogens is more on the order of 19-20. This can most easily be explained by resonance stabilization of the product carbanion, as illustrated in the diagram below.



- In the presence of a proton source, the product can either revert back into the starting ketone or aldehyde or can form a new product, the enol. The equilibrium reaction between the ketone or aldehyde and the enol form is commonly referred to as "keto-enol tautomerism". The ketone or aldehyde is generally strongly favored in this reaction.
- Because carbonyl groups are  **$sp^2$  hybridized** the carbon and oxygen both have unhybridized **p orbitals** which can overlap to form the **C=O  $\pi$  bond**.



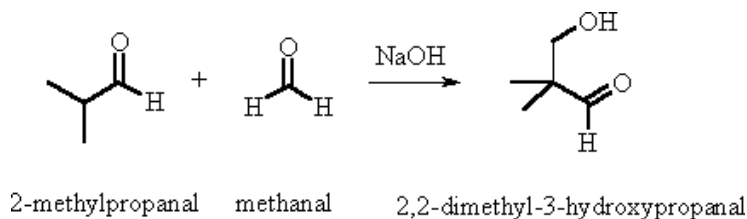
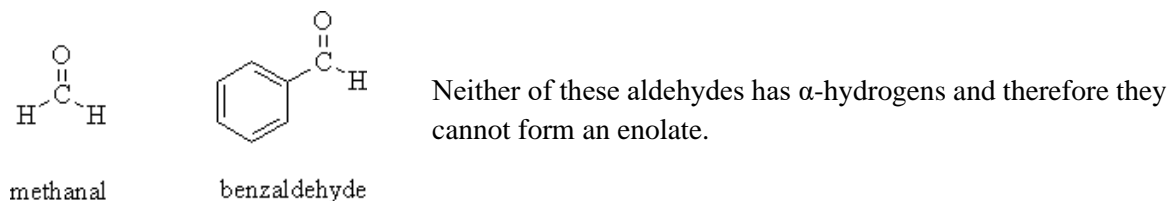
- The presence of these overlapping p orbitals gives  **$\alpha$  hydrogens** (Hydrogens on carbons adjacent to carbonyls) special properties. In particular,  **$\alpha$  hydrogens are weakly acidic** because the conjugate base, called an **enolate**, is stabilized through conjugation with the  $\pi$  orbitals of the carbonyl. The effect of the carbonyl is seen when comparing the  $pK_a$  for the  **$\alpha$  hydrogens** of **aldehydes** (~16-18), **ketones** (~19-21), and **esters** (~23-25) to the  $pK_a$  of an **alkane** (~50).



- Of the two resonance structures of the enolate ion the one which places the negative charge on the oxygen is the most stable. This is because the negative charge will be better stabilized by the greater electronegativity of the oxygen.

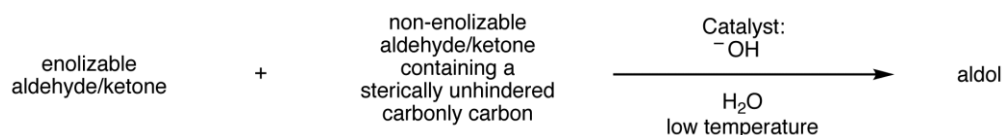
## ❖ Crossed Aldol Condensation Reaction

- The process is also known as Mixed Aldol Condensation and occurs during the combination of two different molecules that contain carbonyl groups. Generally, such a reaction is only practical if **no  $\alpha$ -hydrogens** are present in one of the compounds. This way, only one nucleophile is formed and only a single enol or enolate is generated.

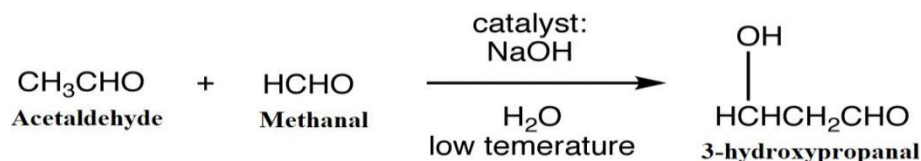


*Only one of this pair of aldehydes has an  $\alpha$ -hydrogen (2-methyl propanal)*

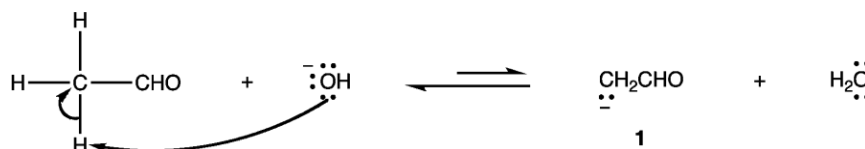
### • General representation of Aldol reaction:



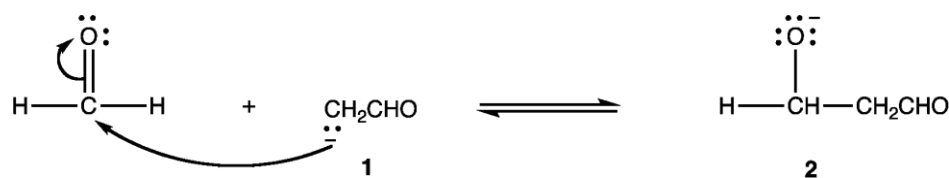
### • Reaction Mechanism



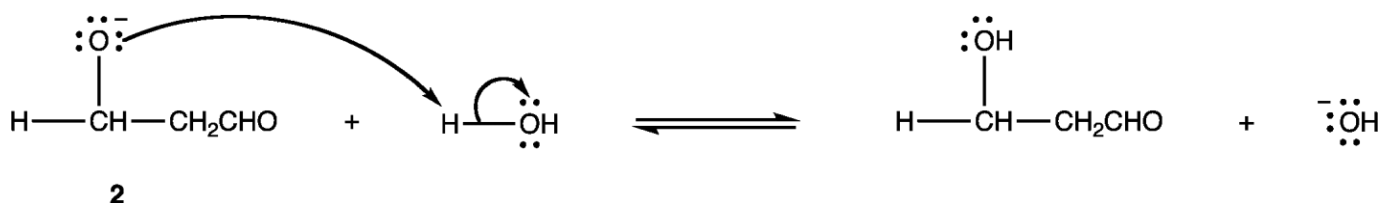
*Step 1: The hydroxide ion deprotonates the enolizable aldehyde reversibly.*



*Step 2: Enolate ion 1 preferentially adds to the non-enolizable aldehyde, which has the Sterically less hindered and, therefore, more accessible carbonyl carbon.*



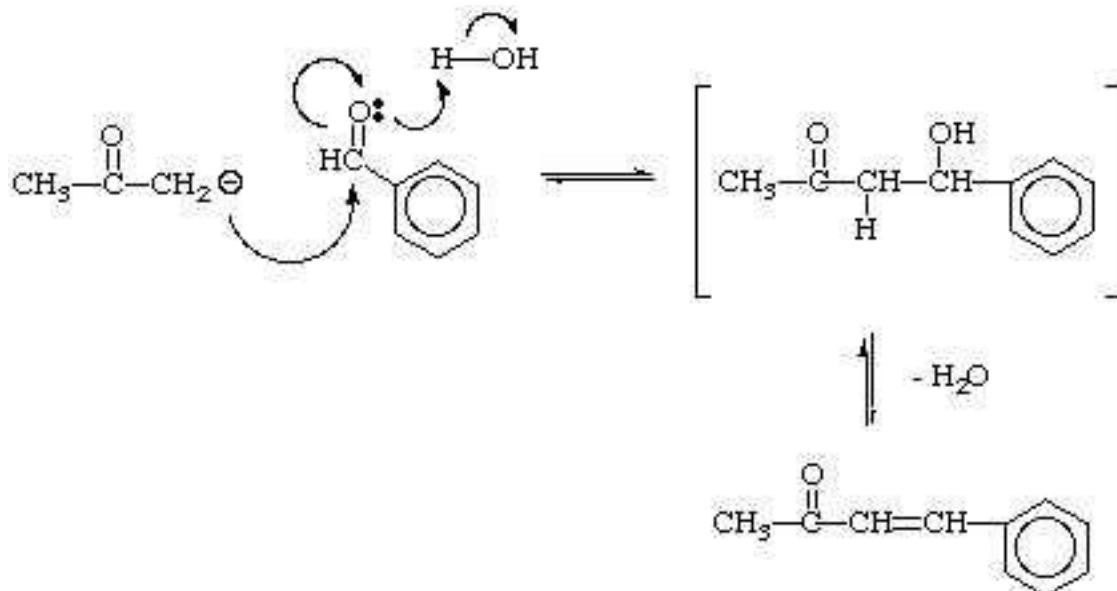
*Step 3: Alkoxide ion 2 is protonated by water.*





• **Claisen-Schmidt Condensation**

- When an enolate forms from an aldehyde, the enolate will normally react with unreacted aldehyde to undergo the "aldol addition" or "aldol condensation" reaction. Since ketones are less reactive toward nucleophilic addition, the enolate formed from a ketone can be used to react with an aldehyde, a modification called the Claisen-Schmidt reaction.
- In cases where the product formed still has reactive alpha hydrogen and a hydroxide adjacent to an aromatic ring, the reaction will quickly undergo dehydration leading to the condensation product.

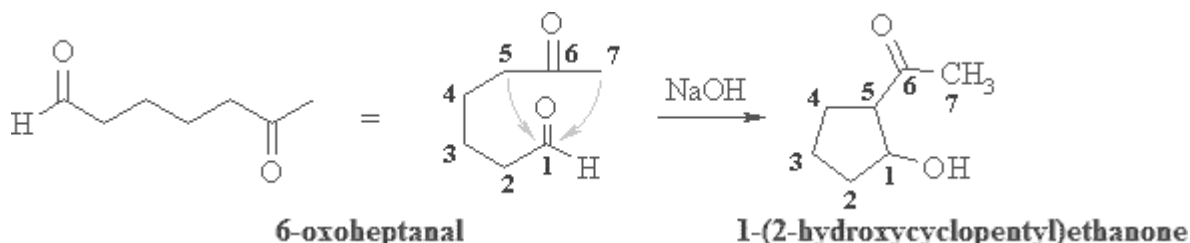


- Enolate ions are formed when molecules with hydrogens alpha to a carbonyl group are treated with a base like sodium hydroxide. For example, acetone reacts with base to give an enolate.



• **Intramolecular Aldols**

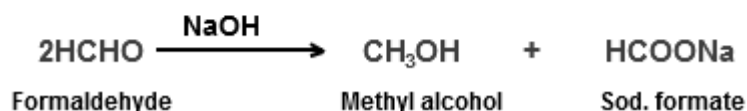
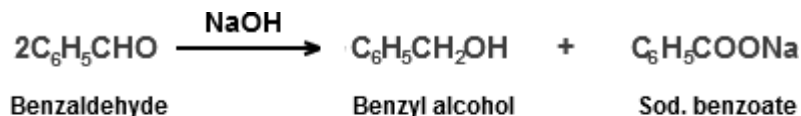
- Dicarbonyl compounds can be used to give *intramolecular Aldol reactions*.



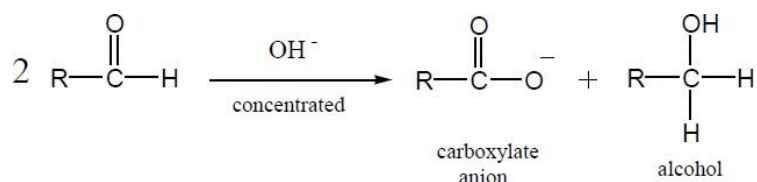
“Every aspect of the world today – even politics and international relations – is affected by chemistry.”

### ❖ Cannizzaro reaction

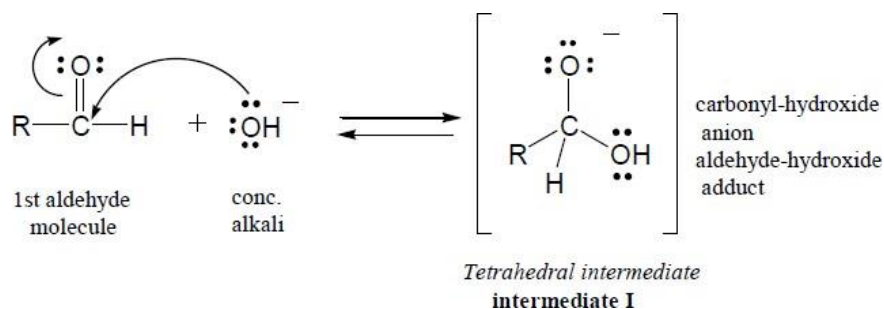
- The Cannizzaro reaction, named after its discoverer *Stanislao Cannizzaro*.
- The disproportionation (self-redox) of aldehydes lacking  $\alpha$ -hydrogen atoms in presence of strong base to form salt of an acid and a primary alcohol is known as **Cannizzaro reaction**.
- Thus, **aromatic aldehydes, formaldehydes, trialkyl acetaldehyde, heterocyclic aldehydes** undergo **Cannizzaro reaction**.



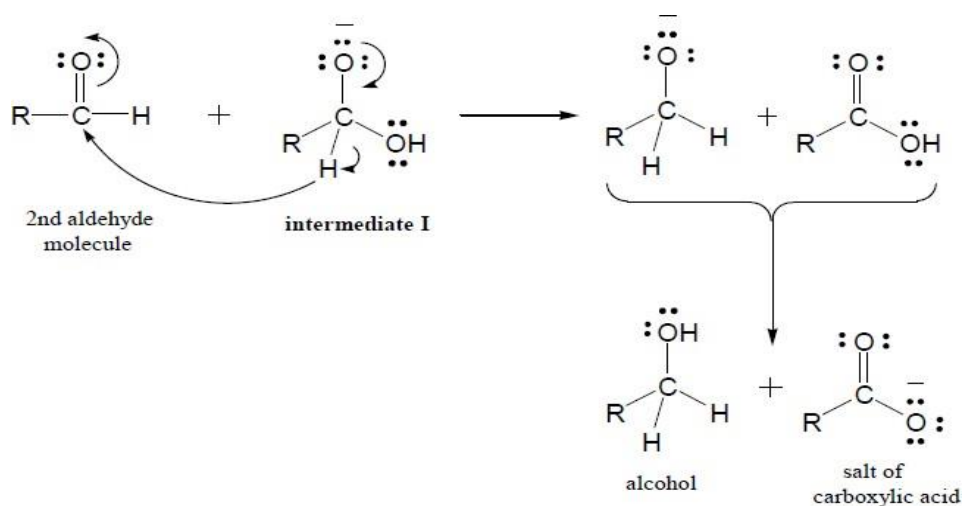
#### - Reaction Mechanism



- ✓ **Step I:** *Nucleophilic addition* of an OH<sup>-</sup> ion to the 1<sup>st</sup> aldehyde molecule gives a tetrahedral intermediate I.

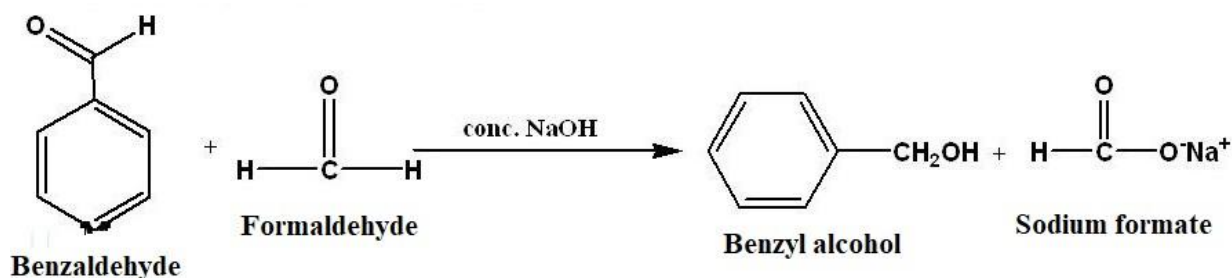
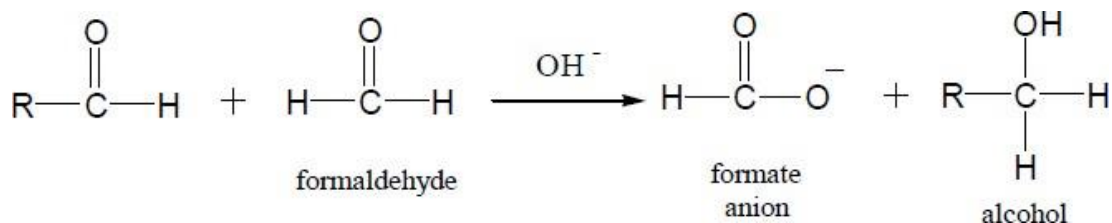


- ✓ **Step II:** *Hydride shift:* The tetrahedral intermediate I, expels a hydride ion “as a leaving group” and is thereby oxidized. A second aldehyde molecule accepts the hydride ion in another nucleophilic addition step and is thereby reduced.

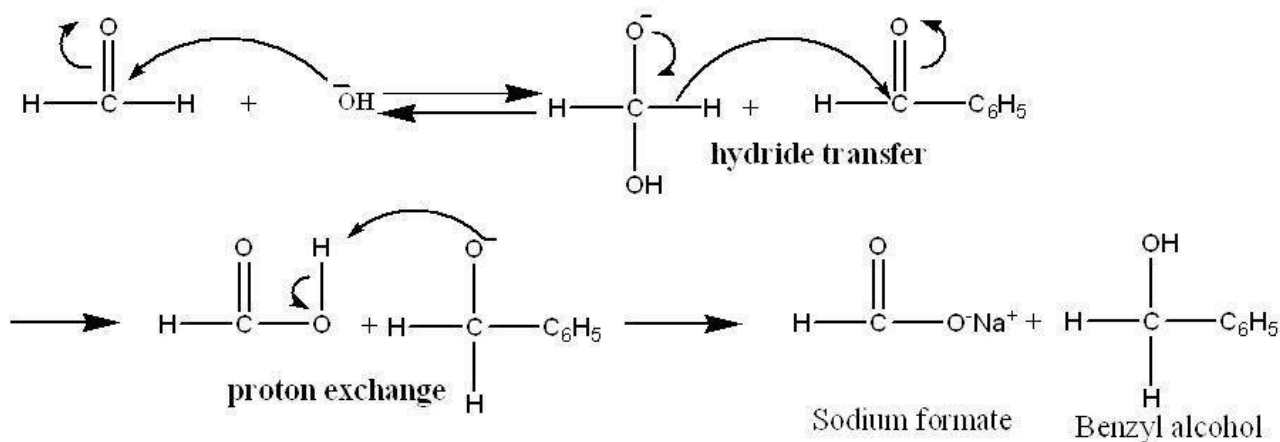


### ❖ Crossed Cannizzaro Reaction

- In general, a mixture of aldehydes undergoes a Cannizzaro reaction to yield all possible products.
- If one of the aldehydes is formaldehyde, the reaction yields almost exclusively salt of formic acid and the alcohol corresponding to the other aldehyde. Such a reaction is called a **Crossed Cannizzaro Reaction**.
- If two different aldehyde having no  $\alpha$ -Hydrogen, it is called **Crossed Cannizzaro Reaction**.



#### - Reaction Mechanism:



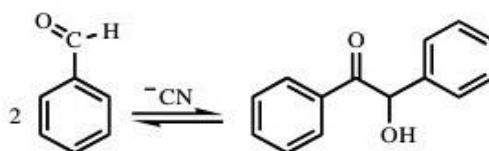
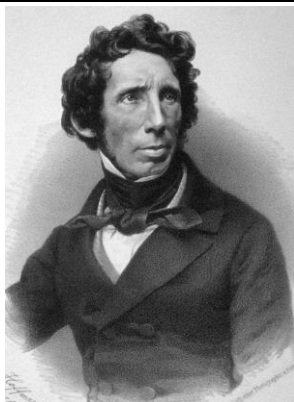
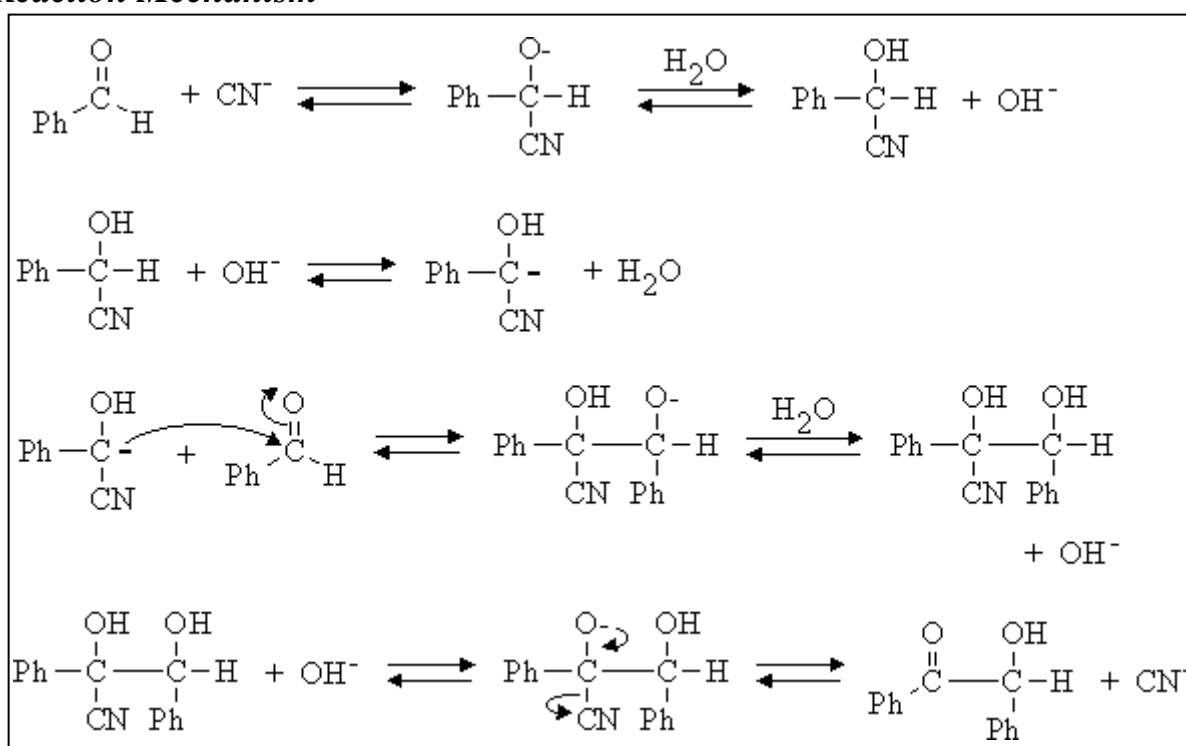
### Stanislao Cannizzaro



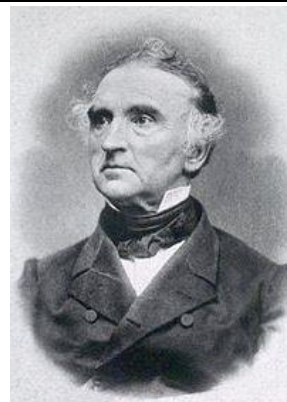
**Born** : 13 July 1826 (Palermo)  
**Died** : 10 May 1910 (aged 83)  
**Nationality** : Italian  
**Known for** : Cannizzaro reaction  
**Awards** : Faraday Lectureship Prize (1872); Copley Medal (1891)  
**Scientific career**: Fields Chemistry

❖ **Benzoin condensation**

- **Benzoin Condensation** is an important reaction in which carbon-carbon bond is formed when two molecules of aldehydes (particularly benzaldehyde) reacts with each other to form a condensed product called **Benzoin**.
- This reaction is named after *Friederich Woehler* and *Justus von Liebig* in 1832.
- This reaction is catalyzed by **cyanide ion**.
  - When 2 moles of aromatic aldehydes react in the presence of KCN, an alpha hydroxyl ketone is obtained

• **Reaction Mechanism**

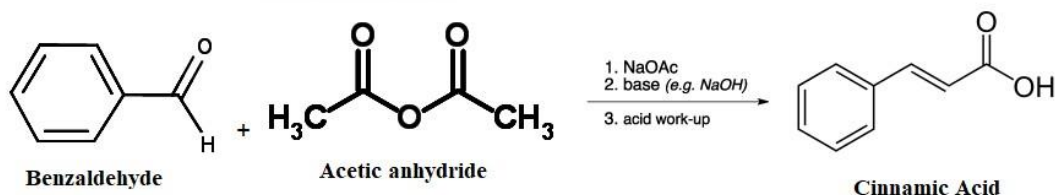
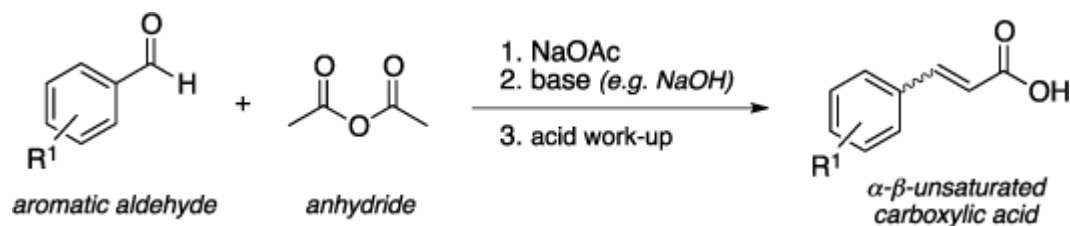
**Sir Friedrich Wöhler** (31 July 1800 – 23 September 1882) was a German chemist, best known for his synthesis of Urea, Benzoin Condensation, but also the first to isolate several chemical elements.



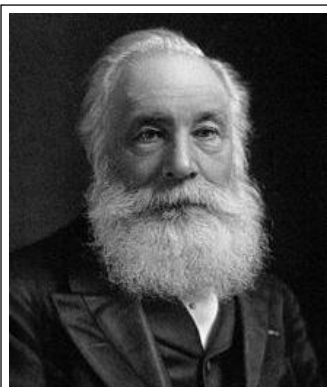
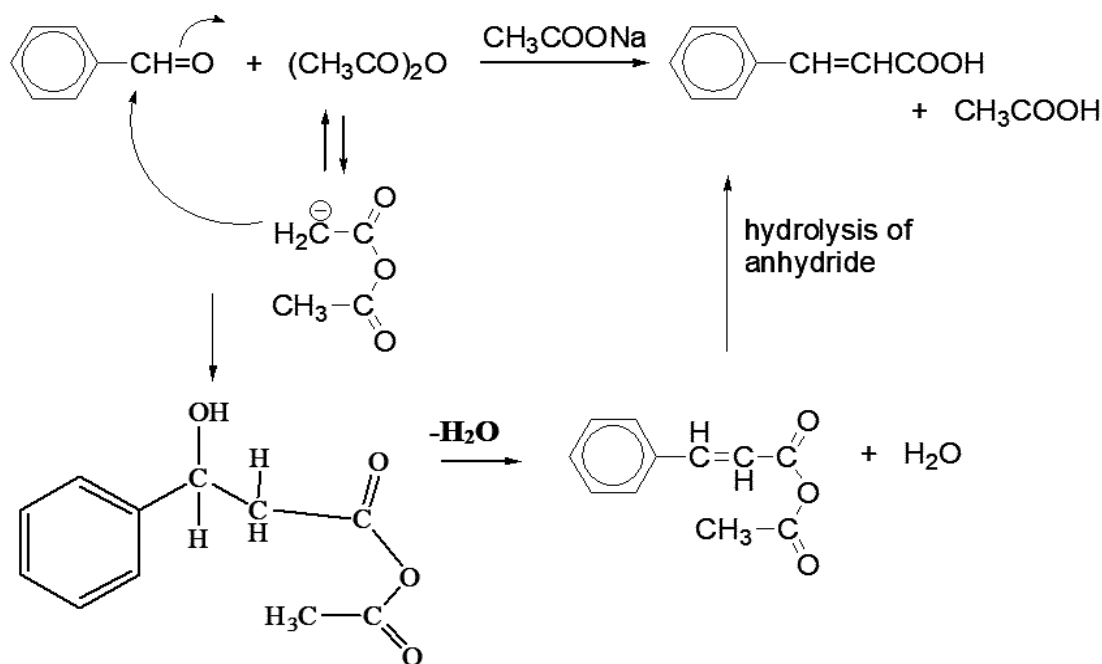
**Sir Justus Freiherr von Liebig** (12 May 1803 – 18 April 1873) was a German chemist who made major contributions to agricultural and biological chemistry, and was considered the founder of organic chemistry. He has been described as the "father of the fertilizer industry",

### ❖ Perkin condensation

- The Perkin reaction is an organic reaction used to convert an aromatic aldehyde and an anhydride to an  $\alpha,\beta$ -unsaturated carboxylic acid using sodium acetate, a base, and an acid work-up.
- The Perkin reaction is an organic reaction developed by *Sir William Henry Perkin* that is used to make **cinnamic acids**.



#### • Reaction Mechanism



- **Sir William Henry Perkin** (12 March 1838 – 14 July 1907) was an English chemist best known for his accidental discovery of the first **aniline dye**: the **purple mauveine**. Though failing in trying to synthesise **quinine** for the treatment of malaria, he became successful in the field of dyes after his discovery at the age of 18.

- **Awards:** Royal Medal (1879)  
 Davy Medal (1889)  
 Albert Medal (1890)  
 Perkin Medal (1906)

“Don't trust atoms, they make up everything”