Aldehydes and **Ketones**

Part 2

B. Pharm. Semester-1
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Learning Outcomes

At the end of this lesson, students will be able to describe

Reactions of Aldehydes and Ketones

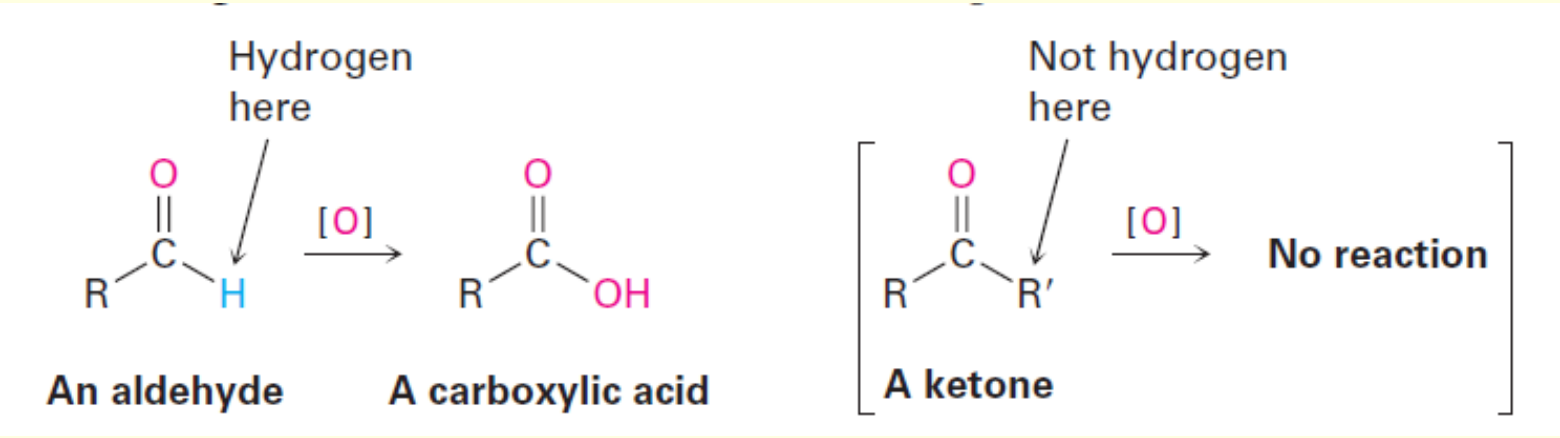
- **Oxidation reactions of Aldehydes and Ketones**
- **Nucleophilic addition reactions of Aldehydes and Ketones**
- **Nucleophilic Addition of H_2O: Hydration**
- **Nucleophilic Addition of HCN: Cyanohydrin formation**
- **Nucleophilic Addition of Grignard Reagents: Alcohol Formation**

Objective

The objective of this course is to give to the students of pharmacy the basic knowledge about the organic chemistry.

Oxidation reactions of Aldehydes and Ketones

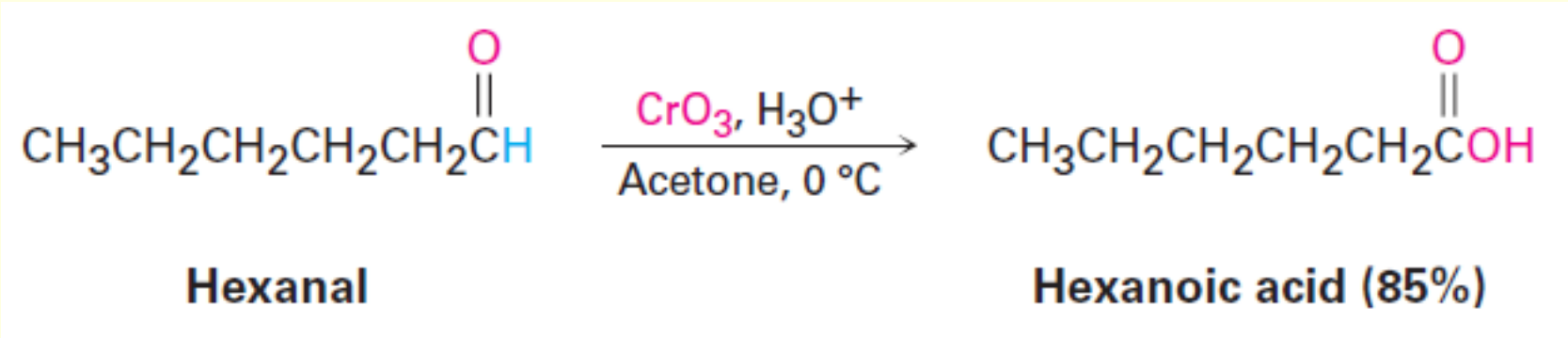
- Aldehydes are easily oxidized to yield carboxylic acids, but ketones are generally inert toward oxidation.
- The difference is a consequence of structure: aldehydes have R-CHO proton that can be abstracted during oxidation, but ketones do not.



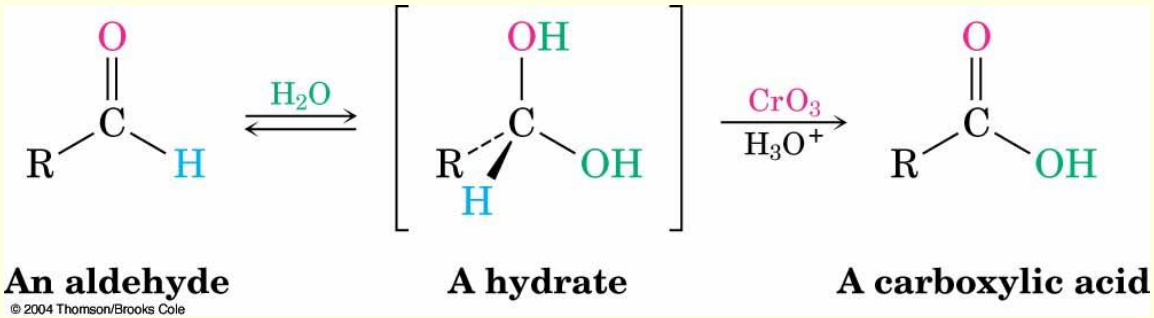
Many oxidizing agents including $KMnO_4$ can convert aldehydes into carboxylic acids, but CrO_3 in aqueous acid is the best choice.

Oxidation reactions of Aldehydes

The oxidation occurs rapidly at room temperature and generally results in good yields.

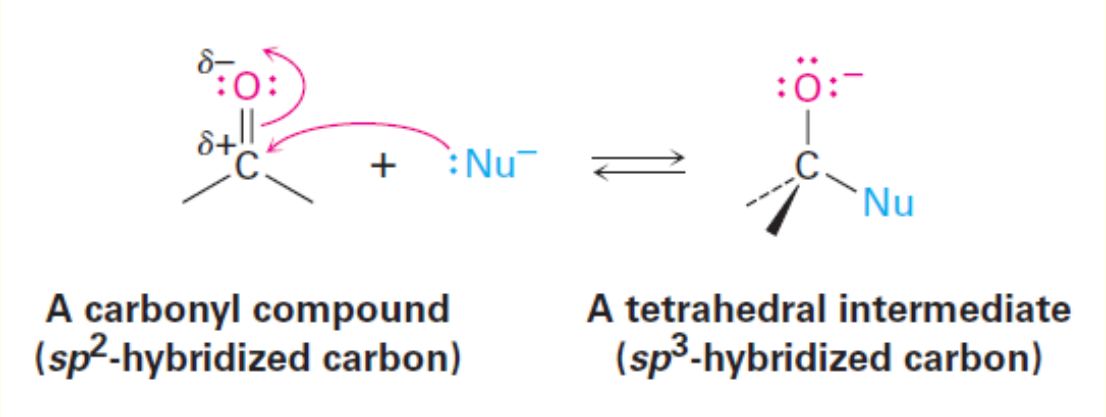


Aldehyde oxidations occur through intermediate 1,1-diols, or hydrates, which are formed by a reversible nucleophilic addition of water to the carbonyl group.



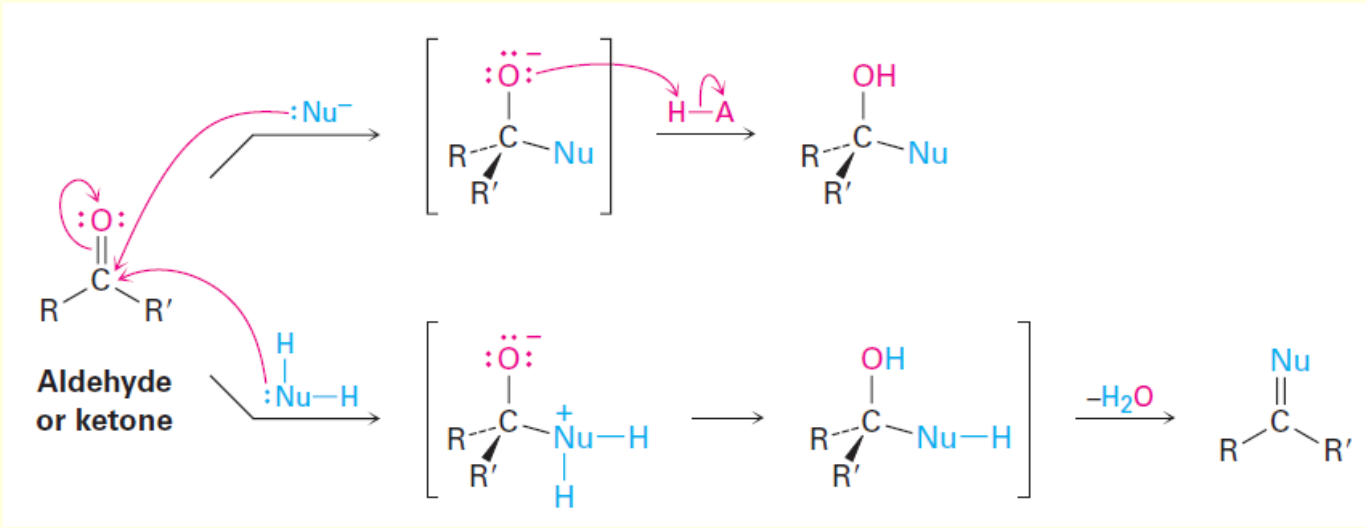
Nucleophilic Addition Reactions of Aldehydes and Ketones

- The most common reaction of aldehydes and ketones is the nucleophilic addition reaction.
- Nucleophile adds to the electrophilic carbon of the carbonyl group.
- Since the nucleophile uses an electron pair to form a new bond to carbon, two electrons from the carbon–oxygen double bond must move toward the electronegative oxygen atom to give an alkoxide anion.

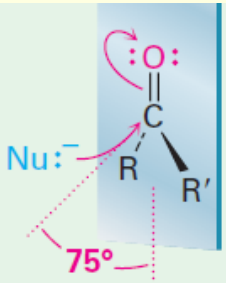


Nucleophilic Addition Reactions of Aldehydes and Ketones

- Depending on the nature of the nucleophile, the tetrahedral alkoxide intermediate can undergo either two further reactions.
- Tetrahedral alkoxide intermediate is protonated by water or acid to form an **alcohol** product.
- Alternatively, the tetrahedral intermediate can be protonated and expel the oxygen to form a new double bond between the carbonyl carbon and the nucleophile.



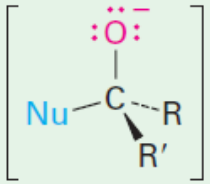
Mechanism of Nucleophilic Addition Reactions of Aldehydes and Ketones



Aldehyde or ketone

1 An electron pair from the nucleophile adds to the electrophilic carbon of the carbonyl group, pushing an electron pair from the C=O bond onto oxygen and giving an alkoxide ion intermediate. The carbonyl carbon rehybridizes from sp^2 to sp^3.

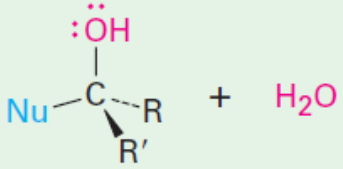
1



Alkoxide ion

2 Protonation of the alkoxide anion intermediate gives the neutral alcohol addition product.

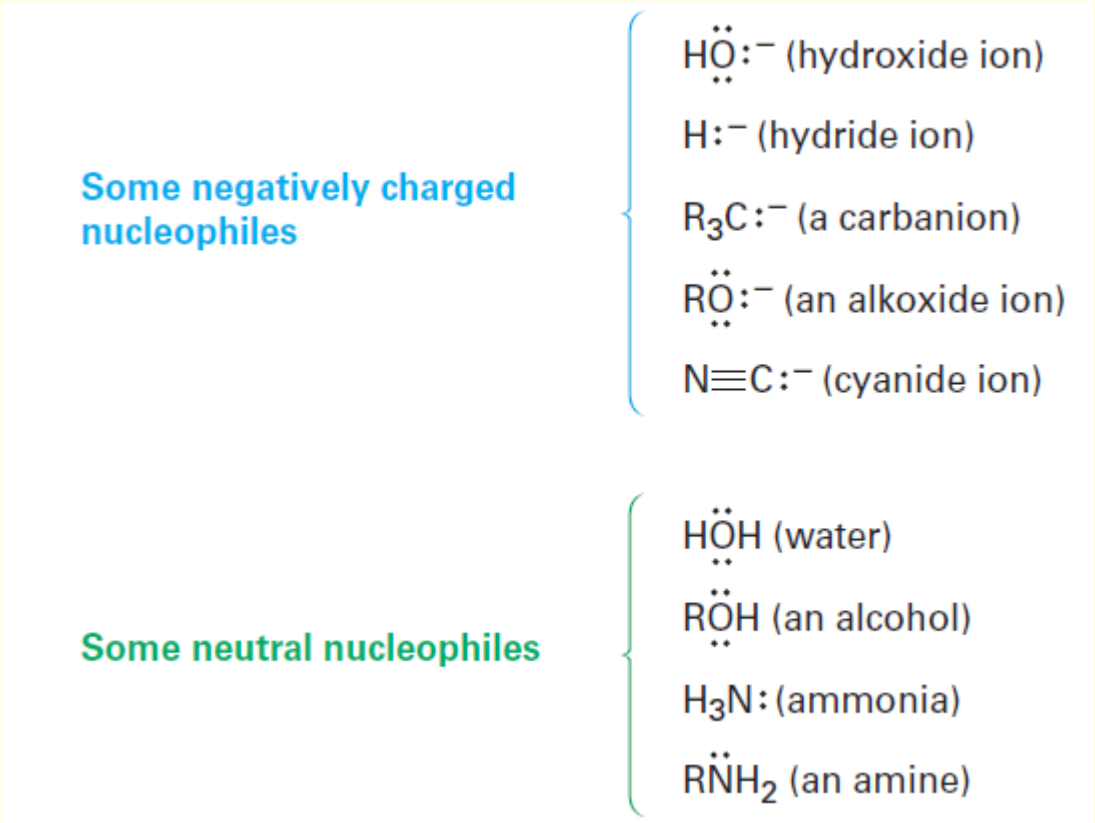
2 H_3O^+



Alcohol

Nucleophiles

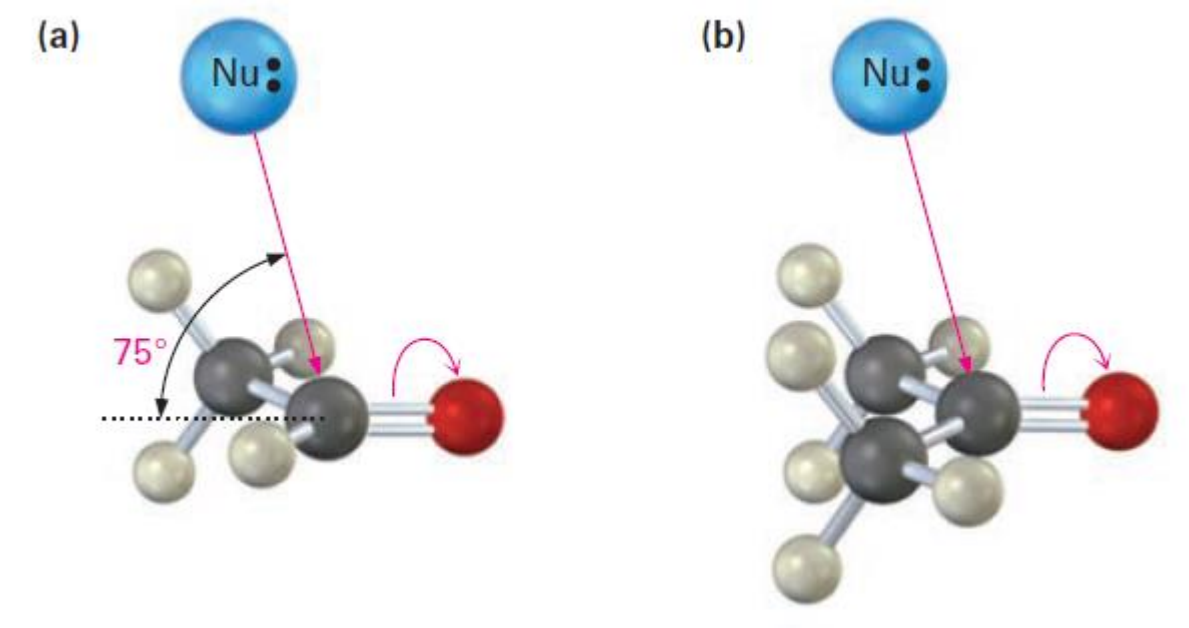
The nucleophile can be either negatively charged ($:Nu^-$) or neutral (:Nu). If it's neutral, it usually carries a hydrogen atom that can subsequently be eliminated, :Nu-H.



Relative Reactivity of Aldehydes and Ketones

- ✓Aldehydes are generally more reactive than ketones in nucleophilic addition reactions for both steric and electronic reasons.
- ✓Sterically, the presence of only one large substituent bonded to the C=O carbon in an aldehyde versus two large substituents in a ketone means that a nucleophile is able to approach an aldehyde more readily.
- ✓Thus, the transition state leading to the tetrahedral intermediate is less crowded and lower in energy for an aldehyde than for a ketone.

Relative Reactivity of Aldehydes and Ketones

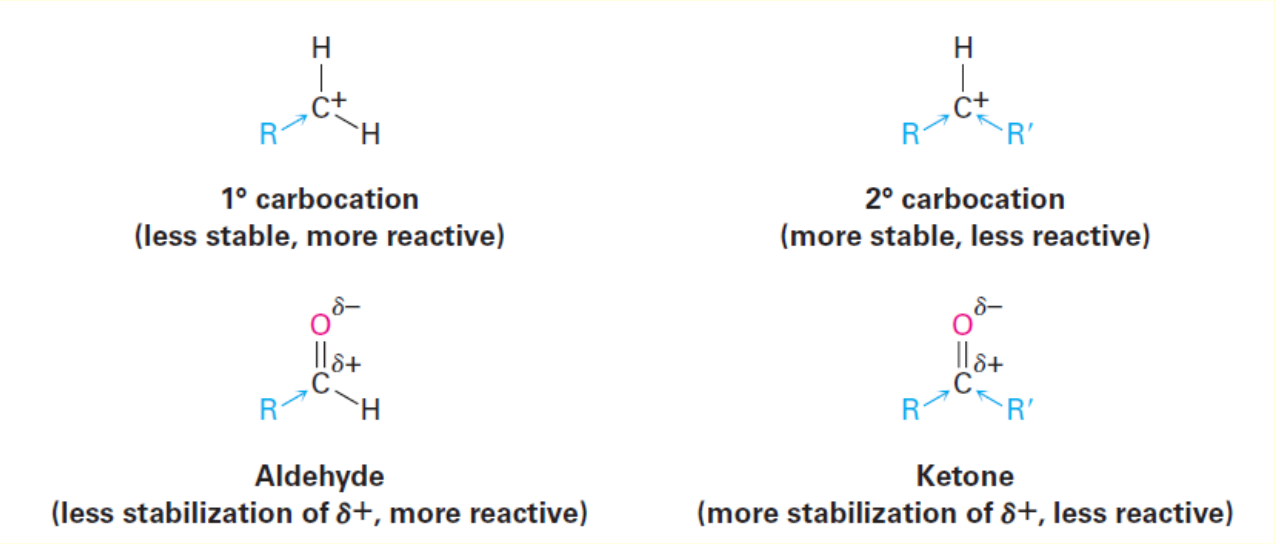


Aldehyde **Ketone**

Electronically, aldehydes are more reactive than ketones because of the greater polarization of aldehyde.

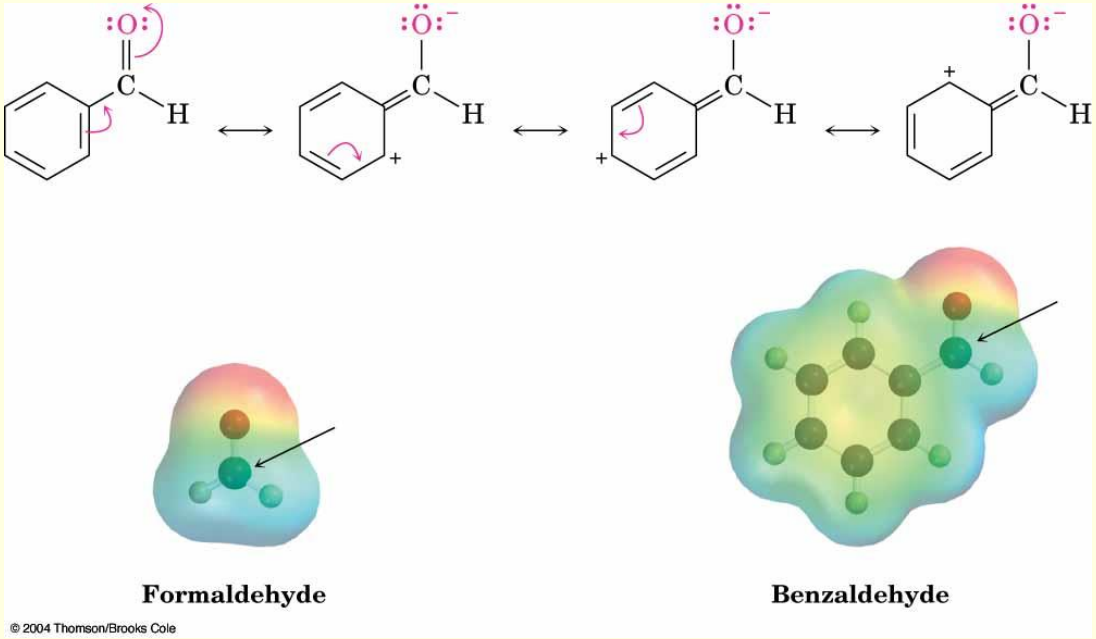
Electrophilicity of Aldehydes and Ketones

- A primary carbocation is higher in energy, so it is more reactive than a secondary carbocation, because it has only one alkyl group inductively stabilizing the positive charge than two.
- In the same way, an aldehyde has only one alkyl group inductively stabilizing the partial positive charge on the carbonyl carbon rather than two, is a bit more electrophilic, and is therefore more reactive than a ketone.



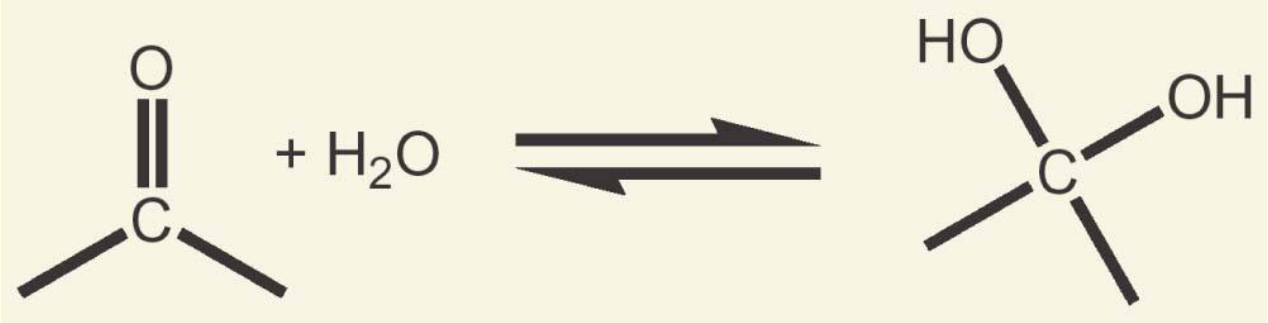
Reactivity of Aromatic Aldehydes

Aromatic aldehydes like benzaldehyde are less reactive in nucleophilic addition reactions than aliphatic aldehydes because the electron-donating resonance effect of the aromatic ring makes the carbonyl group less electrophilic.



Nucleophilic Addition of H_2O: Hydration

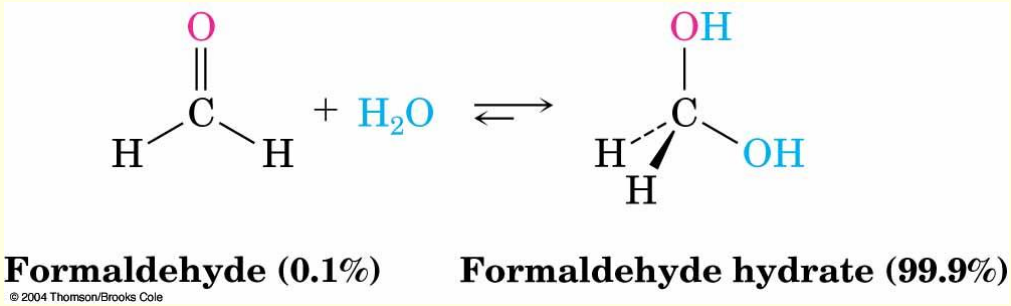
- Aldehydes and ketones react with water to yield 1,1-diols, or geminal (gem) diols.
- The hydration reaction is reversible, and a gem diol can eliminate water to regenerate an aldehyde or ketone.

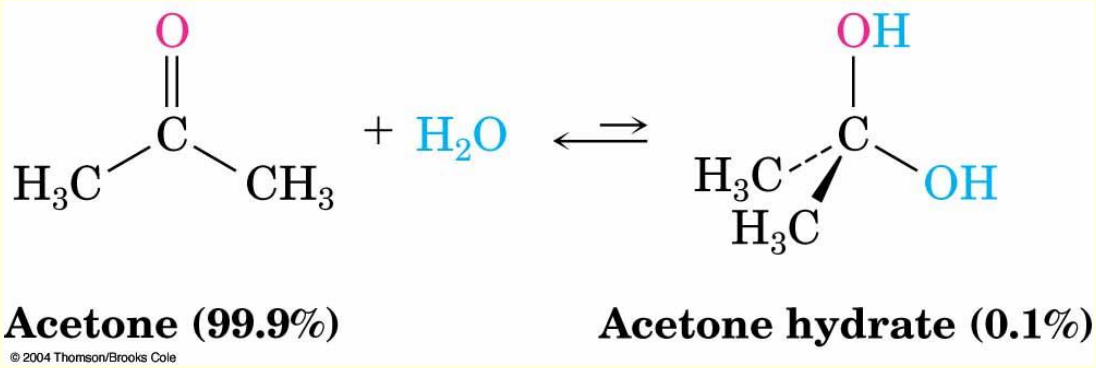


- The equilibrium generally favors the carbonyl compound for steric reasons, but the gem diol is favored for a few simple aldehydes.

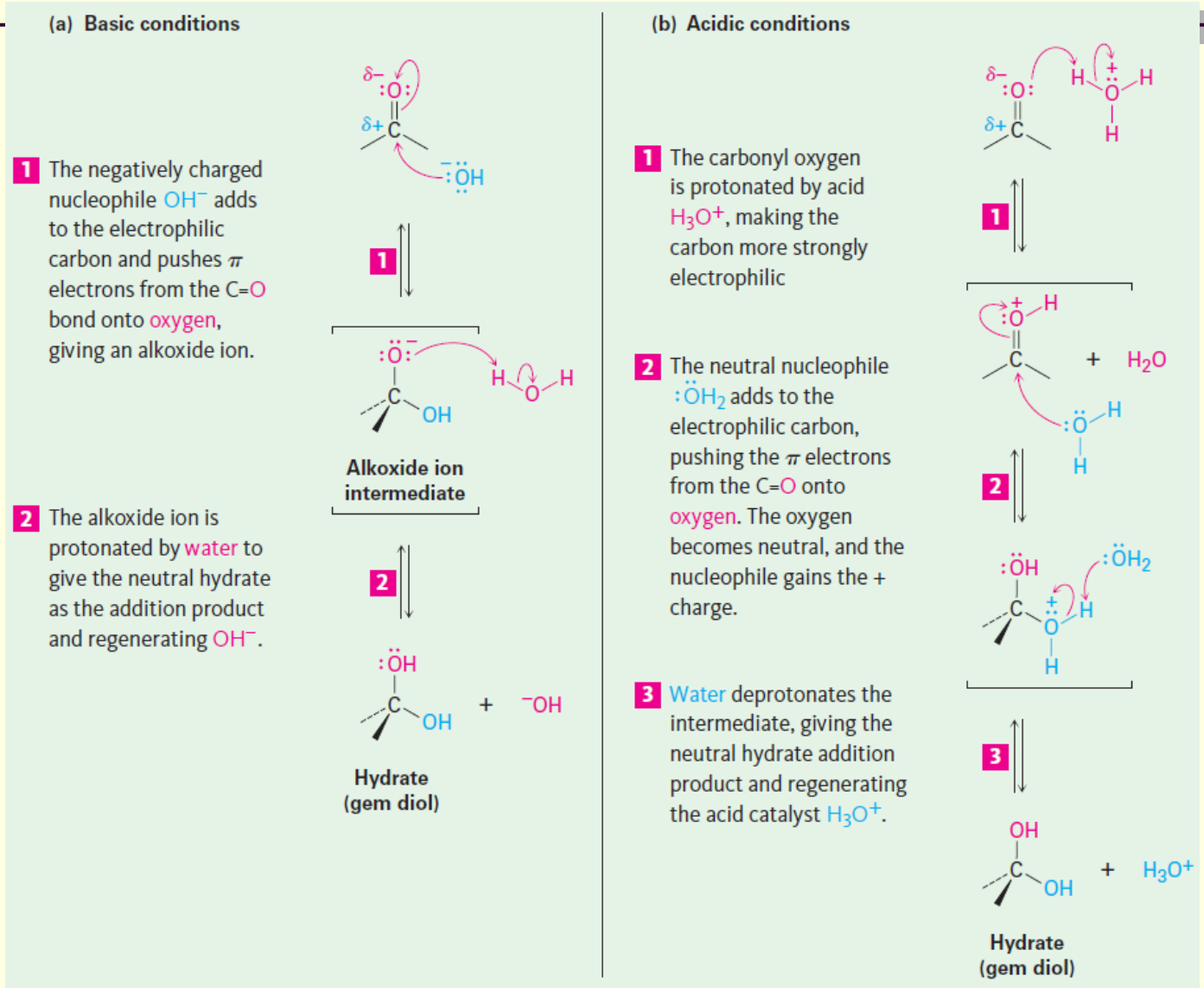
Nucleophilic Addition of H_2O: Hydration

- An aqueous solution of formaldehyde consists of 99.9% gem diol and 0.1% aldehyde at equilibrium, whereas
- An aqueous solution of acetone consists of only about 0.1% gem diol and 99.9% ketone.



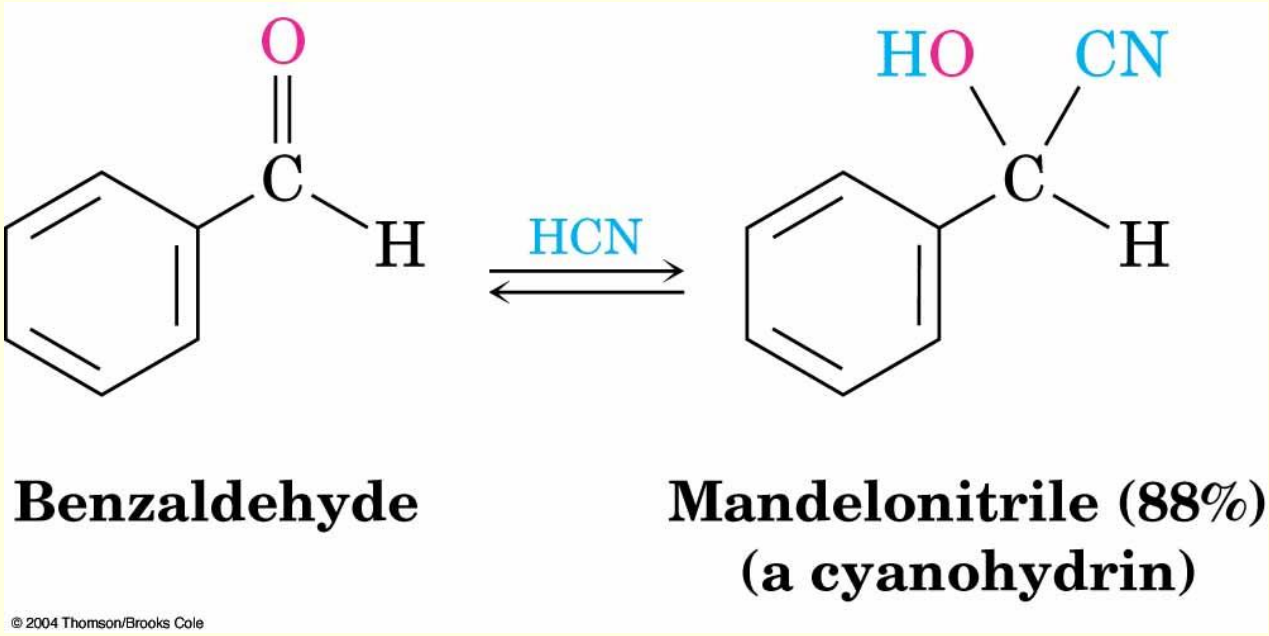


Nucleophilic Addition of H_2O: Mechanism



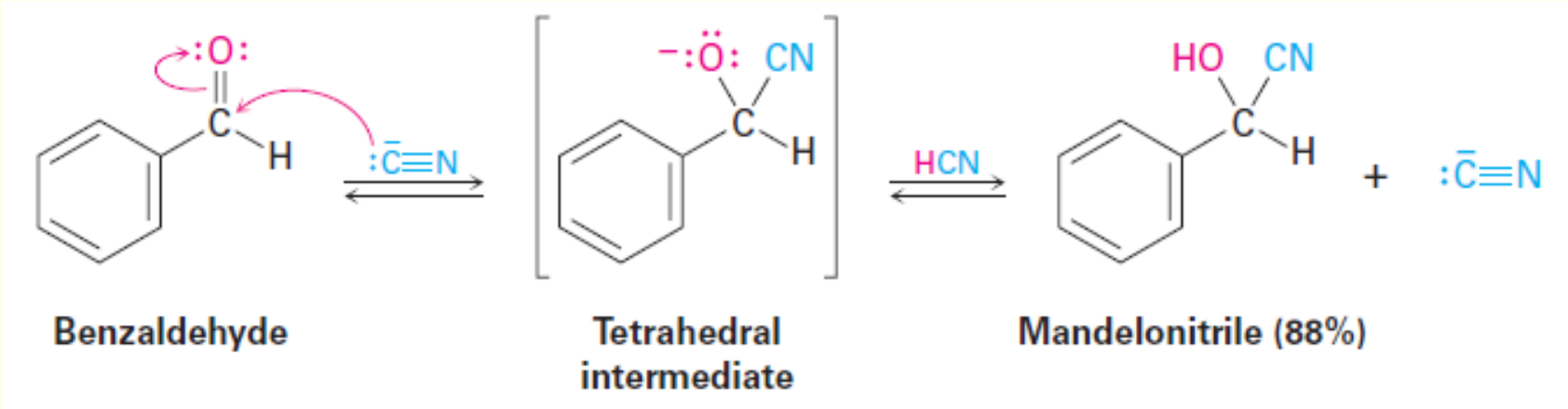
Nucleophilic Addition of HCN: Cyanohydrin formation

Aldehydes and unhindered ketones undergo a nucleophilic addition reaction with HCN to yield cyanohydrins, RCH(OH)C=N.



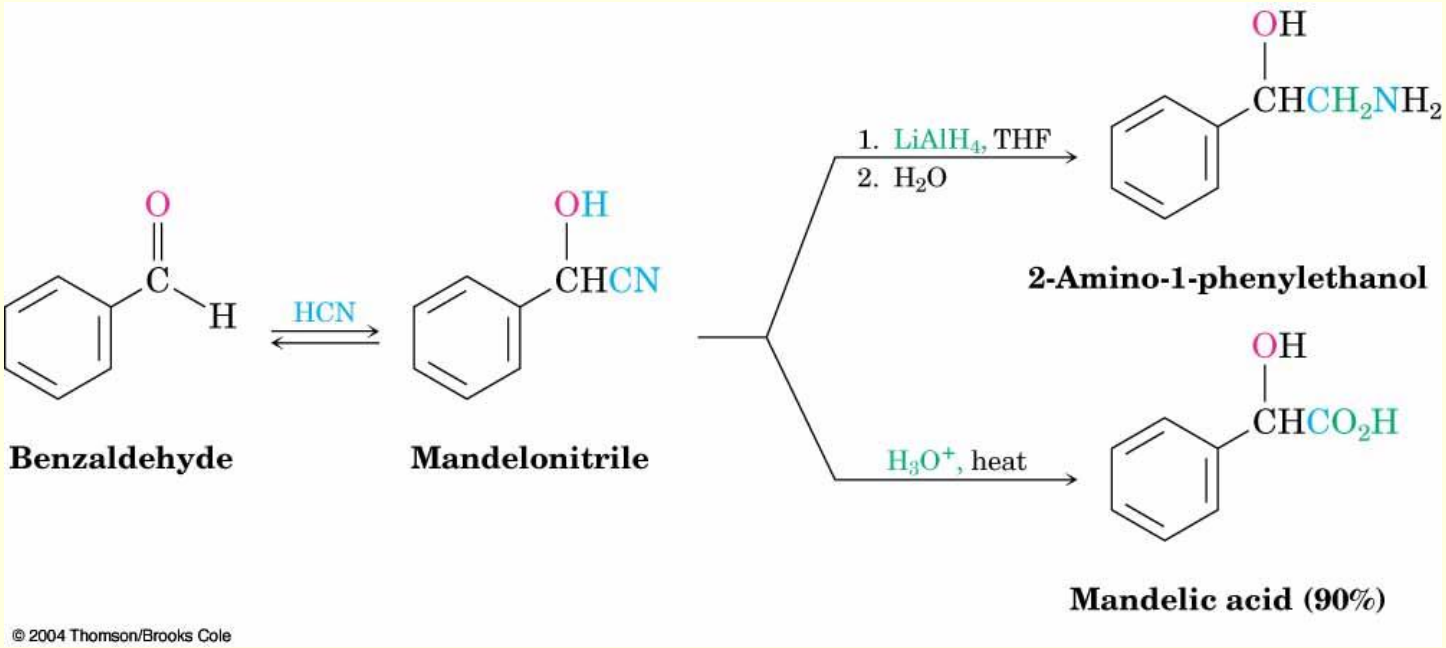
Nucleophilic Addition of HCN: Cyanohydrin formation: Mechanism

Addition of CN^- takes place by a typical nucleophilic addition pathway, yielding a tetrahedral intermediate that is protonated by HCN to give cyanohydrin product plus regenerated CN^-.



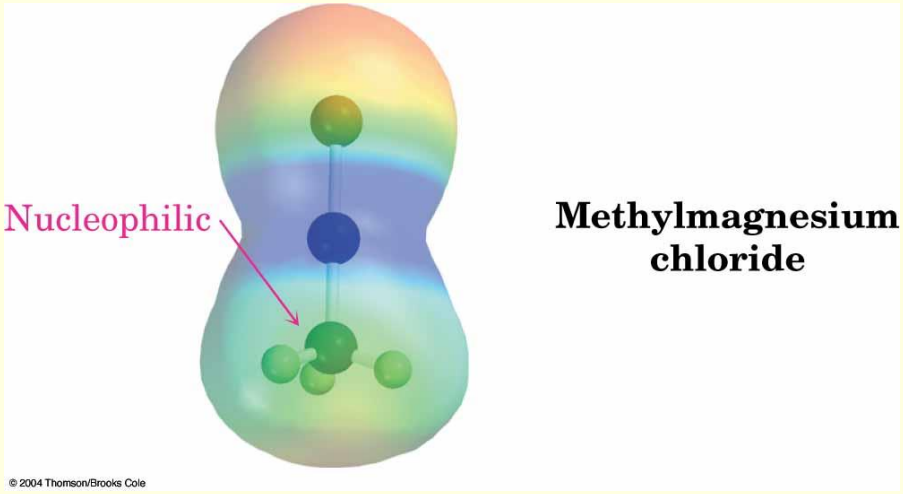
Uses of Cyanohydrin

- ✓ Cyanohydrin formation provides a method for transforming an aldehyde or ketone into a different functional group.
- ✓ A nitrile (R-C≡N) can be reduced with $LiAlH_4$ to yield a primary amine (RCH_2NH_2) and can be hydrolyzed by hot aqueous acid to yield a carboxylic acid.



Nucleophilic Addition of Grignard Reagents: Alcohol Formation

- ✓ Treatment of aldehyde or ketone with Grignard reagents yields an alcohol.
- ✓ Nucleophilic addition of the equivalent of a carbon anion, or carbanion.
- ✓ A carbon–magnesium bond is strongly polarized, so a Grignard reagent ($R:^{-}\ ^{+}Mg\text{-}X$) reacts for all practical purposes.

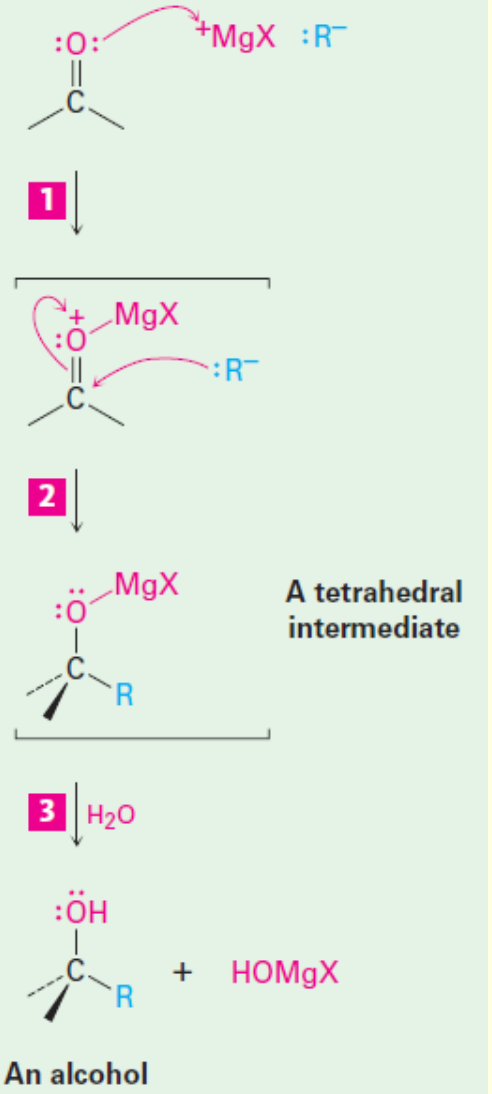


Nucleophilic Addition of Grignard Reagents: Alcohol Formation: Mechanism

1 The Lewis acid Mg^{2+} first forms an acid–base complex with the basic oxygen atom of the aldehyde or ketone, thereby making the carbonyl group a better acceptor.

2 Nucleophilic addition of an alkyl group $:R^-$ to the aldehyde or ketone produces a tetrahedral magnesium alkoxide intermediate . . .

3 . . . which undergoes hydrolysis when water is added in a separate step. The final product is a neutral alcohol.



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2. **Organic Chemistry, 7th Edition, 2010, Authors: Saibal Kanti Bhattacharjee, Robert Thornton Morrison, Robert Neilson Boyd, Publisher: Pearson India, ISBN: 978-0199270293.**
3. **Textbook of Organic Chemistry, 22nd Edition, 2022, Authors: Arun Bahl & B S Bahl, Publisher: S Chand, ISBN: 978-9352531967.**

Supplementary book:

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