Chapter 18 Carbonyl Compounds II
Reactions of Aldehydes and Ketones

- Class II carbonyl compounds are aldehydes and ketones.
  1. Aldehydes: carbonyl carbon is bonded to a hydrogen and to an alkyl group.
  2. Ketones: carbonyl carbon is bonded to two alkyl groups.
- Class II carbonyl compounds do not have a group that can be replaced by a nucleophile. There is no leaving group, because hydride ions (H^-) and carbanions (R^-) are too basic to be displaced by nucleophiles under normal conditions.
- Many compounds found in nature have aldehyde or ketone functional group.

18.1 Nomenclature of Aldehydes and Ketones

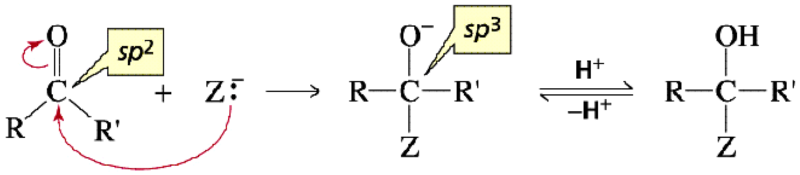
- Aldehydes
  1. Replace the terminal "e" from the name of the parent hydrocarbon with "al".
  2. The position of the carbonyl carbon does not have to be designated, because it is always at the end of the parent hydrocarbon and therefore always has the 1-position.
  3. When common names are used, the position of a substituent is designated by a lowercase Greek letter.
  4. If the aldehyde is attached to a ring, the aldehyde is named by adding "carbaldehyde" to the name of the cyclic component.
  5. If a compound has two functional groups, the one with the lower priority is indicated by its prefix (Table 17.1). The prefix of an aldehyde oxygen that is part of the parent hydrocarbon is "oxo".
- Ketones
  1. Replace the terminal "e" from the name of the parent hydrocarbon with "one".
  2. The chain is numbered in the direction that gives the carbonyl carbon the smaller number. In the cyclic ketones, a number is not necessary because the carbonyl carbon is assumed to be at the 1-position.
  3. The substituents attached to the carbonyl group are cited in alphabetical order, followed by "ketone."
  4. If the ketone has a second functional group of higher naming priority, the ketone oxygen is indicated by the prefix "oxo."

18.2 Relative Reactivities of carbonyl Compounds

- The carbonyl group is polar because oxygen, being more electronegative than carbon, has a greater share of the electrons of the double bond. The partial positive charge on the carbonyl carbon causes carbonyl compounds to be attacked by nucleophiles.
- An aldehyde is less stable than a ketone, and it is more reactive toward nucleophilic attack. An aldehyde has a greater partial positive charge on its carbonyl carbon than does a ketone because a hydrogen is electron withdrawing compared with an alkyl group.
- Steric factors also contribute to the greater reactivity of an aldehyde: the carbonyl carbon of an aldehyde is more accessible to the nucleophile than is the carbonyl carbon of a ketone because of the bulky alkyl groups of a ketone compared to a hydrogen atom of an aldehyde.
- Aldehydes and ketones are less reactive than acyl halides and acid anhydrides, but more reactive than esters, carboxylic acids.

18.3 How Aldehydes and Ketones React

- Since there are no leaving groups in aldehydes and ketones, the major reaction with them is irreversible **nucleophilic addition reactions**.



- When a nucleophile adds to a carbonyl group, the hybridization of the carbonyl carbon changes from sp^2 in the carbonyl compound to sp^3 in the addition product. A compound that has an sp^3 carbon bonded to an oxygen atom generally will be unstable if the sp^3 carbon is also bonded to another electronegative atom. But the tetrahedral addition product is stable, since the addition product has an H or a C nucleophile, which are not electronegative atoms.
- Water will be eliminated from the addition product, and it is called a *nucleophilic addition-elimination reaction*.

18.4 Reactions of Carbonyl Compounds with Carbon Nucleophiles

- The formation of new C-C bonds is very important to synthesize larger organic molecules from smaller molecules.

- When carbon atom is bonded to an electropositive atom, such as metals, the carbon atom can be a carbanion. Then the carbanion can attack any atom that has a positive charge on.
- Grignard reagent (RMgBr): It can be prepared by adding an alkyl halide to magnesium in diethyl ether.
- Attack of a Grignard reagent on a carbonyl carbon forms an alkoxide ion that is complexed with magnesium ion. Addition of water or dilute acid breaks up the complex producing alcohols from aldehydes or ketones.
- A Grignard reagent can also react with carbon dioxide producing a carboxylic acid.
- Class I carbonyl compounds undergo two successive reactions with the Grignard reagent. For example, when an ester reacts with a Grignard reagent, the first reaction is a nucleophilic acyl substitution reaction because an ester has a good leaving group. The product of the reaction is a ketone. And the ketone is more reactive than the ester toward nucleophilic attack producing tertiary alcohol with two identical groups.
- An acetylide ion can attack carbonyl compounds to produce alcohols.
- Hydrogen cyanide adds to aldehydes and ketones to form cyanohydrins. In the first step of the reaction, the cyanide ion attacks the carbonyl carbon. The alkoxide ion then accepts a proton from an undissociated molecule of hydrogen cyanide producing an alcohol. Cyanide ion is relatively weak base, so it can act as a leaving group and can be eliminated from the addition product in basic solution.
- Cyanide ion does not react with esters because the cyanide ion is a weaker base than an alkoxide ion, so the cyanide ion would be eliminated from the tetrahedral intermediate.

18.6 Reactions of Carbonyl Compounds with Hydride Ion

- Addition of hydride ion to an aldehyde or ketone forms an alkoxide ion. Subsequent protonation by an acid produces an alcohol. The overall reaction adds H_2 to the carbonyl group, so the overall reaction is a reduction reaction.
- Sodium borohydride ($NaBH_4$) and lithium aluminum hydride ($LiAlH_4$) are the source of hydride ion. Lithium aluminum hydride (LAH) is more reactive.
- The reaction of a Class I carbonyl compound with hydride ion involves two successive reactions with the nucleophile. $NaBH_4$ is not a sufficiently strong hydride donor, so esters, carboxylic acids, and amides must be reduced with LAH.
- When an ester reacts with hydride ion, the first reaction is a nucleophilic acyl substitution reaction because the alkoxide group would be eliminated by hydride ion,

and the second step is nucleophilic addition reaction producing primary alcohols. The reaction can’t be stopped at the first step (aldehyde) because an aldehyde is more reactive than an ester. Diisobutylaluminum hydride (DIBALH) is used as the hydride donor to stop the reaction at the aldehyde stage. The reaction is carried out at low temperature (-78 ℃)

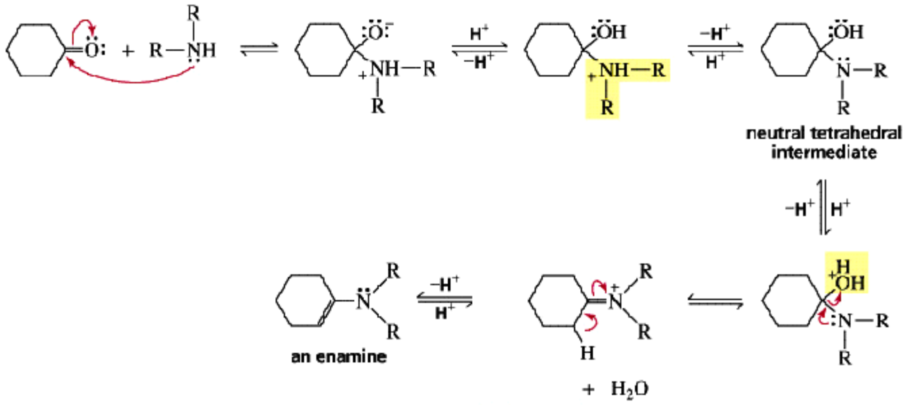
- The reaction of a carboxylic acid with LAH forms a single primary alcohol. In the first step of the reaction, a hydride ion reacts with the acidic hydrogen of the carboxylic acid, forming H_2 and a carboxylate ion, which do not react with nucleophiles because of the negative charge. In this case, LAH accepts a pair of electrons from the carboxylate ion and forms a new hydride donor. Then hydride ion from attached LAH is added to the carbonyl carbon twice to produce a primary alcohol.
- Acyl chlorides undergo two successive additions of hydride ion when treated with LAH.
- Amides also undergo two successive additions of hydride ion when they react with LAH producing amines. So the reaction converts a carbonyl group into a methylene group. The mechanism of the reaction is similar to that of the reaction with a carboxylic acid.

18.8 Reactions of Aldehydes and Ketones with Amines and Derivatives of Amines

- Aldehydes and ketones react with a primary amine to form an imine, which contains a carbon-nitrogen double bond. The product is called a Schiff base. The orbital model of a C=N is similar to the orbital model of a C=O group.
- Aldehydes and ketones react with a secondary amine to form an **enamine**, which is an α,β-unsaturated tertiary amine.
- Addition reaction of primary amines requires a catalytic amount of acid. In the first step, the amine attacks the carbonyl carbon. Gain a proton by the alkoxide ion and loss of a proton by the ammonium ion forms a neutral tetrahedral intermediate, which is called a carbinolamine. The carbinolamine is in equilibrium with two protonated forms. Protonation can take place on either the nitrogen or the oxygen atom. Elimination of water from the oxygen-protonated intermediate forms a protonated imine that loses a proton to yield the imine.
- The equilibrium favors the nitrogen-protonated tetrahedral intermediate because nitrogen is more basic than oxygen. The equilibrium can be forced toward the imine by removing water as it is formed or by precipitation of the imine product.

- The overall reaction of addition of a nitrogen nucleophile to an aldehyde or a ketone is a nucleophilic addition-elimination reaction. Aldehydes and ketones undergo nucleophilic addition reactions with carbon and hydrogen nucleophiles.
- There must be sufficient acid present to protonate the tetrahedral intermediate so that H_2O rather than the much more basic HO^- is the leaving group. So the pH must be controlled carefully (Fig. 17.2). However, if too much acid is present, it will protonate all of the reactant amine. Protonated amines are not nucleophiles, so they can’t react with carbonyl groups.
- Imine formation is reversible: In acidic aqueous solutions, imines are hydrolyzed back to the carbonyl compound and amine.
- Aldehydes and ketones react with secondary amines to from enamines with an aid of an acid catalyst. The mechanism is exactly the same until the last step. In the last step, the positively charged nitrogen is not bonded to a hydrogen, so a stable neutral molecule is obtained by removing a proton from the α-carbon of the compound derived from the carbonyl compound.

mechanism for enamine formation



this intermediate cannot lose a proton from N, so it loses a proton from an α-carbon

- In aqueous acidic solution, an enamine is hydrolyzed back t the carbonyl compound. And secondary amine.
- Hydroxylamines, hydrazine, and semicarbazides can react with aldehydes and ketones to produce oximes, hydrazone, and semicarbazones.
- Phenyl-substituted hydrazines react with aldehydes and ketones to form phenylhydrazones.
- A ketone or an aldehyde is heated in a basic solution of hydrazine, the carbonyl group is converted into a methylene group. This process is called deoxygenation, and the reaction is known as Wolff-Kishner reduction. Initially the ketone reacts with hydrazine to form a hydrazone. Then hydroxide ion removes a proton from the NH_2

group. The negative charge can be delocalized onto carbon, which abstracts a proton from water. This process is repeated to form the oxygenated product and nitrogen gas.

18.9 Reactions of Aldehydes and Ketones with Ketones and Water

- Water adds to an aldehyde or a ketone to form a hydrate, *gem-diols*. Hydrates of aldehydes or ketones are generally too unstable to be isolated because the tetrahedral carbon is attached to two oxygen atoms.
- Water is a poor nucleophile, so the rate of the reaction can be increased by an acid catalyst.
- The extent to which an aldehyde or a ketone is hydrated in an aqueous solution depends on the aldehyde or ketone. The equilibrium constant for a reaction depends on the relative stabilities of the reactants and products (electronic and steric effects). Electron donating alkyl groups make a carbonyl compound more stable, and make the hydrate less stable because of the steric interactions between the alkyl groups.
- If the amount of hydrate formed from the reaction of water with a ketone is too small to detect, how do we know that the reaction has occurred? => labeling experiment with ^{18}O.

18.10 Reactions of Aldehydes and Ketones with Alcohols

- When one equivalent of an alcohol is added to an aldehyde, hemiacetal is formed. When two equivalent of an alcohol is added to an aldehyde, an acetal is formed. These reactions require an acid catalyst.
- In the first step of acetal formation, the acid protonates the carbonyl oxygen, making the carbonyl carbon more susceptible to nucleophilic attack. Loss of a proton from the protonated tetrahedral intermediate gives the hemiacetal (or hemiketal).
- Because the reaction is carried out in acidic condition, the hemiacetal is in equilibrium with its protonated form. The two oxygen atoms are equally basic, so either one can be protonated. Loss of water from the tetrahedral intermediate with a protonated OH group forms a compound that is very reactive because of its electron-deficient carbon. Nucleophilic attack on this compound by a second molecule of alcohol, followed by loss of a proton, forms the acetal.
- Although the tetrahedral carbon of an acetal or ketal is bonded to two oxygen atoms, causing us to predict that the acetal or ketal is not stable, the acetal or ketal can be isolated if the water eliminated from the hemiacetal is removed from the reaction

mixture, because the only compound the acetal or ketal can form is an O-methylated carbonyl compound, which is less stable than the acetal or ketal.

- The acetal or ketal can be transformed back to the aldehyde or ketone in an acidic aqueous solution.

18.11 Protecting Groups

- If a compound has two functional groups that will react with a given reagent and you want only one of them, it is necessary to protect one of them from the reagent. A group that protects a functional group is called a protecting group.
- Keto functional group can be protected by forming ketal, which is very stable. The protecting group must be converted back to the keto form easily.
- One of the best way to protect an OH group of an alcohol is to convert it to a trimethylsilyl (TMS) ether by treating the alcohol with chlorotrimethylsilane and a tertiary amine. The ether is formed through an SN2 reaction. It is possible with silicon, because Si-C bond is longer than C-C bonds reducing steric hindrance at the site of nucleophilic attack. The TMS ether is stable in neutral and basic solutions, can be removed with aqueous acid under mild conditions.

18.12 Addition of Sulfur Nucleophiles

- Aldehydes and ketones react with thiols to form thioacetals and thioketals. The mechanism is the same as that of an alcohol.

18.13 The Wittig Reaction Forms an Alkene

- An aldehyde or a ketone reacts with a phosphonium ylide to form an alkene (converting C=O into C=C). And this reaction is called a *Wittig reaction*.
- An ylide is a compound that has opposite charges on adjacent covalently bonded atoms with complete octets. The ylide can be written in the double bond form.
- The Wittig reaction is a concerted [2+2] cycloaddtion reaction, with the nucleophilic carbon of the ylide attacking the electrophilic carbon of the carbonyl compound. Elimination of triphenylphosphine oxide forms the alkene product.
- The phosphonium ylide is prepared by an S_N2 reaction between triphenylphosphine and alkyl halides with the appropriate number of carbons.

- If two sets of reagents are available for the synthesis of an alkene, it is better to use the one that requires the less sterically hindered alkyl halide for synthesis of the ylide. It is the best way to make a terminal alkene.
- The stereoselectivity of the Wittig reaction depends on the structure of the ylide.
- Stabilized ylides have a group that can share the carbanion's negative charge.
- Stabilized ylides form primarily E isomers, and unstabilized ylides form primarily Z isomers.

18.14 Stereochemistry of Nucleophilic Addition Reactions: *Re* and *Si* Faces

- A carbonyl carbon bonded to two different substituents is a prochiral carbonyl carbon because it will become a chirality center if it adds a group unlike either of the groups already bonded to it. The addition product will be a pair of enantiomers.
- The Re face: the face closest to the observer when decreasing priorities are in a clockwise direction.
- The Si face: the face closest to observer when decreasing priorities are in a counterclockwise direction.
- Whether attack on the Re face forms the R or S enantiomer depends on the priority of the attacking nucleophile.

18.16 Nucleophilic Addition to α,β-Unsaturated Aldehydes and Ketones

- According to the resonance contributors for an α,β-unsaturated carbonyl compound, there are two electrophilic sites: the carbonyl carbon and the β-carbon.
  1. Nucleophilic addition to the carbonyl carbon is called **direct addition** or 1,2-addition.
  2. Nucleophilic addition to the β-carbon is called **conjugate addition**.
- After 1,4-addition has occurred, the initial product, an enol, tautomerizes to a ketone, so the overall reaction is the addition to C=C, with the nucleophile addition to the β-carbon and a proton from the reaction mixture adding to the α-carbon.
- Whether the product is direct addition product or the conjugate addition product depends on the nature of the nucleophile, the structure of the carbonyl compound, and the conditions under which the reaction is carried out.
  1. Nucleophiles that form unstable addition products, that are nucleophiles that are weak bases, such as, halide ions, cyanide ion, thiols, alcohols and amines, form conjugate addition product because conjugate addition is not reversible, and the

conjugate addition product is more stable.

2. Nucleophiles that form stable addition products, nucleophiles that are strong bases making direct addition irreversible, such as hydride ion and carbanions, can form either direct addition products or conjugate addition products.
3. Which one is the major product depends on the reactivity of the carbonyl group. Compounds with reactive carbonyl groups form primarily direct addition products because for those compounds, direct reaction is faster, whereas compounds with less reactive carbonyl groups form primarily conjugate addition products because for those compounds, conjugate addition is faster.

- If the rate of direct addition is slowed down by steric hindrance, a Grrignard reagent will form a conjugate addition product because conjugate addition becomes the faster reaction.
- Only conjugate addition occurs when Gilman reagents react with α,β-unsaturated aldehyde and ketones.
- Hard electrophiles and nucleophiles are more polarized than soft ones. Hard nucleophiles prefer to react with hard electrophiles, and soft nucleophiles prefer to react with soft electrophiles. Therefore, a Grignard reagent with a highly polarized C-Mg bond prefers to react with the harder C=O bond, whereas a Gilman reagent with a much less polarized C-Cu bond prefers to react with the softer C=C bond.

18.17 Nucleophilic Addition to α,β-Unsaturated Carboxylic Acid Derivatives

- α,β-Unsaturated carboxylic acid derivatives can undergo conjugate addition or nucleophilic acyl substitution.
- They undergo nucleophilic acyl substitution rather than direct addition because the α,β-unsaturated carbonyl compound had a group that can be prepared by a nucleophile.
- Conjugate addition products are formed from the reaction of nucleophiles with less reactive carbonyl groups, such as esters and amides.

18.18 Enzyme-Catalyzed Additions to α,β-unsaturated Carbonyl Compounds

- Several biological reactions involve addition to α,β-unsaturated carbonyl compounds.