

Chapter 16: Aldehydes and Ketones

- 16.2: Naming aldehydes and ketones
 - Aldehydes: -al suffix. The aldehyde is always in position 1, so there is no need to number it (i.e. butanal). If the aldehyde is a substituent, it is named a carbaldehyde group.
 - Ketone: -one suffix. The position is numbered with the lowest possible number (i.e. 2-hexanone). Ketones as substituents are generically known as acyl groups. Methyl ketones are called acetyl groups.
 - If both a ketone and aldehyde are present, the ketone is named as an oxo substituent.
- 16.3: Physical properties
 - The carbonyl bond is strongly polar. The carbon has positive character while the oxygen has a partial negative charge
 - This polarity results in aldehydes and ketones having higher boiling points than ethers or alkanes. The polarity effect is weaker than H-bonding, so their boiling points are lower than alcohols.
- 16.4: Reactivity of aldehydes and ketones
 - Because oxygen is more electronegative than carbon, the C=O bond is polarized so that the carbon is partially positively charged and the oxygen partially negatively charged. The carbon of the carbonyl is an electrophile. A wide range of nucleophiles will react with carbonyls by adding to this carbon.
 - Strong nucleophiles (OH^- , H^- , R_3C^- , RO^- , NC^-) add directly to carbonyls. After protonation an alcohol product is obtained.
 - Weak nucleophiles (H_2O , ROH , RNH_2) usually require acid or base catalysts to promote addition. Under acidic conditions, the initial alcohol product can be dehydrated. This is the key step in the formation of an acetal or imine (discussed below).
 - Aldehydes are stronger electrophiles (more reactive) than ketones. Alkyl groups are inductive electron donating groups, so they make carbonyl carbon less electrophilic.
- 16.5: Addition of Carbon nucleophiles
 - Grignard reagents (RMgX) behave as carbanions and can serve as nucleophiles. The Grignard agent can be used to add a carbon fragment to a ketone or aldehyde to give an alcohol. The reaction is similar to reduction of carbonyls, but a carbon group is added instead of H. The reaction must be made acidic in the final step to protonate the alkoxide anion formed.
 - Primary alcohols can be made by Grignard addition to formaldehyde ($\text{H}_2\text{C=O}$)
 - Secondary alcohols are made by Grignard addition to aldehydes
 - Tertiary alcohols are made by Grignard addition to ketones
 - Organolithium reagents react in the same way as Grignard reagents.

- Grignard and organolithium reagents are very reactive and are strong bases. Thus there are several other functional groups that are incompatible with a Grignard reagent. These groups must be protected in order to be used with a Grignard reagent.
 - Acidic functional groups: —OH, —NH, —SH, —CO₂H
 - Electrophilic functional groups: aldehydes, ketones, amides, esters, nitriles, —NO₂, —SO₂R
- Acetylide anions can also be added to carbonyls to give alkynyl alcohols.
 - Recall that the acetylide anion can be made by deprotonation of a terminal alkyne with NaNH₂.
 - These alkyne products can then be used to do the reactions we have learned in CH 231.
- Cyanide is a much weaker nucleophile than acetylide, but can still add to aldehydes and ketones. The resulting cyanoalcohol product is known as a cyanohydrin.
 - The reaction is generally carried out with HCN and a small amount of base. The base generates the cyanide anion, which adds to the carbonyl. The resulting alkoxide anion then deprotonates another molecule of HCN.
 - This reaction is an equilibrium. Under basic conditions, HCN can be eliminated to regenerate the carbonyl. For aldehydes and most ketones, the cyanohydrin product is favored in the equilibrium.
- 16.6: Addition of phosphorus-ylides: the Wittig reaction
 - Ylides: Ylides are molecules that have a positive and negative charge on adjacent atoms.
 - Phosphorus ylides: Phosphonium salts can be deprotonated at the carbon attached to the phosphorus using a strong base, such as butyl lithium. The C-H bond is more acidic because the carbanion will be stabilized by the neighboring positive charge on phosphorus. This is an inductive effect because resonance is not possible. Most commonly, alkyl triphenylphosphonium salts are used. These can be made by an S_N2 reaction between triphenylphosphine and an alkyl halide.
 - Phosphorus ylides can be used to make alkenes from carbonyl compounds. This reaction is known as the Wittig reaction.
 - The phosphorus ylide is a nucleophile. The carbanion will add to carbonyl compounds to give a betaine intermediate (molecule with both positive and negative charges on nonadjacent atoms).
 - The positively charged phosphorus and the alkoxy ion then form a bond to give a 4-membered ring product (oxaphosphetane).
 - The ring then falls apart to give an alkene product and triphenylphosphine oxide. The phosphine oxide is very stable, which drives this reaction.
 - The Wittig reaction can be used to make the thermodynamically less stable product (less substituted). In an elimination reaction, the thermodynamically most stable product is formed. In the Wittig reaction, it is possible to make the less stable product.

- Depending on the substituents on phosphorus, the Wittig reaction can favor *E*- or *Z*-alkene formation.
 - Ylides without resonance stabilizing groups on the anionic carbon generally favor the *Z*-alkene.
 - Ylides with resonance stabilization (i.e. carbonyls connected to the anionic carbon) favor *E*-alkene formation.
 - The Horner-Emmons-Wadsworth modification of the Wittig reaction uses trimethylphosphite (P(OMe)₃) in place of triphenylphosphine. The ylide is made with an α -haloester (XCH₂CO₂R). The resulting ylide is highly *E*-selective.
- 16.7: Addition of oxygen nucleophiles
 - Water adds to aldehydes and ketones to give a hydrate. A hydrate is a functional group in which two –OH groups are on the same carbon.
 - The addition of water is an equilibrium process. For most ketones, only a small amount of hydrate (0.1 %) is formed. With more electrophilic carbonyls, a larger amount of hydrate is formed. Formaldehyde forms the hydrate almost completely (99.9%) in water. Trichloroacetaldehyde (Cl₃CCHO) also forms the hydrate almost completely in water. The hydrate is known as chloral hydrate. Chloral hydrate are knock out drops. In old movies, chloral hydrate was used when someone was slipped a Mickey.
 - Alcohols add to carbonyls in the same way that water does. The reaction can be catalyzed by base or acid. The addition product is known as a hemiacetal (OH and OR groups attached to same carbon)
 - Base catalysis: Alcohols are not a strong enough nucleophile to add to a carbonyl, but alkoxides are. The alkoxide adds to give the deprotonated form of a hemiacetal. This anion is protonated by the alcohol, which regenerates the alkoxide catalyst.
 - Acid catalysis: Under acidic conditions, the carbonyl can be protonated. The protonated carbonyl is more electrophilic, so the alcohol will add directly to it to give a protonated hemiacetal. Deprotonation with water regenerates the acid catalyst.
 - Water follows identical mechanisms to generate the hydrate.
 - Molecules with alcohols and carbonyls in the same molecule can form cyclic hemiacetals. This is a common reaction for sugars, such as glucose.
 - Under acidic conditions, the hemiacetal is not stable. The OH group is replaced by another alkoxy group to give an acetal (two OR groups on same carbon). The mechanism is similar to an S_N1 reaction. The OH group is protonated. Water leaves to give a carbocation stabilized by the neighboring alkoxy group. Another alcohol adds to the carbocation. Loss of a proton gives the acetal product.
 - An acetal cannot be formed under basic conditions. Under basic conditions, acetal formation would require an S_N2-like reaction, which is not possible.
 - Acetal and hemiacetal formation is reversible. Hemiacetal formation can be reversed under both acid and base conditions.

- Acetals can be converted back to carbonyls under aqueous (H₂O) acidic conditions. This reaction is known as hydrolysis (addition of water). The mechanism is the exact reverse of acetal formation. One of the acetal oxygens is protonated and the alcohol leaves to give a carbocation. Water adds to the carbocation, which gives a hemiacetal after loss of a proton. The remaining alkoxy group is protonated and leaves as an alcohol. This gives a protonated carbonyl, which gives the carbonyl after loss of the proton.
 - Acetals cannot be hydrolyzed under basic conditions, since they cannot be made under basic conditions. Again, this would require an S_N2-like reaction, which is not possible.
 - Acetals are useful protecting groups for aldehydes and ketones. An acetal is not very electrophilic, so it will not react in the same way as a carbonyl.
 - If we want to form a Grignard of a haloketone, we must protect the ketone by converting it to an acetal.
 - Often cyclic acetals derived from a dialcohol are used as they are more stable.
 - Once the acetal is formed, we can make the Grignard reagent and do the reaction with an aldehyde or ketone.
 - Treatment of the acetal with aqueous acid will hydrolyze the acetal to regenerate the ketone.
 - Tetrahydropyrans are another acetal-based protecting group. They are used to protect alcohols.
 - The tetrahydropyran (THP) protecting group is made by reacting an alcohol with tetrahydropyran under acidic conditions.
 - This occurs by the same mechanism as electrophilic addition to an alkene.
 - The acid protonates the alkene. The carbocation is formed next to the O because of the resonance stabilization.
 - The alcohol then adds to the alkene and is deprotonated to give an acetal.
 - Treatment with aqueous acid decomposes the THP acetal to give back the alcohol.
- 16.8: Addition of nitrogen nucleophiles
 - Primary amines will react with aldehydes and ketones under acidic conditions to give an imine, which is a functional group with a carbon-nitrogen double bond. The mechanism is similar to acetal formation.
 - The amine, which is more nucleophilic than an alcohol, adds directly to the carbonyl. Proton transfer gives a carbinolamine intermediate (analogous to a hemiacetal). The OH group is then protonated and water leaves with assistance from the lone pair on nitrogen. Deprotonation at nitrogen gives the imine.
 - Imines are important in biology as many enzymes form imine bonds between amine groups on the enzyme and aldehyde functional groups (i.e. rhodopsin).

- Any NH_2 group can form an imine. Hydroxylamine (H_2NOH) forms an oxime ($\text{R}_2\text{C}=\text{NOH}$); hydrazine forms a hydrazone ($\text{R}_2\text{C}=\text{NNH}_2$).
 - Imine formation is reversible. Thus, treatment of an imine with acidic water will regenerate the carbonyl and give an ammonium ion. The mechanism is the reverse of imine formation. The imine is protonated, which makes it more electrophilic. Water adds to give a protonated carbinol amine. Proton transfer moves the proton to the nitrogen, which then is eliminated to give a protonated carbonyl and the amine. Deprotonation of the carbonyl gives the free carbonyl and an ammonium ion.
- Secondary amines react in a similar way, but give an enamine product (vinyl amine).
 - The mechanism is the same as imine formation through the elimination of water to give the iminium ion. With a secondary amine, there is no proton on nitrogen. Instead, a proton is removed from the carbon next to the iminium ion, which gives the enamine product.
 - Enamine formation is also reversible. Protonation of the enamine on the carbon not attached to the nitrogen gives an iminium ion. From here, the mechanism is the same as hydrolysis of the imine.
- 16.10: Oxidation of aldehydes and ketones
 - Oxidation of aldehydes produces a carboxylic acid. Pretty much any oxidizing agent will work (CrO_3 , Ag_2O , KMnO_4). PCC will not oxidize the aldehyde, however.
 - Oxidation with Ag_2O gives silver as a byproduct. This is known as the Tollens reagent. It is used as a test for aldehydes. A silver mirror is produced on the flask.
 - Ketones are difficult to oxidize
 - Normal oxidation reagents will not oxidize ketones
 - A ketone can be oxidized to a dicarboxylic acid by treatment with nitric acid at high temperature. This is used industrially to convert cyclohexanone to adipic acid, which is a precursor to nylon.
- 16.11: Reduction
 - Alcohols can be made by reducing (adding hydrogen) carbonyls ($\text{C}=\text{O}$ bonds).
 - An aldehyde will give a primary alcohol
 - A ketone will give a secondary alcohol
 - Sodium borohydride (NaBH_4) or lithium aluminum hydride (LiAlH_4) can be used to reduce ketones and aldehydes.
 - These reagents act as hydride (H^-) sources and the hydride nucleophilically adds to the electrophilic carbonyl carbon.
 - Acid (H_3O^+) must be added in a second step to hydrolyze the boron or aluminum alkoxide salts that are formed.
 - Reductive amination

- Imines can be reduced similar to aldehydes or ketones to give an amine. The reduction can be done catalytically (H_2/Ni) or with a metal hydride reagent.
- The imine formation and reduction can be carried out in the same step. In this case, $NaBH_3CN$ (sodium cyanoborohydride) is used. This reaction is an effective way to convert carbonyls to amines in one step.
- Reduction of ketones or aldehydes to alkanes.
 - The reductions above reduce carbonyls to alcohols, but do not remove the O from the C. There are two ways that the carbonyl can be reduced all the way to an alkane.
 - Clemmensen reduction: Treatment of a ketone with zinc mercury amalgam ($Zn(Hg)$) and HCl will replace the carbonyl oxygen with two hydrogens.
 - Wolf-Kishner reduction: Treatment of a ketone with hydrazine under strongly basic conditions (KOH) will give an alkane with elimination of nitrogen and water.
 - ◆ The reaction involves the formation of a hydrazone as described above. The base then deprotonates the NH_2 group of the hydrazone. You can write a resonance structure with the negative charge on the imine carbon. Protonation at carbon gives a product with an $N=N$ bond. Removal of the second proton at nitrogen results in elimination of nitrogen to give a carbanion, which is protonated by water.

We will come back to discuss sections 16.9 and 16.12 when we get to chapter 19.