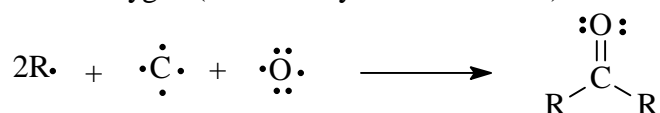
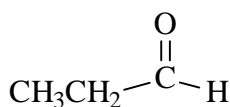


**ALDEHYDES AND KETONES***Jack DeRuiter***I. Introduction**

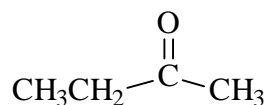
Aldehyde and ketones are "carbonyl" derivatives of the hydrocarbons. A carbonyl is defined as an organic functional group consisting of a carbon atom involved in a double-bonding ( $\pi$ ) arrangement with oxygen. Recall that carbon has a valence of four and thus requires four electrons or bonds to achieve an octet. Oxygen has a valence of six and thus requires two electrons or bonds to satisfy its octet. Thus carbon can form single bonds with oxygen (as in the alcohols and ethers) or double bond with oxygen (as in aldehydes and ketones) in the neutral state:



Organic compounds containing the carbonyl functional group can be classified as aldehydes or ketones depending on the relative position of the carbonyl moiety. In aldehyde the carbonyl is a "terminal" or end-carbon functionality; in aldehydes the carbonyl is bound to a carbon and a hydrogen atom. In ketones the carbonyl is contained within a hydrocarbon structure, and not on one terminus; the carbonyl carbon is bound to two other carbon atoms. The general structural difference between aldehydes and ketones is illustrated in the examples below. This difference is important in terms of the relative reactivity of these compounds as discussed in the sections that follow.

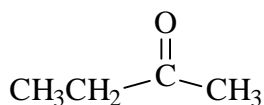


Aldehyde

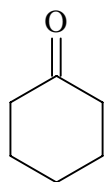


Ketone

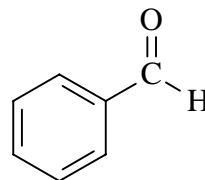
Carbonyl groups may be present in simple aliphatic compounds, in cycloaliphatics and as substituents of aromatic systems. Again, the relative "placement" or bonding of a carbon within the greater organic structure is important for reactivity as discussed in the sections that follow:



Aliphatic ketone

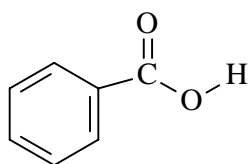


Cycloaliphatic ketone

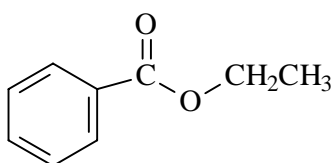


Aromatic Aldehyde

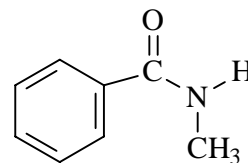
It is important to note that other organic functional groups may also contain a carbonyl group, such as acids, esters and amides. These are not classified as aldehydes or ketones and their chemistry is significantly different than aldehydes and ketones, as noted in the appropriate tutorials:



Carboxylic Acid



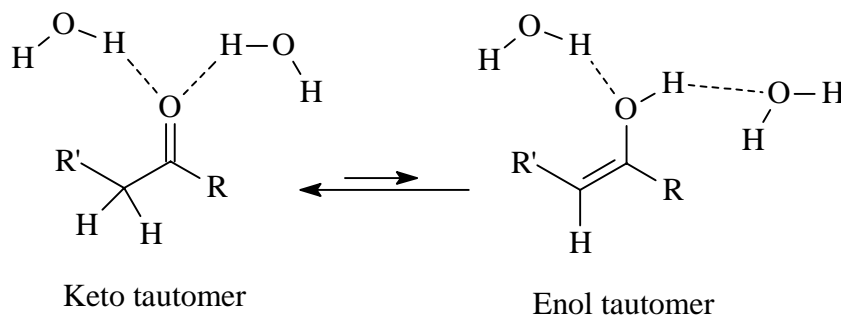
Ester



Amide

## II. Aldehyde and Ketone Solubility

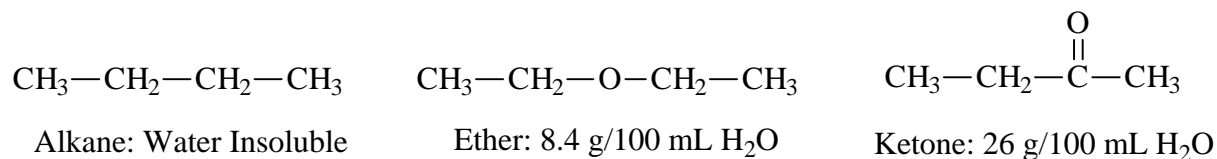
The carbonyl function (C=O) of these compounds is a relatively strong dipole since oxygen is significantly more electronegative than carbon, and the  $\pi$ -bond electrons are easily distorted toward oxygen. This dipole allows the oxygen of the carbonyl to act as a H-bond acceptor as shown below. Furthermore, ketones and, to a lesser extent, aldehydes exist in equilibrium with their "enol" tautomeric forms which can both donate and accept hydrogen bonds with water.



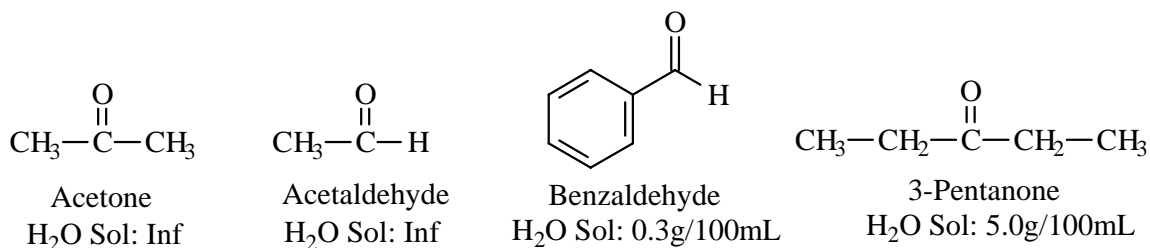
Keto tautomer

Enol tautomer

As a result of these properties, aldehydes and ketones have significantly higher water solubilities than non-polar (hydrocarbon) compounds of similar size. Furthermore, the hydrogen bonding interactions formed between water and aldehydes and ketones are more numerous and stronger than those formed with comparable ethers since aldehydes and ketones have a stronger carbonyl dipole, and some enolization to give an O-H dipole:



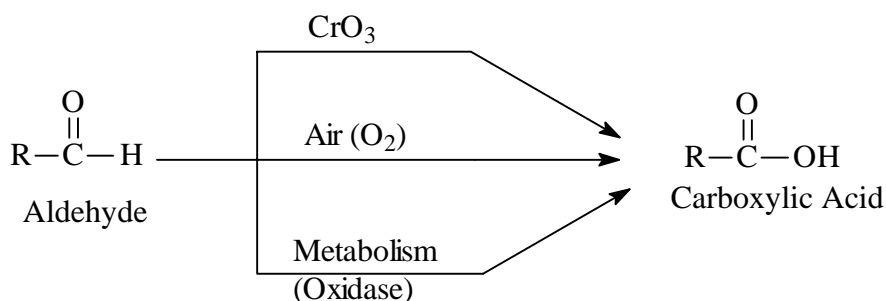
It is important to note that as the non-polar (hydrocarbon) portion of aldehydes and ketones increases, water solubility decreases due to increased van der Waals interactions between the non-polar portions of the molecules. The carbonyl group of aldehydes and ketones can solubilize up to four carbon atoms. Hence acetaldehyde and acetone are infinitely "soluble" in water, while larger aldehydes and ketones such as benzaldehyde and 3-pentanone show only limited water solubility:



### III. Aldehyde and Ketone Reactivity

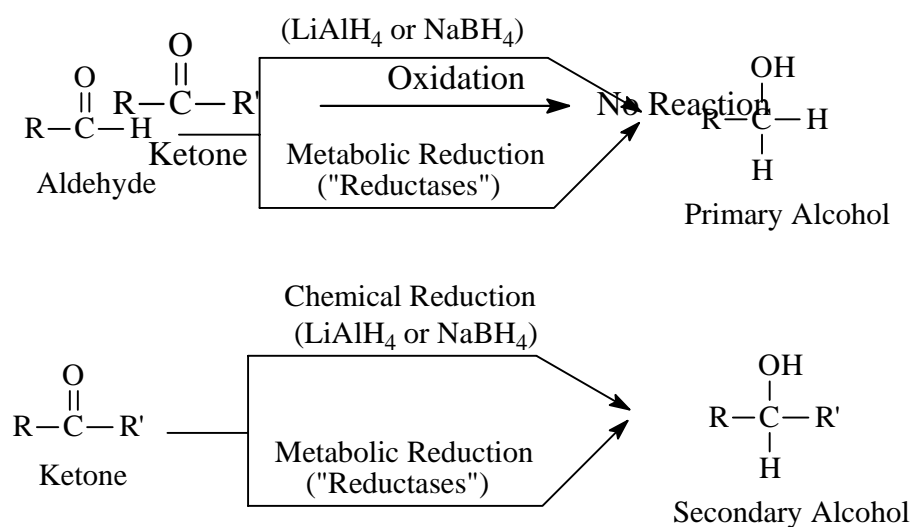
#### A. Oxidations and Reductions:

The carbonyl group of aldehydes contains a hydrogen atom and thus is susceptible to oxidation. Aldehydes can be oxidized by chemical oxidizing reagents such as chromium trioxide, by metabolic enzymes and even in the presence of air. The oxidation product formed in each case is the corresponding acid:



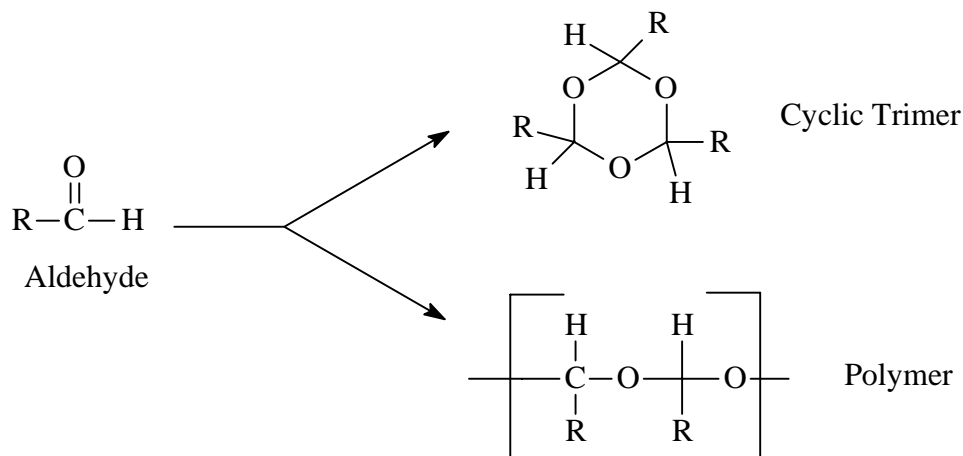
In ketones the carbonyl group is linked to two carbon atoms and thus is less susceptible to direct oxidation, both chemically (except under extreme conditions) and metabolically. There is some "indirect" oxidation that occurs with ketones and this is covered in the Metabolism Tutorial:

Because of the dipolar  $sp^2$ -hybridized carbonyl group present in aldehydes and ketones, both of these types of compounds are susceptible to reduction, both by chemical reducing agents and metabolic enzymes. Aldehydes are reduced to their corresponding primary alcohols, while ketones are reduced to their corresponding secondary alcohols. The secondary alcohols formed from ketones may be chiral if the ketone form which they were generated was "prochiral" (bearing two dissimilar substituents as shown in the example below):



B. Polymerization

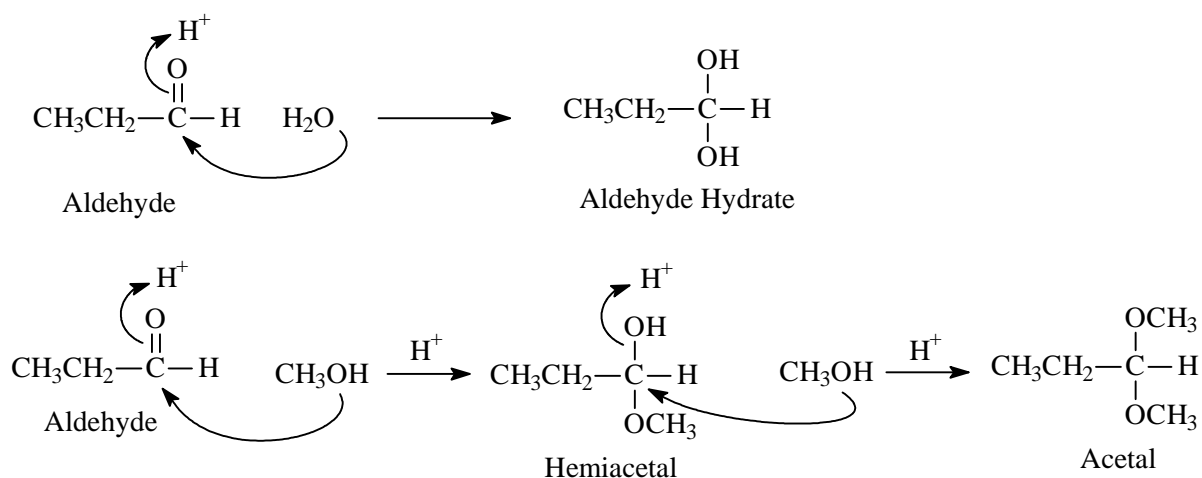
Low molecular weight ("small") aldehydes can undergo trimerization to form six membered ring systems, or polymerize to yield polyethers:

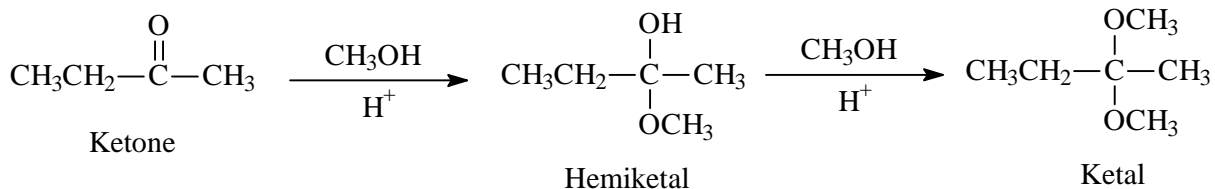


Such polymerization reactions do not occur readily with ketones due to the increased steric bulk on the carbonyl carbon. Recall that an aldehyde carbonyl is bound to another carbon atom and a small, non-bulky hydrogen atom. In ketones the carbonyl is bound to two carbon atoms, thus there is more steric bulk at the reaction site. This bulk limits polymerization reactions in ketones.

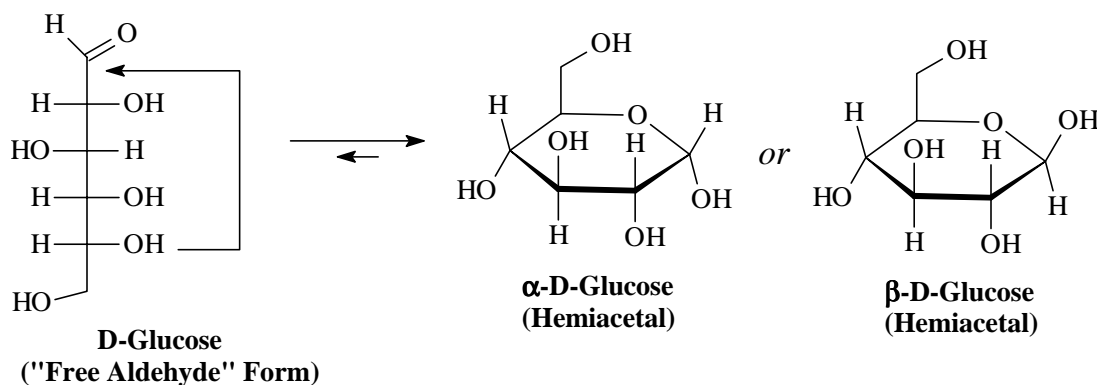
C. Electrophilic/Nucleophilic Reactions at Carbonyl

The dipole associated with the carbonyl functionality renders the carbon electrophilic and therefore susceptible to "nucleophilic attack". In such reactions the "leaving group" in the nucleophilic reaction may simply be a pair of electrons, or it may be the oxygen atom, depending on the nature of the attacking nucleophile. A number of nucleophilic reactions involving aldehydes and ketones are shown in the examples below.

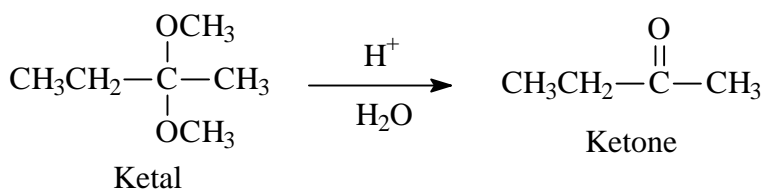
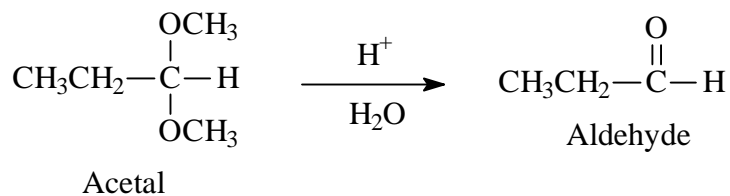
1. *Reactions with Oxygen Nucleophiles: Hydrates, Hemiacetal/Acetals and*

**Hemiketal/Ketals**

Hemiacetal/hemiketal formation reactions can occur intramolecularly as illustrated in the example of glucose below. Note in this example a nucleophilic OH in one portion of the molecule reacts with the electrophilic carbonyl (aldehyde) to form the cyclic hemiacetals. Also note that this reaction generates a new chiral center and thus two diastereoisomers (or anomers) of glucose hemiacetal are possible from one stereoisomeric form of glucose:

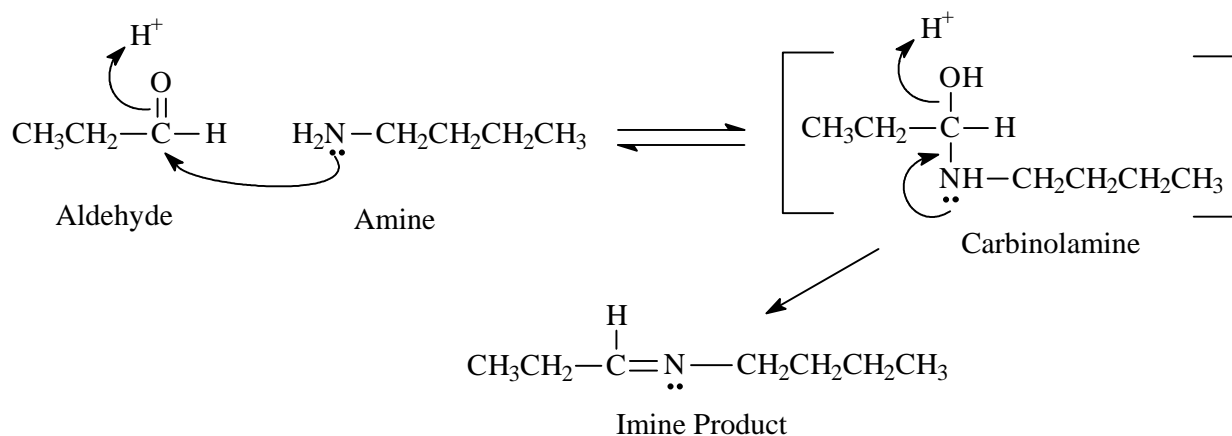


The examples above show the reaction of water and alcohols with aldehydes and ketones, a reaction of interest for a number of drug products (see Drug Tutorials). Note that under dehydrating conditions two molecules of alcohol can sequentially attack the original carbonyl carbon, resulting in replacement of the carbonyl oxygen with two alkoxy substituents (acetal, ketal). It is also important to note that these reactions are reversible and thus acetals and ketals can be hydrolyzed back to the corresponding aldehyde or ketone in aqueous acid:

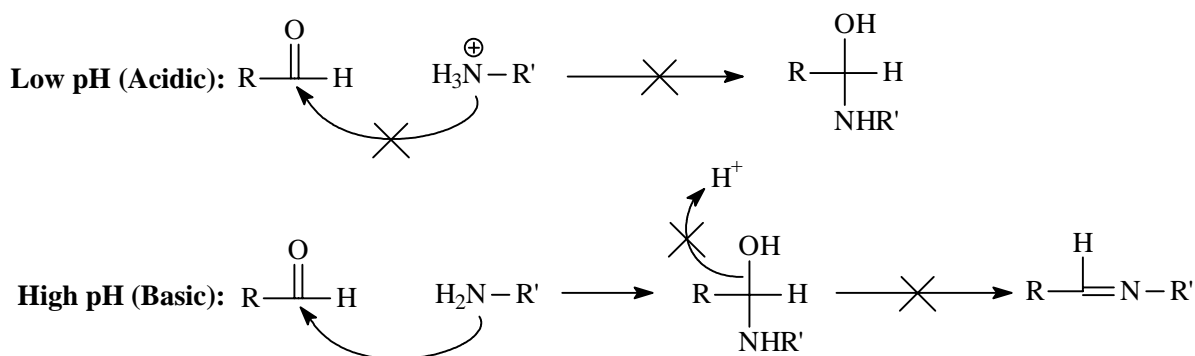


## 2. Reactions with Nitrogen Nucleophiles: Imine formation and Reductive Amination

The carbonyl moieties of aldehydes and, to a lesser extent, ketones react with amines to form imines as illustrated below. This is a reaction of great importance in biochemistry and drug science as illustrated in the individual Drug Tutorials. Note that this reaction involves initial attack of the electron rich (nucleophilic) amine nitrogen at the electron deficient (electrophilic) carbonyl to form a carbinolamine intermediate. These intermediates typically are unstable and can either reverse to starting materials, or eliminate the hydroxyl group with the formation of a second nitrogen to carbon bond (imine):

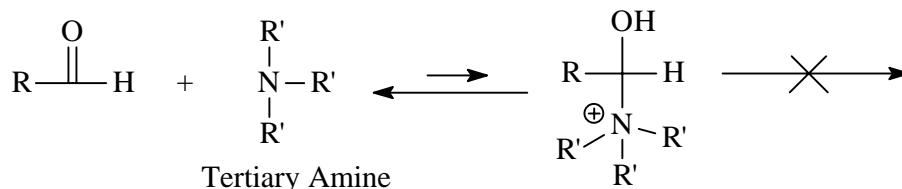
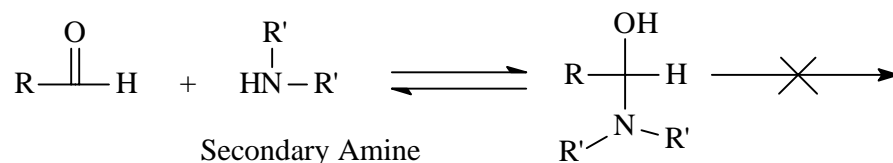


Imine formation reactions are dependent on a number of factors including pH of the reaction medium and the electronic and steric nature of the carbonyl electrophile and amine nucleophile. The nucleophile in this reaction is also basic and thus will be largely protonated at low pHs. In its protonated form, the amine cannot function as a nucleophile and thus the initial reaction (carbinolamine formation) cannot proceed. Also, imine formation also does not typically occur under highly basic conditions (high pH). At high pH there is not sufficient proton available to catalyze the elimination of hydroxyl from the carbinolamine to yield the imine. Thus imine formation reactions proceed best under conditions of intermediate pH!

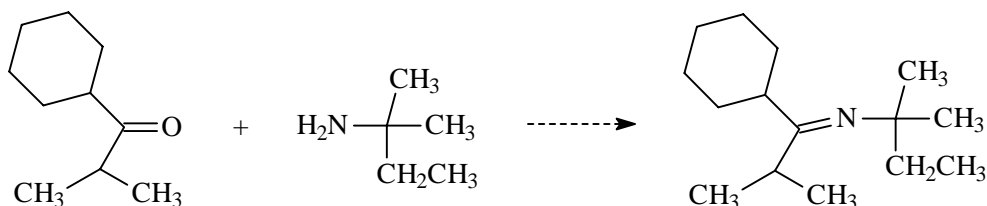


The electronic and steric nature of the carbonyl electrophile (aldehyde or ketone) and amine nucleophile also are important factors in imine formation reactions. These factors are illustrated by the following examples.

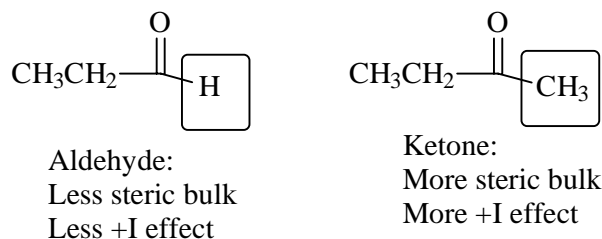
- Secondary and tertiary amines cannot form imine with carbonyl compounds since they lack the two hydrogens on nitrogen (primary amine) necessary for the reaction to go to completion:



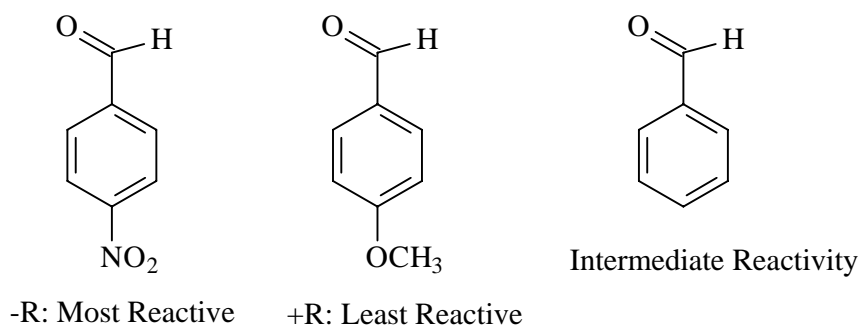
- Sterically bulky amines and/or carbonyl compounds react only slowly to form imines:



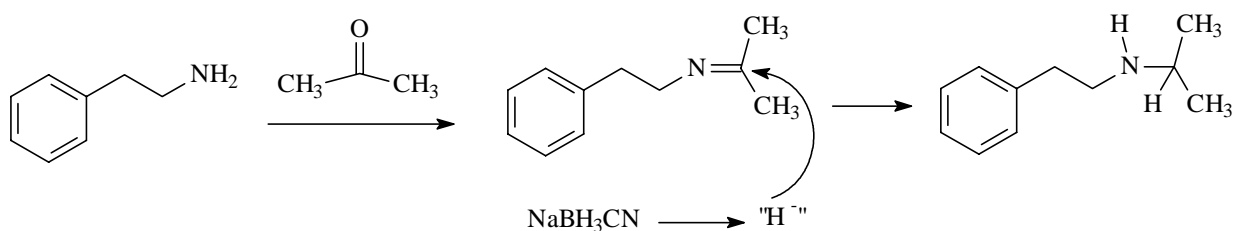
- Aldehydes react more readily than ketones in imine formation reactions. This is a result on two factors: (a) there is less steric bulk at the reaction site in aldehydes versus ketones, and (b) the additional carbon substituent present in ketones versus aldehydes is electron donating by induction (+I), and thereby reduces the electrophilicity of ketones relative to aldehydes.



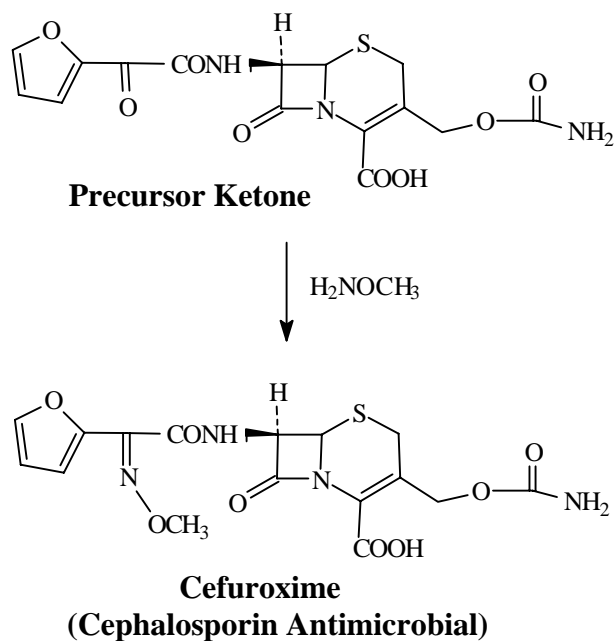
- The reactivity of the aldehyde or ketone carbonyl is influenced by substituents capable of donating or withdrawing electron density by resonance (R) or induction (I). Consider the three aldehydes shown below. The carbonyl of nitrobenzaldehyde is most reactive since the nitro group withdraws electron density from this carbon by resonance (-R), making it more electrophilic. On the other hand, the methoxybenzaldehyde is least reactive since the methoxy group donates electron density by resonance (+R) to the carbonyl carbon, thereby reducing the electrophilicity. The unsubstituted benzaldehyde would display intermediate reactivity in imine formation reactions:



In the laboratory the reaction of an aldehyde or ketone with an amine is frequently used to prepare N-alkylated amines in a process referred to as "reductive amination" or "reductive alkylation". Most commonly in this reaction the carbonyl compound and amine are combined in the presence of a mild and selective reducing agent such as sodium cyanoborohydride ( $\text{NaBH}_3\text{CN}$ ). The reducing agent preferentially reduces the imine formed, to yield a new, "alkylated" amine as shown below:



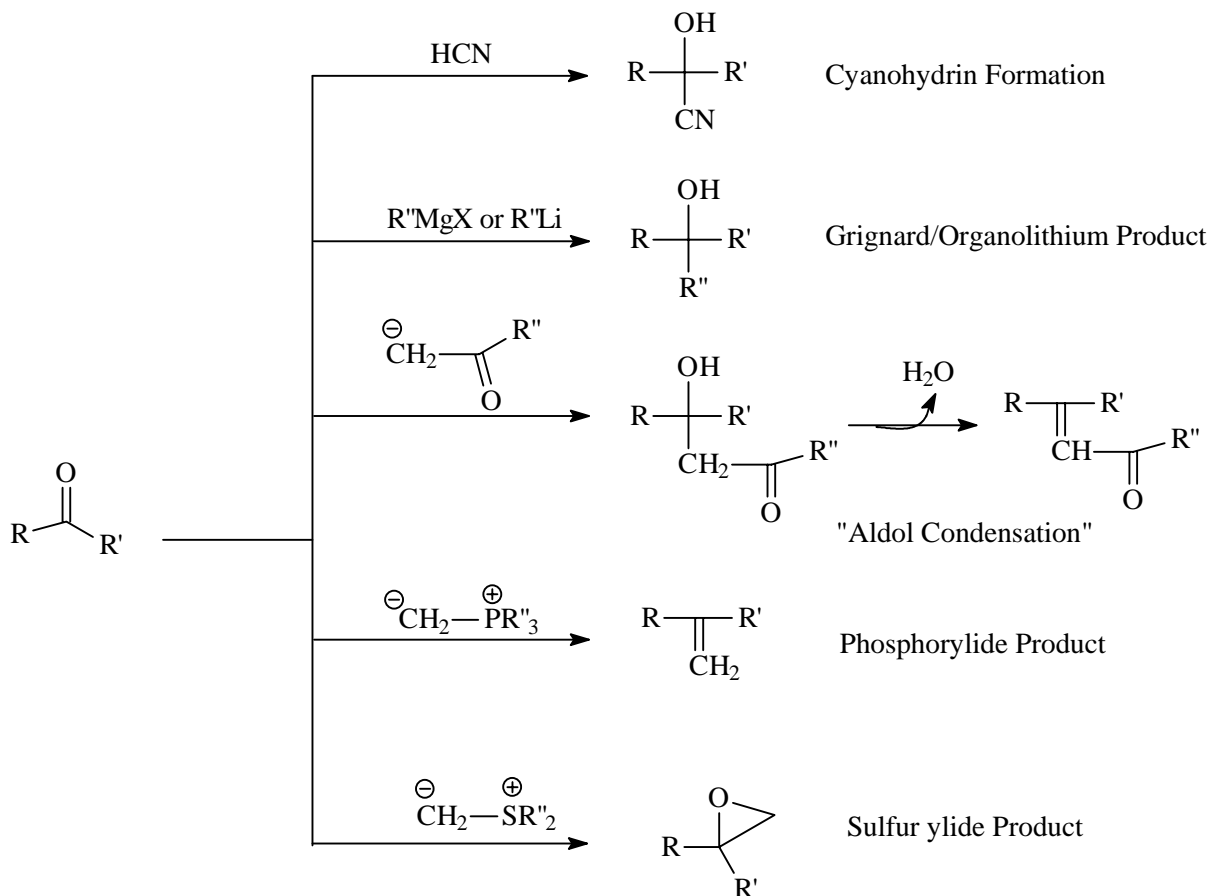
Note that in addition to amines, other nucleophilic nitrogen-containing compounds can form "imine-like" reaction products with aldehydes and ketones. For example, hydroxy- and alkoxyamines react with carbonyl compounds to form oximes (alkoximines). This function group is important in a number of drug compounds such as the cephalosporins:





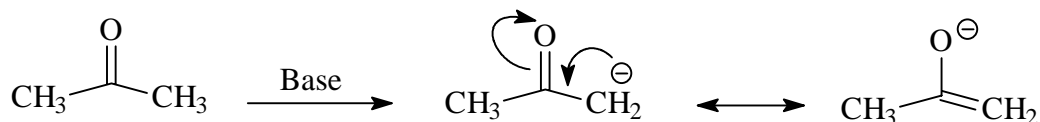
### 3. Reactions with Carbon Nucleophiles

Aldehydes and ketones can undergo a variety of reactions at carbonyl with carbon nucleophiles as summarized in the schemes below. While some reactions of this type are significant biochemically, the primary importance of most of these reactions is in organic synthesis. More details about these reactions can be found in any standard organic chemistry textbook:

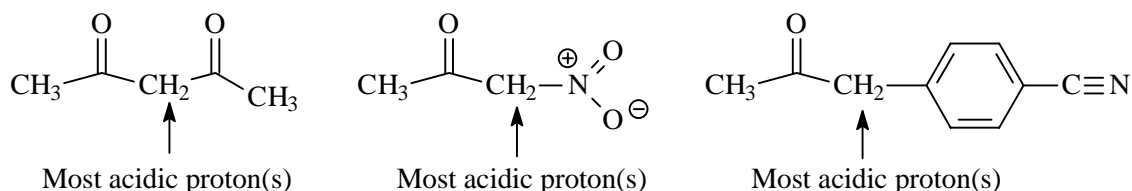


#### D. Acidity and Nucleophilic reactions at the $\alpha$ -Carbon:

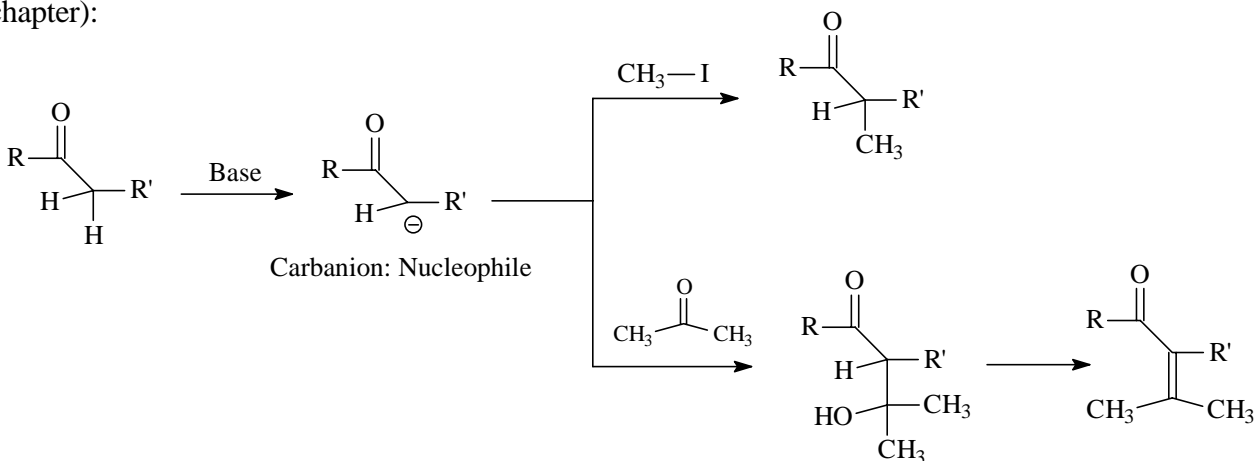
The carbonyl dipole present in aldehydes and ketones draws electron density towards oxygen. This serves to weaken adjacent or  $\alpha$ -carbon C-H bonds if present. This bond weakening results in an enhanced acidity (proton donor) for compounds containing this arrangement of atoms. In addition, resonance stabilization of the resulting anion is possible. Though the presence of a single aldehyde or ketone is insufficient to produce a compound which will ionize below pH 14.



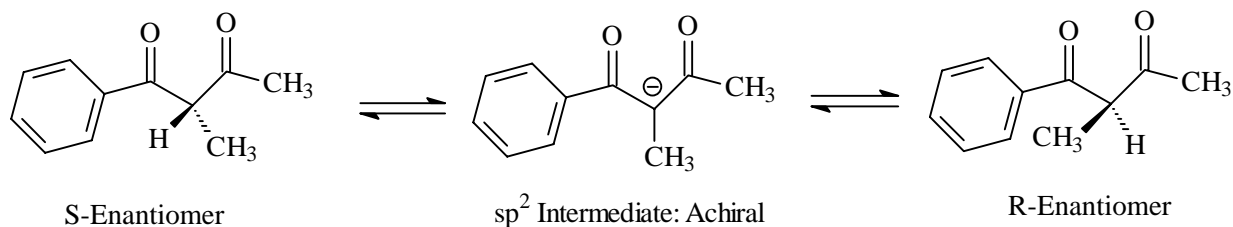
Furthermore, this ionization effect is cumulative so that if additional electron withdrawing groups are present relatively acidic compounds are possible. Consider the example below. In each case there are two groups capable of withdrawing electron density by resonance linked to a carbon with at least one hydrogen atom (an " $\alpha$ -carbon"). These compounds are even more acidic than the example above, because the conjugate base formed is extensively stabilized by resonance delocalization of the negative charge (see Resonance Tutorial for greater discussion of these principles):



The relative acidity of protons on  $\alpha$ -carbons in aldehydes and ketones (and other functional groups) is important for a variety of reasons. In organic synthetic chemistry it means these compounds can be converted to nucleophiles in the presence of a base, and used in displacement reactions, some of which are illustrated in the examples below (see also "Reactions with Carbon Nucleophiles" in this chapter):

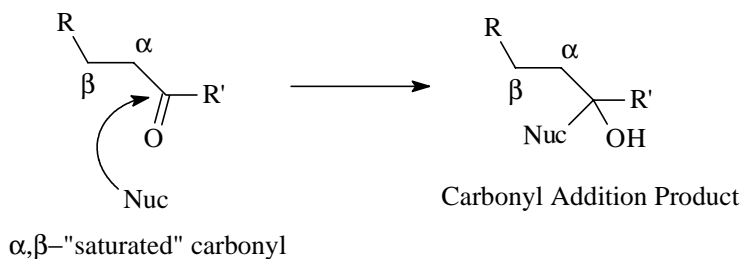
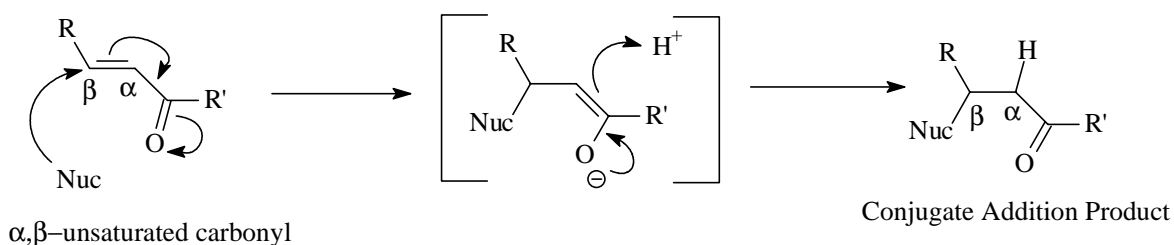


The acidity of  $\alpha$ -carbon protons in carbonyl systems also is important in drug stability, particularly for some chiral drugs. If an  $\alpha$ -carbon in an aldehyde or ketone (or another carbonyl-containing compound) is chiral and possesses a proton, this center can racemize under acidic or basic conditions. This can result in loss of stereochemistry essential to bind to a specific target and produce a desired effect:

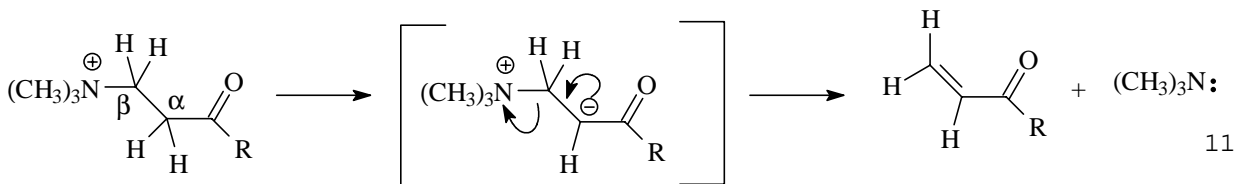


E. Nucleophilic/Elimination Reactions at the  $\gamma$ -Carbon in Unsaturated Carbonyl Systems:

The majority of the reactions of aldehydes and ketones involve either the carbonyl group, or a carbon atom adjacent to the carbonyl group as discussed in the preceding sections. Certain aldehydes and ketones are capable of participating in reactions at sites in addition to, or different from, the carbonyl carbon or  $\alpha$ -carbon. Such is the case for  $\alpha, \beta$ -unsaturated carbonyl systems as shown below. In structures such as these there is an "alkene" group conjugated with the carbonyl moiety, and the positions of C=C unsaturation are designated as the  $\alpha$  and  $\beta$  carbons. In these systems, the  $\beta$  carbon is most electron deficient (electrophilic). Thus when  $\alpha, \beta$ -unsaturated aldehydes or ketones are allowed to react with a nucleophile, addition occurs at the  $\beta$  carbon, rather than the carbonyl carbon as shown below. This reaction is called "conjugate addition" or a "Michael addition" if the nucleophile is carbon. Note the role the carbonyl plays in stabilizes the intermediate negative charge in this reactions. Also note that the product formed has the nucleophile (Nuc) covalently linked at the  $\beta$  carbon and the  $\alpha$ -carbon is protonated. Compare this to the carbonyl compound lacking the additional  $\alpha, \beta$ -unsaturated carbons where addition occurs at the carbonyl carbon. This reaction is very important in drug chemistry and metabolism as is discussed in the individual Drug Tutorials:

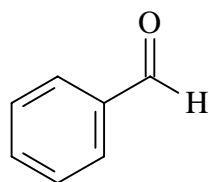


It should also be noted that "conjugate addition products" or  $\beta$ -substituted carbonyl compounds are also capable of undergoing "retro-addition" or decomposition to the parent  $\alpha, \beta$ -unsaturated carbonyl compound. This "reverse" reaction is likely to occur when (1) there is a sufficiently acidic proton on the carbon  $\alpha$  to the carbonyl so that ionization can occur, AND (2) the substituent at the  $\beta$ -carbon is a sufficiently good leaving group. For example, there are derivatives of the neuromuscular blocking drugs that have such a structural pattern and are prone to "retro-addition" or "reverse-conjugate addition" reactions as shown below. Note in this example that there is an acidic proton on the  $\alpha$ -carbon (the adjacent carbonyl can stabilize the charge that forms), and that the  $\beta$ -substituent is a quaternary amine (a cation) and thus a good leaving group (to quench the positive charge on nitrogen):

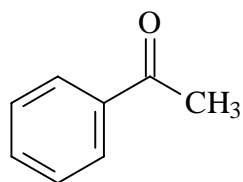


**IV. Problems**

1. Answer the questions a.- e. below for the two carbonyl compounds (A and B) shown below:

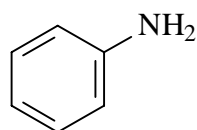


**A**



**B**

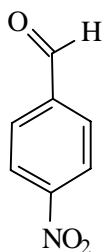
- Classify each compound based on their carbonyl functionality
- Show the hemiacetal that would form from reaction of compound A with ethanol
- Show the product that would form from reaction of compound A and B with aniline. Which compound would react more readily with aniline and why?



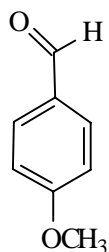
**Aniline**

- Which compound (A or B) is more soluble in water? Provide two reasons to support your answer.
- Show the "partial" and "complete" reduction products for compound B

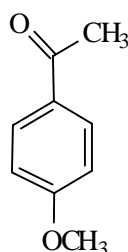
2. Identify the compound below that would be most likely to form an imine with a primary amine. Identify the compound below LEAST likely to form an imine:



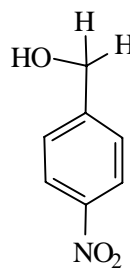
**A**



**B**

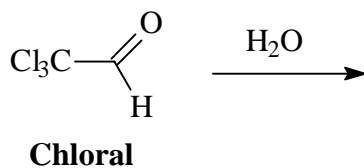


**C**



**D**

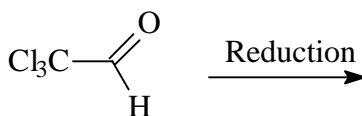
3. Trichloroacetaldehyde (Chloral) is a very effective sedative-hypnotic drug. The aldehyde form is an oil and difficult to formulate as a solid dosage form. The hydrate form, known as chloral hydrate, is a crystalline solid and is often used to prepare solid dosages. Draw the structure of chloral hydrate.



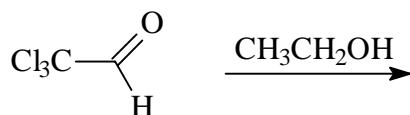
4. Explain why, in solution, chloral exists to a greater degree (100%) in the hydrate form than acetaldehyde (60%).



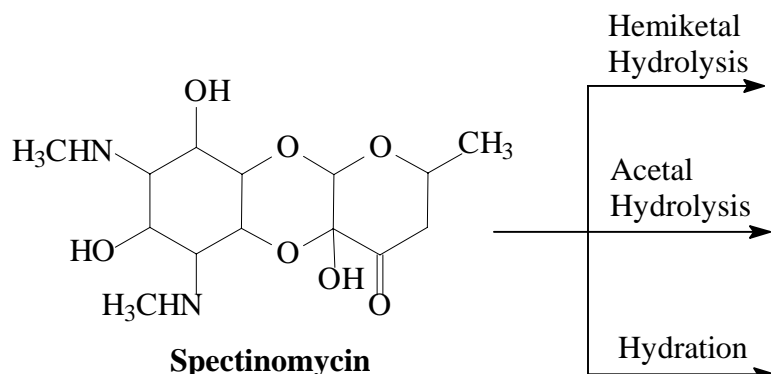
5. The active metabolite of trichloroacetaldehyde is the alcohol reduction product, trichloroethanol (TCE). Draw the structure of TCE.



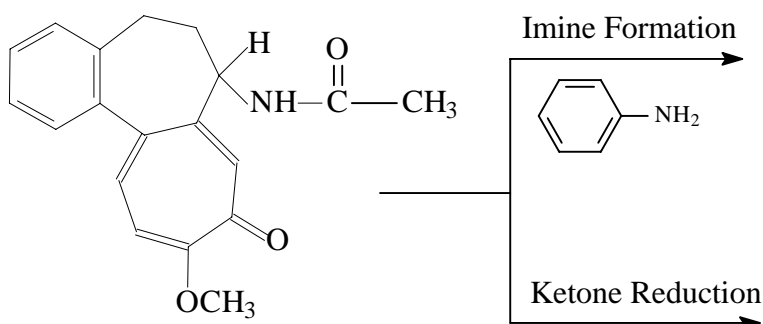
6. When chloral is given as a solution in ethanol, the combination is a fast acting hypnotic reported to be more potent than the parent drug. This combination, referred to as a “Mickey Finn”, produces a hemiacetal product. Draw the structure of this hemiacetal.



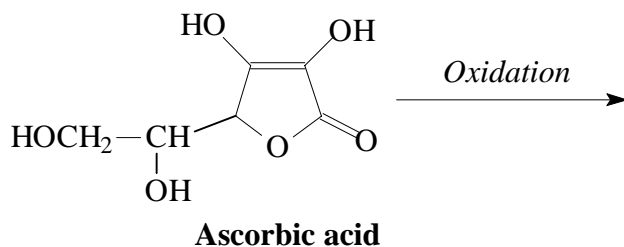
7. Using the structure for spectinomycin shown below illustrate the products from acetal hydrolysis, hemiketal hydrolysis and hydrate formation.



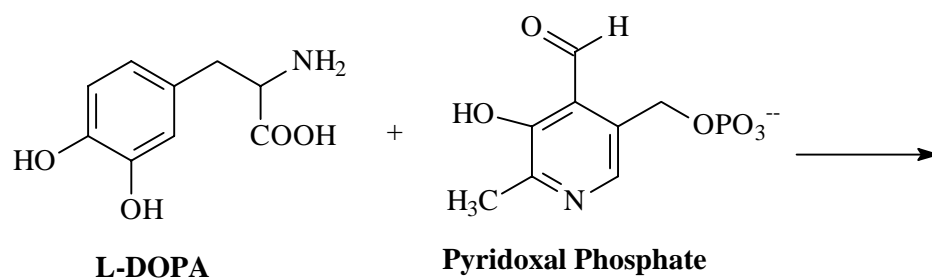
8. Show the results of the following chemical transformations using the structure for colchicine as the starting point.



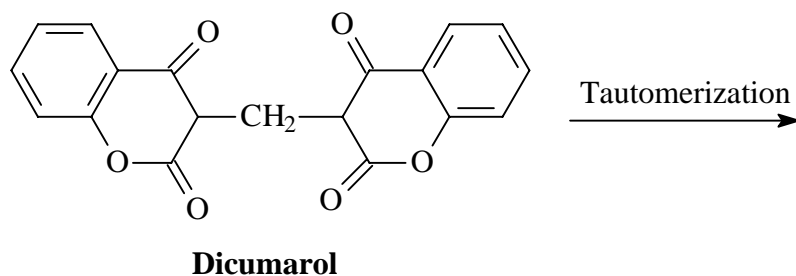
9. Ascorbic acid (vitamin C) is often used in solutions of pharmaceutical products to prevent oxidative decomposition of the drug species in solution. This antioxidant property of ascorbic acid is mediated by its' relative ease of oxidation. Show the product resulting from the antioxidant effects of ascorbic acid.



10. The antiparkinson drug L-DOPA is decarboxylated to dopamine (DA) post-administration. This reaction is mediated by the enzyme L-aromatic amino acid decarboxylase and the cofactor pyridoxal phosphate. The initial step of this reaction involves the formation of an imine (Schiff base) between L-DOPA and pyridoxal on the surface of the enzyme. Draw the structure of this imine intermediate. Also, explain the role of pyridoxal in the decarboxylation reaction that follows imine formation.



11. Dicumarol is an anticoagulant drug used alone or in combination with heparin to prevent intravascular clotting. One of the structural features for anticoagulant activity in this class of compounds is the ability to form an enol tautomer under physiologic conditions. In fact, dicumarol probably exists as a di-enol. Draw the structure of the dienol tautomer of dicumarol.



12. Show the hydrolysis product for the following reaction.

